The Journal of Nutrition
Issues and Opinions

The Ketogenic Diet: Evidence for Optimism but High-Quality Research Needed

David S Ludwig

New Balance Foundation Obesity Prevention Center, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA

ABSTRACT

For >50 y, dietary guidelines in the United States have focused on reducing intakes of saturated and total fat. However, rates of obesity and diabetes rose markedly throughout this period, with potentially catastrophic implications for public health and the economy. Recently, ketogenic diets have received substantial attention from the general public and nutrition research community. These very-low-carbohydrate diets, with fat comprising >70% of calories, have been dismissed as fads. However, they have a long history in clinical medicine and human evolution. Ketogenic diets appear to be more effective than low-fat diets for treatment of obesity and diabetes. In addition to the reductions in blood glucose and insulin achievable through carbohydrate restriction, chronic ketosis might confer unique metabolic benefits of relevance to cancer, neurodegenerative conditions, and other diseases associated with insulin resistance. Based on available evidence, a well-formulated ketogenic diet does not appear to have major safety concerns for the general public and can be considered a first-line approach for obesity and diabetes. High-quality clinical trials of ketogenic diets will be needed to assess important questions about their long-term effects and full potential in clinical medicine. *J Nutr* 2020;150:1354–1359.

Keywords: ketogenic diet, low-carbohydrate diet, low-fat diet, vegan diet, ketones, obesity, diabetes, cardiovascular disease, cancer, Alzheimer disease

A century ago, the ketogenic diet was a standard of care in diabetes, used to prolong the life of children with type 1 diabetes and to control the symptoms of type 2 diabetes in adults (1). Because all forms of diabetes share a basic pathophysiological problem, carbohydrate intolerance, restriction of carbohydrate on a ketogenic diet (typically ≤50 g/d with >70% fat) often produced rapid and remarkable clinical improvement. Discovery of insulin in the 1920s enabled people with diabetes to control hyperglycemia on high-carbohydrate diets. However, the human toll and economic burden from diabetes complications continue to mount, despite increasingly sophisticated insulin analogs and drugs for associated conditions such as dyslipidemia, hypertension, and coagulopathy. Contrary to expectation, adoption of a higher-carbohydrate (lower-fat) diet by the US public in the second half of the 20th century could have contributed to the increasing prevalence of obesity (2), a major risk factor for type 2 diabetes. Despite commonly voiced concerns about the safety of, and lack of supporting evidence for, this putative fad (3), the ketogenic diet has a long track record—not only in clinical medicine but also through human evolution—providing evidence for optimism in the search for more effective dietary prevention and treatment of chronic diseases.

The author reported no funding received for this study.
Author disclosures: DSL, has received royalties for books on obesity and nutrition that recommend a carbohydrate-modified, but not ketogenic, diet, and grants from the NIH and philanthropic organizations unaffiliated with the food industry for obesity-related research.
Address correspondence to DSL (e-mail: david.ludwig@childrens.harvard.edu).

Carbohydrate Restriction Is More Effective than Fat Restriction for Obesity Treatment

For decades, dietary fat was considered uniquely fattening due to its high energy density and palatability, leading to "passive overconsumption" relative to all carbohydrates (4). However, recent research underscores a biological basis for body weight control, by which the metabolic effects of food, more so than calorie content of specific foods or nutrients, determine body weight over the long term. According to the carbohydrate-insulin model of obesity (5, 6) the processed carbohydrates (e.g., most breads, rice, potato products, and added sugar) that replaced dietary fats during the low-fat diet era promote fat storage, increase hunger, and lower energy expenditure, predisposing to obesity and diabetes in susceptible individuals.

Most clinical trials comparing macronutrient-varying diets have employed low-intensity interventions, insufficient to produce significant long-term dietary change. Therefore, it is

Manuscript received September 23, 2019. Initial review completed October 23, 2019. Revision accepted November 22, 2019.
First published online December 11, 2019; doi: https://doi.org/10.1093/jn/nxz308.

not surprising that meta-analyses of these trials would show little long-term weight loss, and little difference between diet groups. Even so, meta-analyses have found that conventional low-fat diets are inferior to all higher-fat comparisons including ketogenic diets (7–10).

Anecdotal reports for many years have suggested that low-carbohydrate diets suppress hunger to a greater degree than conventional approaches, taking rate of weight loss into account. For example, in a small clinical trial from the 1950s, female college students with high body weight were given calorie-restricted diets varying in carbohydrate-to-fat ratio. Students on the low-fat diet reported a "lack of 'pep' throughout most of the study… [and feeling] discouraged because they were always conscious of being hungry." In contrast, those on the very-low-carbohydrate diet reported "satisfaction" and that "[h]unger between meals was not a problem," even though they had lost more weight (11). In a more recent crossover study, 17 men with obesity consumed ad libitum for 4 wk very-low-carbohydrate (4%) or moderate-carbohydrate (35%) diets controlled for protein. The participants consumed less dietary energy, lost more weight, and reported less hunger on the very-low-carbohydrate diet (12). This effect could relate to the improved circulating metabolic fuel concentration observed in the late postprandial period on a low-glycemic-load diet, and also to advantageous changes in metabolic hormones (e.g., lower ghrelin) (13, 14).

Carbohydrate restriction can also increase energy expenditure, a major goal of obesity research conventionally sought with drugs and exercise (15). In a 20-wk weight-loss-maintenance feeding study with 164 participants, those assigned to a low- (20%) compared with a high- (60%) carbohydrate diet had higher energy expenditure (~200–250 kcal/d), with evidence of effect modification by insulin secretion as predicted by the carbohydrate-insulin model (13, 16). Although a meta-analysis (17) suggested no benefit of low-carbohydrate compared with low-fat diets for energy expenditure, most of the included studies were too short (median duration <1 wk) to exclude well-described transient metabolic adaptations (5, 18). Behavioral trials with more powerful interventions lasting ≥1–2 y, and feeding studies of ≥4 wk, will be needed to test the true efficacy of carbohydrate restriction and clarify mechanisms.

Low-Carbohydrate Diets Show Promise for Diabetes Treatment

The US NIH sponsored several large multicentered studies of low-fat diets, such as the Women's Health Initiative dietary modification trial (prevention of diabetes as a secondary outcome) (19) and Look Ahead [prevention of cardiovascular disease (CVD) in people with diabetes as the primary outcome] (20). In both cases, the low-fat diet showed no benefit, even though the comparison groups were given lower-intensity interventions. The Diabetes Prevention Program intensive lifestyle intervention reduced incidence of type 2 diabetes among high-risk participants (21), but the multicomponent nature of the intervention (including calorie restriction, fat restriction, exercise, and behavior modification) makes attribution of effects to the low-fat diet problematic. Unfortunately, no comparable studies of very-low-carbohydrate diets have been conducted, but smaller trials and observational studies suggest promise.

A 2019 Consensus Report from the American Diabetes Association concluded that low-carbohydrate diets (including those that aim for nutritional ketosis) "are among the most studied eating patterns for type 2 diabetes" and that these "eating patterns, especially very-low-carbohydrate … have been shown to reduce [Hb]A1C [glycated hemoglobin] and the need for antihyperglycemic medications" (22). In a pragmatic trial including 262 adults with type 2 diabetes assigned to a very-low-carbohydrate diet, mean weight loss was 11.9 kg and HbA1c decreased by 1.0%, even with substantial reductions in the use of hypoglycemic medications other than metformin (23). Few clinical trials have examined carbohydrate restriction in type 1 diabetes, possibly due in part to concerns about hypoglycemia and ketoacidosis. In a survey of 316 children and adults following a very-low-carbohydrate diet for type 1 diabetes, exceptional glycemic control (mean HbA1c = 5.7%), low rates of hypoglycemia and ketoacidosis, an overall healthful CVD risk profile, and high satisfaction with diabetes management were documented (24).

Low-Carbohydrate Diets Might Lower CVD Risk despite High Saturated Fat Content

Although LDL cholesterol—an established CVD risk factor—can increase on low-carbohydrate diets (25), in part due to high saturated fat content, lipoprotein size distribution can indicate a relatively lower risk, characterized by larger, more buoyant particles (26). Consistent with this possibility, individuals with isolated elevated LDL cholesterol, compared with those who also have high triglycerides and low HDL cholesterol, were at lower risk for coronary events and benefited less from statins in the Scandinavian Simvastatin Survival Study (27). Indeed, there is precedent for reduced cardiovascular risk in the context of higher LDL cholesterol: treatment with sodium-glucose cotransporter 2 inhibitors (28). The mechanisms elicited by this drug class share similarity on the physiological, if not molecular, level with a ketogenic diet. Both shift substrate utilization from carbohydrates to lipids, cause ketosis, reduce glycemic excursions, lower insulin concentrations, produce weight loss, promote natriuresis, and lower blood pressure—actions that can counterbalance or attenuate any adverse cardiovascular effects of elevated LDL cholesterol.

Carbohydrate restriction benefits multiple components of the metabolic syndrome, a major CVD risk factor. A low-carbohydrate diet improves hyperglycemia, triglycerides, HDL cholesterol, small dense LDL subclass phenotype, oxidized plasma lipids, and hepatic steatosis, whereas a low-fat diet can adversely affect some of these components (26, 29–34).

The relation between dietary fat and mortality in observational research is controversial due to methodological challenges involving confounding, reverse causality, and effect modification (e.g., overall diet quality, physical activity level). In a high-quality, 2-cohort study, high intake of fat as a proportion of total energy was associated with reduced risk of premature death, although the type of dietary fat importantly modified risk: decreased with unsaturated fat and increased with saturated fat (35). However, the relation between saturated fat and mortality observed in a general population might not apply to those consuming a ketogenic diet due to exceptionally high rates of saturated fat oxidation and low rates of de novo lipogenesis (36). Demonstrating this point, serum saturated fat

TABLE 1 Conditions under study with a ketogenic or low-carbohydrate diet[1]

Condition	Proposed mechanisms[2]
Cancer (ancillary treatment)	Warburg effect; reduced concentration of insulin and other growth-stimulating hormones and factors; immune modulation; reduced side effects of chemotherapy, radiation
Brain	
Breast	
Colon	
Endometrial	
Lymphoma	
Pancreaticobiliary	
Prostate	
Cardiovascular	Weight loss; reduced postprandial glycemia, insulinemia; anti-inflammatory effects of ketones
Chronic inflammation	
Dyslipidemia	
Endothelial dysfunction	
Insulin resistance	
Endocrine	
Diabetes, type 1	Reduced postprandial glycemic excursions, lower insulin requirement
Diabetes, type 2	As above; weight loss
Obesity	Reduced anabolic stimulation of adipose; partitioning of metabolic fuels
Gastrointestinal	
Fatty liver, nonalcoholic	Reduced postprandial glycemia, insulinemia; enhanced fat oxidation
Irritable bowel syndrome	Microbiome; carbohydrate fermentation
Neurological	Neuroprotective effects of ketones through reduced inflammation, edema oxidative damage, apoptosis, amyloid deposition; neural energy metabolism; epigenetic effects; microbiome
Alzheimer disease	
Epilepsy	
Mild cognitive impairment	
Multiple sclerosis	
Oxygen toxicity (underwater diving)	
Traumatic brain injury	
Spinal cord injury	
Psychological/psychiatric	Reduced withdrawal symptoms; reduced craving and reward, mediated by nucleus accumbens; reduced neuroinflammation; neuronal metabolism; microbiome
Alcoholism	
Autism spectrum disorder	
Bipolar disorder	
Mood disorders	
Schizophrenia	
Well-being/quality of life	
Miscellaneous	
Exercise tolerance, physical performance	Improved access to metabolic fuels
Gangliosidoses	Increased efficacy, reduced side effects of primary treatment
Infectious endocarditis, diagnosis	Enhanced signal-to-noise ratio with ^{18}F-FDG PET scan
Lymphedema	Endothelial cell function; lymphatic transport
Obstructive sleep apnea	Weight loss; decreased visceral fat

[1] Listed on clinicaltrials.gov as "Not yet recruiting," "Recruiting," or "Active, not recruiting" as of July 31, 2019. ^{18}F-FDG PET, [^{18}F]fluoro-2-deoxyglucose positron emission tomography.
[2] List not exhaustive.

did not increase through a wide range of saturated fat intakes for 3-wk intervals in a study of 16 adults with metabolic syndrome (37).

Chronic Ketosis Might Provide Unique Metabolic Benefits

Ketosis, an evolutionarily ancient metabolic pathway, might confer additional benefits, beyond those of prevailing high-fat diets, through modulation of the inflammasome, oxidative damage, histone acetylation, mitophagy, cellular redox state, and other mechanisms (38, 39). Ketones have been termed a "superfuel" for the brain (39), upon which infants can be especially dependent (40). Based on these pleiotropic actions, a ketogenic diet has been considered for a wide range of health conditions. The website clinicaltrials.com currently lists 85 planned or active trials of a ketogenic or low-carbohydrate diet for diseases of numerous organ systems, including cardiovascular, endocrine, gastrointestinal, neurological, and psychiatric (see **Table 1**). Additional trials have been completed but not yet published.

The metabolic effects of a ketogenic diet can have special relevance to oncology. Many cancers contain mitochondrial defects, making them reliant on glycolytic fermentation, an inefficient energy generation pathway compared with oxidative phosphorylation (41, 42). A ketogenic diet targeting this Warburg effect might starve cancer cells without toxicity to normal cells, by decreasing fasting and postprandial blood

glucose concentrations. Other mechanisms recruited by this diet include reduced secretion of insulin, a hormonal driver of some tumors, and ketones themselves, through metabolic and signaling actions. Because blood glucose concentrations remain in the low-normal range, and other fermentable fuels are available (e.g., glutamine), a ketogenic diet would not be expected to cure cancer as a stand-alone treatment. However, this diet might act synergistically with other treatments, such as phosphoinositide 3-kinase inhibitors (43), and aid prevention, possibilities that warrant investigation.

In view of the potent effects of ketones in the brain, a ketogenic diet has also generated considerable interest for neurodegenerative and neuropsychiatric disorders. Preliminary reports suggest that patients with Alzheimer disease, characterized by central insulin resistance, show clinical improvement with a ketogenic formula or exogenous ketones (44, 45). After a brief transitional period (46), a ketogenic diet can also improve general mood, although findings vary among studies (47).

Ketogenic Diets Have a Long Track Record of Safety

Concern has been expressed about the safety of ketogenic diets (3) based on case reports of children with epilepsy describing gastrointestinal problems, nephrolithiasis, cardiac abnormalities, and poor growth, but these reports need to be interpreted cautiously for several reasons. First, the ketogenic diet used in this clinical context is typically more extreme (with ≥85% energy as fat) than would be recommended for virtually any other purpose. Second, patients with epilepsy can have other health problems or medication use predisposing to complications, for which the general public would not be at risk. Third, case reports inevitably involve major selection bias; the absence of widespread adverse events in public health surveillance, despite the popularity of the ketogenic diet today (e.g., 5 of the top 10 best-selling diet books on Amazon.com), provides considerable reassurance.

Furthermore, without adequate attention to food quality, any macronutrient-focused eating pattern can have adverse effects. A low-fat diet containing high amounts of sugar and other processed carbohydrates raises risk of fatty liver and metabolic syndrome; a vegan diet without adequate attention to key micronutrients can cause growth retardation in children. Public health guidelines do not discourage low-fat and plant-based diets, but instead focus on measures to encourage healthful versions of these eating patterns to minimize risk and maximize benefits. With the substantial evidence of benefit as described above, diets that restrict carbohydrate warrant the same consideration.

There Is No Human Requirement for Dietary Fiber or Carbohydrate

Some have argued that the greatest risk "of the ketogenic diet may be the one most overlooked: the opportunity cost of not eating high-fiber, unrefined carbohydrates" (3), pointing to a meta-analysis of observational studies finding protective associations of whole-grain intake with CVD, cancer, and total mortality (48). However, such studies can only address the *relative* healthfulness of a specific food compared with foods that would have otherwise been consumed. Although strong evidence indicates benefits of consuming whole grains instead of refined grains (the typical trade-off in populations with grain-based diets), a more relevant question to this debate is how whole grains compare with low-carbohydrate foods allowed on a ketogenic diet. Bearing on this issue, a recent meta-analysis of clinical trials found that diets high in whole grains, compared with control diets, had no overall effect on measures of body fatness; among the trials with "unhealthy individuals" (having diabetes, metabolic syndrome, or overweight/obesity), whole-grain consumption increased BMI (49).

Admittedly, high-carbohydrate diets have been consumed by some populations with low rates of obesity-related chronic disease (e.g., "blue zones" in Asia), although these have typically had high levels of occupational physical activity (e.g., subsistence farming) and limited total calorie availability. However, the health benefits of grain consumption among populations with highly prevalent obesity and insulin resistance have not been established. In fact, diets with virtually no carbohydrate (and therefore, no fiber) throughout most of the year have been consumed by humans—for example, Native Americans of the Great Plains, Laplanders, the Inuit, and other traditional hunter-gatherer societies in temperate and arctic climates—much longer than a low-fat, high-carbohydrate diet as adopted by grain-based agrarian societies.

Conclusions

Both low-fat and low-carbohydrate diets can produce adverse effects in susceptible individuals (the former especially so among those with insulin resistance, comprising the majority in the United States). However, beyond fatigue and other transitional symptoms upon initial adoption, a well-formulated ketogenic diet does not appear to have major safety concerns for the general population. Based on available evidence, a ketogenic diet can be considered a first-line approach for the treatment of obesity and type 2 diabetes. A ketogenic diet also holds promise for a range of other chronic, sometimes intractable, conditions associated with metabolic dysfunction, such as type 1 diabetes, steatohepatitis, neurodegenerative disease, and cancer.

However, the lack of high-quality clinical trials hinders scientific understanding and public health translation. Key unresolved questions warranting research priority include: How does LDL cholesterol elevation with carbohydrate restriction affect cardiovascular risk versus triglyceride elevation with fat restriction? Does the reduction of HbA1c in diabetes on a ketogenic diet translate into reductions in micro- and macrovascular disease? Are there uniquely susceptible populations (e.g., LDL cholesterol "hyperresponders") or conditions (liver or kidney disease, pregnancy) for which a ketogenic diet would be relatively contraindicated? What is the efficacy of a ketogenic diet for weight loss compared with other approaches in trials incorporating powerful methods to facilitate long-term behavior change? Does chronic ketosis provide unique metabolic benefits, beyond those that can be obtained with less restrictive regimens, such as a low-glycemic index, moderate-carbohydrate diet?

Finally, it is worth noting that the ketogenic diet has elicited controversy, in part because conventional nutritional teaching has for years emphasized the harms of high total and saturated fat intakes. Polarization might have also arisen from the misconception that ketogenic diets require high intakes of animal products—engendering concern among those who advocate plant-based diets for health, ethical, or environmental reasons.

In fact, a ketogenic diet can be vegetarian (containing eggs and dairy products) or vegan, with plant-based fats (e.g., avocado, nuts, seeds, coconut, flax, olive oil), proteins (e.g., tofu, tempeh, seitan, lupini beans, pea protein), nonstarchy vegetables, and limited amounts of low-sugar fruits, as exemplified by the Eco-Atkins diet (50). This flexibility allows individualization of dietary choice on a ketogenic diet for obesity and diabetes.

Acknowledgments

The sole author was responsible for all aspects of this manuscript.

References

1. Henderson G. Court of last appeal – the early history of the high-fat diet for diabetes. J Diabetes Metab 2016;7(8):696.
2. Ludwig DS. Lowering the bar on the low-fat diet. JAMA 2016;316(20):2087–8.
3. Joshi S, Ostfeld RJ, McMacken M. The ketogenic diet for obesity and diabetes—enthusiasm outpaces evidence. JAMA Intern Med 2019;179:1163–4.
4. Blundell JE, MacDiarmid JI. Fat as a risk factor for overconsumption: satiation, satiety, and patterns of eating. JADA 1997;97(7 Suppl):S63–9.
5. Ludwig DS, Ebbeling CB. The carbohydrate-insulin model of obesity: beyond "calories in, calories out". JAMA Intern Med 2018;178(8):1098–103.
6. Ludwig DS, Friedman MI. Increasing adiposity: consequence or cause of overeating? JAMA 2014;311(21):2167–8.
7. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr 2013;110(7):1178–87.
8. Mancini JG, Filion KB, Atallah R, Eisenberg MJ. Systematic review of the Mediterranean diet for long-term weight loss. Am J Med 2016;129(4):407–15.e4.
9. Mansoor N, Vinknes KJ, Veierod MB, Retterstol K. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. Br J Nutr 2016;115(3):466–79.
10. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2015;3(12):968–79.
11. Cederquist DC, Brewer WD, Wagoner AN, Dunsing D, Ohlson MA. Weight reduction on low-fat and low-carbohydrate diets. J Am Diet Assoc 1952;28(2):113–16.
12. Johnstone AM, Horgan GW, Murison SD, Bremner DM, Lobley GE. Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum. Am J Clin Nutr 2008;87(1):44–55.
13. Ebbeling CB, Feldman HA, Klein GL, Wong JMW, Bielak L, Steltz SK, Luoto PK, Wolfe RR, Wong WW, Ludwig DS. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. Br Med J 2018;363:k4583.
14. Walsh CO, Ebbeling CB, Swain JF, Markowitz RL, Feldman HA, Ludwig DS. Effects of diet composition on postprandial energy availability during weight loss maintenance. PLoS One 2013;8(3):e58172.
15. Tseng YH, Cypess AM, Kahn CR. Cellular bioenergetics as a target for obesity therapy. Nat Rev Drug Discov 2010;9(6):465–82.
16. Ludwig DS, Lakin PR, Wong WW, Ebbeling CB. Scientific discourse in the era of open science: a response to Hall et al. regarding the Carbohydrate-Insulin Model. Int J Obes (Lond)[Internet] 2019. doi: 10.1038/s41366-019-0466-1.
17. Hall KD, Guo J. Obesity energetics: body weight regulation and the effects of diet composition. Gastroenterology 2017;152(7):1718–27.e3.
18. Sherrier M, Li H. The impact of keto-adaptation on exercise performance and the role of metabolic-regulating cytokines. Am J Clin Nutr 2019;110(3):562–73.
19. Tinker LF, Bonds DE, Margolis KL, Manson JE, Howard BV, Larson J, Perri MG, Beresford SA, Robinson JG, Rodríguez B, et al. Low-fat dietary pattern and risk of treated diabetes mellitus in postmenopausal women: the Women's Health Initiative randomized controlled dietary modification trial. Arch Intern Med 2008;168(14):1500–11.
20. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369(2):145–54.
21. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6):393–403.
22. Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, Mitri J, Pereira RF, Rawlings K, Robinson S, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care 2019;42(5):731–54.
23. Athinarayanan SJ, Adams RN, Hallberg SJ, McKenzie AL, Bhanpuri NH, Campbell WW, Volek JS, Phinney SD, McCarter JP. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. Front Endocrinol (Lausanne) 2019;10:348.
24. Lennerz BS, Barton A, Bernstein RK, Dikeman RD, Diulus C, Hallberg S, Rhodes ET, Ebbeling CB, Westman EC, Yancy WS, Jr, et al. Management of type 1 diabetes with a very low-carbohydrate diet. Pediatrics 2018;141(6):e20173349.
25. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, Jr, Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166(3):285–93.
26. Faghihnia N, Tsimikas S, Miller ER, Witztum JL, Krauss RM. Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. J Lipid Res 2010;51(11):3324–30.
27. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. Circulation 2001;104(25):3046–51.
28. Basu D, Huggins LA, Scerbo D, Obunike J, Mullick AE, Rothenberg PL, Di Prospero NA, Eckel RH, Goldberg IJ. Mechanism of increased LDL (low-density lipoprotein) and decreased triglycerides with SGLT2 (sodium-glucose cotransporter 2) inhibition. Arterioscler Thromb Vasc Biol 2018;38(9):2207–16.
29. Browning JD, Baker JA, Rogers T, Davis J, Satapati S, Burgess SC. Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. Am J Clin Nutr 2011;93(5):1048–52.
30. Gepner Y, Shelef I, Komy O, Cohen N, Schwarzfuchs D, Bril N, Rein M, Serfaty D, Kenigsbuch S, Zelicha H, et al. The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. J Hepatol 2019;71(2):379–88.
31. Hyde PN, Sapper TN, Crabtree CD, LaFountain RA, Bowling ML, Buga A, Fell B, McSwiney FT, Dickerson RM, Miller VJ, et al. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. JCI Insight 2019;4(12):128308.
32. Mardinoglu A, Wu H, Bjornson E, Zhang C, Hakkarainen A, Rasanen SM, Lee S, Mancina RM, Bergentall M, Pietiläinen KH, et al. An integrated understanding of the rapid metabolic benefits of a carbohydrate-restricted diet on hepatic steatosis in humans. Cell Metab 2018;27(3):559–71.e5.
33. Volek JS, Phinney SD, Forsythe CE, Quann EE, Wood RJ, Puglisi MJ, Kraemer WJ, Bibus DM, Fernandez ML, Feinman RD. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids 2009;44(4):297–309.
34. Westman EC, Yancy WS, Jr, Olsen MK, Dudley T, Guyton JR. Effect of a low-carbohydrate, ketogenic diet program compared to a low-fat diet on fasting lipoprotein subclasses. Int J Cardiol 2006;110(2):212–16.
35. Wang DD, Li Y, Chiuve SE, Stampfer MJ, Manson JE, Rimm EB, Willett WC, Hu FB. Association of specific dietary fats with total and cause-specific mortality. JAMA Intern Med 2016;176(8):1134–45.
36. Forsythe CE, Phinney SD, Feinman RD, Volk BM, Freidenreich D, Quann E, Ballard K, Puglisi MJ, Maresh CM, Kraemer WJ, et al. Limited effect of dietary saturated fat on plasma saturated fat in the context of a low carbohydrate diet. Lipids 2010;45(10):947–62.

37. Volk BM, Kunces LJ, Freidenreich DJ, Kupchak BR, Saenz C, Artistizabal JC, Fernandez ML, Bruno RS, Maresh CM, Kraemer WJ, et al. Effects of step-wise increases in dietary carbohydrate on circulating saturated fatty acids and palmitoleic acid in adults with metabolic syndrome. PLoS One 2014;9(11): e113605.
38. Ludwig DS, Willett WC, Volek JS, Neuhouser ML. Dietary fat: from foe to friend? Science 2018;362(6416):764–70.
39. Cahill GF, Jr, Veech RL. Ketoacids? Good medicine? Trans Am Clin Climatol Assoc 2003;114:149–61; discussion 62–3.
40. Kraus H, Schlenker S, Schwedesky D. Developmental changes of cerebral ketone body utilization in human infants. Hoppe Seylers Z Physiol Chem 1974;355(2):164–70.
41. Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. Carcinogenesis 2014;35(3):515–27.
42. Weber DD, Aminzadeh-Gohari S, Tulipan J, Catalano L, Feichtinger RG, Kofler B. Ketogenic diet in the treatment of cancer – where do we stand? Mol Metab [Internet] 2019. doi: 10.1016/j.molmet.2019.06.026.
43. Hopkins BD, Pauli C, Du X, Wang DG, Li X, Wu D, Amadiume SC, Goncalves MD, Hodakoski C, Lundquist MR, et al. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature 2018;560(7719):499–503.
44. Ota M, Matsuo J, Ishida I, Takano H, Yokoi Y, Hori H, Yoshida S, Ashida K, Nakamura K, Takahashi T, et al. Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease. Neurosci Lett 2019;690:232–6.
45. Taylor MK, Sullivan DK, Mahnken JD, Burns JM, Swerdlow RH. Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. Alzheimers Dement (NY) 2018;4:28–36.
46. Wing RR, Vazquez JA, Ryan CM. Cognitive effects of ketogenic weight-reducing diets. Int J Obes Relat Metab Disord 1995;19(11): 811–16.
47. Brietzke E, Mansur RB, Subramaniapillai M, Balanza-Martinez V, Vinberg M, Gonzalez-Pinto A, Rosenblat JD, Ho R, McIntyre RS. Ketogenic diet as a metabolic therapy for mood disorders: evidence and developments. Neurosci Biobehav Rev 2018;94: 11–16.
48. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, Tonstad S, Vatten LJ, Riboli E, Norat T. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. Br Med J 2016;353:i2716.
49. Sadeghi O, Sadeghian M, Rahmani S, Maleki V, Larijani B, Esmaillzadeh A. Whole-grain consumption does not affect obesity measures: an updated systematic review and meta-analysis of randomized clinical trials. Adv Nutr 2019;11(2):280–92.
50. Jenkins DJ, Wong JM, Kendall CW, Esfahani A, Ng VW, Leong TC, Faulkner DA, Vidgen E, Greaves KA, Paul G, et al. The effect of a plant-based low-carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. Arch Intern Med 2009;169(11):1046–54.

CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will determine which patients need to undertake a protein-sparing modified fast

JULIA CHANG, BS, MSIII
Case Western Reserve University School of Medicine, Cleveland, OH

SANGEETA R. KASHYAP, MD*
Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic; Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

The protein-sparing modified fast for obese patients with type 2 diabetes: What to expect

ABSTRACT

The protein-sparing modified fast (PSMF) is a very-low-calorie diet containing mostly protein and little carbohydrate. This article reviews the principles of the PSMF and its potential benefits in terms of weight loss, glycemic control, insulin resistance, cardiovascular risk factors, and related complications for patients with type 2 diabetes.

KEY POINTS

The PSMF is indicated in patients who have a body mass index (BMI) of 30 kg/m^2 or more, or a BMI of 27 kg/m^2 or more with one or more comorbidities such as type 2 diabetes.

The PSMF provides less than 800 kcal/day during an initial intensive phase of about 6 months, with gradual reintroduction of calories during a refeeding phase lasting 6 to 8 weeks.

Patients on the PSMF under medical supervision rapidly lose fat while maintaining lean body mass.

Unfortunately, many patients tend to regain weight after completing a PSMF program. Additional strategies are needed to maintain weight loss.

*Dr. Kashyap has disclosed consulting for Ethicon.

doi:10.3949/ccjm.81a.13128

Eighty percent of people with type 2 diabetes mellitus are obese or overweight.[1] Excess adipose tissue can lead to endocrine dysregulation,[2] contributing to the pathogenesis of type 2 diabetes, and obesity is one of the strongest predictors of this disease.[3]

For obese people with type 2 diabetes, diet and exercise can lead to weight loss and many other benefits, such as better glycemic control, less insulin resistance, lower risk of diabetes-related comorbidities and complications, fewer diabetic medications needed, and lower health care costs.[4–7] Intensive lifestyle interventions have also been shown to induce partial remission of diabetes and to prevent the onset of type 2 diabetes in people at high risk of it.[5–7]

A very-low-calorie diet is one of many dietary options available to patients with type 2 diabetes who are overweight or obese. The protein-sparing modified fast (PSMF) is a type of very-low-calorie diet with a high protein content and simultaneous restriction of carbohydrate and fat.[8,9] It was developed in the 1970s, and since then various permutations have been used in weight loss and health care clinics worldwide.

MOSTLY PROTEIN, VERY LITTLE CARBOHYDRATE AND FAT

The PSMF is a medically supervised diet that provides less than 800 kcal/day during an initial intensive phase of about 6 months, followed by the gradual reintroduction of calories during a refeeding phase of about 6 to 8 weeks.[10]

During the intensive phase, patients obtain

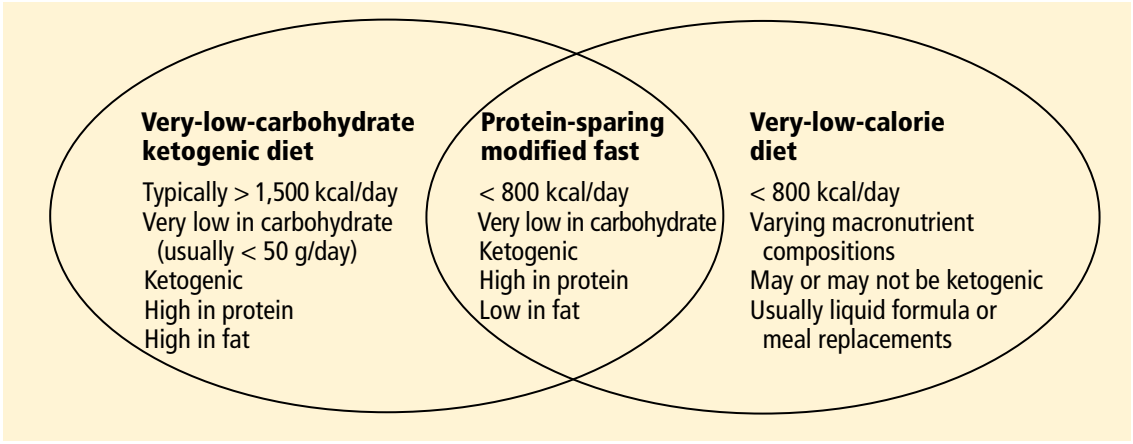


FIGURE 1. The protein-sparing modified fast combines a very-low-carbohydrate ketogenic diet and a very-low-calorie diet. It may contrast with other very-low-calorie diets, which may contain higher amounts of carbohydrate and lower amounts of fat. In addition, the protein-sparing modified fast differs from many very-low-carbohydrate ketogenic diets because of its additional caloric and fat restriction.

most of their calories from protein, approximately 1.2 to 1.5 g/kg of ideal body weight per day. At the same time, carbohydrate intake is restricted to less than 20 to 50 g/day; additional fats outside of protein sources are not allowed.[9] Thus, the PSMF shares features of both very-low-calorie diets and very-low-carbohydrate ketogenic diets (eg, the Atkins diet), though some differences exist among the three (FIGURE 1).

Diet and exercise can lead to weight loss and many other benefits

Patients rapidly lose weight during the intensive phase, typically between 1 and 3 kg per week, with even greater losses during the first 2 weeks.[8,9] Weight loss typically plateaus within 6 months, at which point patients begin the refeeding period. During refeeding, complex carbohydrates and low-glycemic, high-fiber cereals, fruits, vegetables, and fats are gradually reintroduced. Meanwhile, protein intake is reduced to individually tailored amounts as part of a weight-maintenance diet.

LIPOLYSIS, KETOSIS, DIURESIS

The specific macronutrient composition of the PSMF during the intensive phase is designed so that patients enter ketosis and lose as much fat as they can while preserving lean body mass.[9,11] FIGURE 2 illustrates the mechanisms of ketosis and the metabolic impact of the PSMF.

With dietary carbohydrate restriction, serum glucose and insulin levels decline and glycogen stores are depleted. The drop in serum insulin allows lipolysis to occur, resulting in loss of adipose tissue and production of ketone bodies in the liver. Ketone bodies become the primary source of energy for the brain and other tissues during fasting and have metabolic and neuroprotective benefits.[12,13]

Some studies suggest that ketosis also suppresses appetite, helping curb total caloric intake throughout the diet.[14] Protein itself may increase satiety.[15]

Glycogen in the liver is bound to water, so the depletion of glycogen also results in loss of attached water. As a result, diuresis contributes significantly to the initial weight loss within the first 2 weeks on the PSMF.[9]

WHO IS A CANDIDATE FOR THE PSMF?

The PSMF is indicated only for adults with a body mass index (BMI) of at least 30 kg/m^2 or a BMI of at least 27 kg/m^2 and at least one comorbidity such as type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, osteoarthritis, or fatty liver.[12] Patients must also be sufficiently committed and motivated to make the intensive dietary and behavioral changes the program calls for.

The PSMF should be considered when more conventional low-calorie approaches to weight loss fail or when patients become discouraged by the slower results seen with traditional diets.[8] Patients undergoing a PSMF are usually encouraged by the initial period of

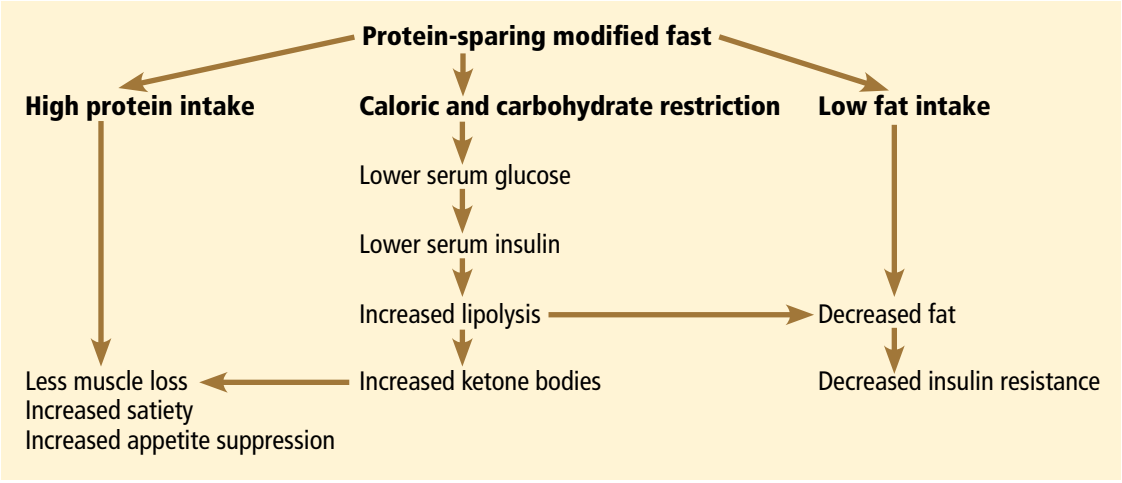


FIGURE 2. As a result of carbohydrate restriction, high protein intake, and ketosis, the protein-sparing modified fast leads to lower blood glucose levels as well as rapid weight loss, mostly in the form of fat mass, while lean body mass (muscle) is preserved.

MODIFIED FROM BAKER S, JERUMS G, PROIETTO J. EFFECTS AND CLINICAL POTENTIAL OF VERY-LOW-CALORIE DIETS (VLCDS) IN TYPE 2 DIABETES. DIABETES RES CLIN PRACT 2009; 85:235–242.

rapid weight loss, and such diets have lower dropout rates.[16]

This diet may also be recommended for obese patients who have poorly controlled type 2 diabetes and growing resistance to medications, to bring down the blood glucose level. Another use is before bariatric surgery to reduce the risk of obesity-related complications.[8] Patients who regain weight after bariatric surgery may also benefit.

MEAL REPLACEMENTS OR A DIET PLAN?

The PSMF program at Cleveland Clinic is based on modified preparation and selection of conventional foods. Details of the program are described in TABLE 1. Protein sources must be of high biologic value, containing the right mix of essential amino acids (eg, lean meat, fish, poultry, egg whites).[9]

Some commercially available very-low-calorie diets (eg, OPTIFAST, Medifast) that are advertised as PSMFs consist mainly of meal replacements. In the program at Cleveland Clinic, meal replacements in the form of commercial high-protein shakes or bars can be used occasionally for convenience and to maintain adherence to the diet.

However, preparation of PSMF meals from natural, conventional foods is thought to play an important role in long-term behavior modification and so is strongly encouraged. Patients learn low-fat cooking methods, portion control, and how to make appropriate choices in shopping, eating, and dining out. These lessons are valuable for those who struggle with long-term weight loss. Learning these behaviors through the program may help ease the transition to the weight-maintenance phase and beyond. For some patients, cooking is also a source of enjoyment, as is the sight, smell, and taste of nonliquid foods.[10]

In addition, patients appreciate being able to eat the same foods as others in their household, except for omitting high-carbohydrate foods. It has also been reported that patients on a food-based PSMF were significantly less hungry and preoccupied with eating than those on a liquid formula diet.[17]

Patients are usually encouraged by the initial period of rapid weight loss

CONTRAINDICATIONS AND SAFETY CONCERNS

Contraindications to the PSMF include a BMI less than 27 kg/m^2, recent myocardial infarction, angina, significant arrhythmia, decompensated congestive heart failure, cerebrovascular insufficiency or recent stroke, end-stage renal disease, liver failure, malignancy, major psychiatric illness, pregnancy or lactation, and wasting disorders. It is also not recommended for patients under age 16 or over age 65.

In view of the risk of diabetic ketoacidosis and the difficulty of titrating required

TABLE 1

The protein-sparing modified fast program at Cleveland Clinic

At baseline and ongoing

Baseline assessment (history, physical examination, electrocardiography) by physician or nurse practitioner and dietitian, with continued follow-up
- Dietitian visits every 2 weeks for first month and monthly thereafter
- Physician or nurse practitioner visits every 6 to 8 weeks

Laboratory tests at baseline, every 2 weeks for first month, and monthly thereafter
- Comprehensive metabolic panel
- Uric acid

Behavior modification

Exercise

Intensive phase (up to 6 months)

Per day:

1.5 g protein/kg ideal body weight
(typically a total of 12–17 oz in the form of lean meat, poultry, fish, seafood, eggs, low-fat cheese, tofu)

< 20 g carbohydrate
(two servings of low-starch vegetables, unlimited lettuce salad)
- Trace carbohydrates from other foods and shakes

Restriction of fats not found in protein sources
(no butter, margarine, oils, nuts, seeds, or dips; protein sources should contain < 3 g fat per ounce)

Required supplements
- Multivitamin/mineral tablet
- Potassium 16–20 mEq
- Calcium 1,000–1,200 mg
- Magnesium 400–500 mg
- Sodium 1,500–2,000 mg

At least 64 oz of fluid

Refeeding phase (6–8 weeks)

Slowly reintroduce complex carbohydrates and fats; reduce protein
- Month 1: up to 45 g carbohydrate
- Month 2: up to 90 g carbohydrate
- Low-glycemic, high-fiber cereals, fruits, vegetables
- Low-fat foods
- Daily protein reduced by 1–2 oz each month

Stop potassium and magnesium supplements after week 2

doses ofinsulin, patients with type 1 diabetes mellitus are usually not advised to undergo a low-carbohydrate or very-low-calorie diet.[8,12] However, we and others have found that the PSMF can be used in some obese patients with type 1 diabetes if it is combined with appropriate education and careful monitoring.[12]

Major concerns about the safety of the PSMF stem from experiences with the first very-low-calorie diets in the 1970s, which were associated with fatal cardiac arrhythmias and sudden death.[18] These early diets used liquid formulas with hydrolyzed collagen protein of poor biologic value and were deficient in many vitamins and minerals. Today's very-low-calorie diets use protein sources of high biologic value (chiefly animal, soy, and egg for the PSMF) and are supplemented with necessary vitamins and minerals, reducing the risk of electrolyte and cardiac abnormalities.[9,19,20] Furthermore, before starting the PSMF all patients must have an electrocardiogram to be sure they have no arrhythmias (eg, heart block, QT interval prolongation) or ischemia.

Relative contraindications

A known history of cholelithiasis is a relative contraindication to a very-low-calorie diet and may be of concern for some patients and providers. While obesity itself is already a risk factor for gallstones, gallstone formation has also been associated with bile stasis, which occurs from rapid weight loss with liquid formula diets of low fat intake (< 10 g/day).[21] However, in the PSMF, fat intake from protein sources, though low (45–70 g/day), is considered high enough to allow adequate gallbladder contraction, thus decreasing the risk of gallstone formation.[22]

Gout is another relative contraindication, as hyperuricemia with risk of gout is also linked to high-protein diets.[9] Palgi et al[23] found that uric acid levels rose by a mean of 0.4 mg/dL during the diet. The risk of gout, however, seemed to be small, occurring in fewer than 1% of patients in the study. Furthermore, in a recent study by Li et al,[24] uric acid levels were found to significantly decrease in patients on a high-protein, very-low-calorie diet. Nonetheless, uric acid levels should be monitored regularly in patients on the PSMF.

SIDE EFFECTS OF THE DIET

Common side effects of the PSMF include headache, fatigue, orthostatic hypotension, muscle cramps, cold intolerance, constipa-

tion, diarrhea, fatigue, halitosis, menstrual changes, and hair thinning. Most of these are transient and may be alleviated by adjusting fluid, salt, and supplement intake. Other side effects may disappear as the patient is weaned off the diet.[8,9]

REGULAR FOLLOW-UP WITH HEALTH CARE PROVIDERS

Current PSMF programs are considered safe when used in combination with regular follow-up with health care providers.[8,12]

At Cleveland Clinic, patients meet with a dietitian twice in the first month and monthly thereafter (or more frequently if needed) for weight monitoring and education on nutrition and behavior modification (TABLE 1). Since the PSMF does not provide complete nutrition, daily supplementation with vitamins and minerals is required.

Daily exercise is encouraged throughout the program to increase fitness and to help keep the weight off during the refeeding phase and after.

Patients also meet every 6 to 8 weeks with the referring nurse practitioner or physician for further monitoring and evaluation of vital signs, laboratory results, and side effects. The PSMF protocol at Cleveland Clinic enables both primary care physicians and specialists (including nurse practitioners) within our network to monitor the patient's status. Use of a common electronic medical record system is particularly valuable for easy communication between providers. If a primary care physician feels unable to appropriately counsel and supervise a patient in the PSMF program, referral to an endocrinologist or weight loss specialist is recommended.

In addition to baseline electrocardiography and monitoring of uric acid levels, a comprehensive metabolic panel is drawn at baseline, twice in the first month, and monthly thereafter to check for electrolyte imbalances and metabolic and tissue dysfunction such as dehydration, excessive protein loss, and liver or kidney injury.

Patients should not attempt the PSMF without medical supervision. Many patients have friends or family members who want to try the PSMF along with them, but this can be dangerous, especially for those with hypertension or type 2 diabetes. The medications prescribed for these conditions can result in hypotension or hypoglycemia during the PSMF.

Although there are no standard guidelines for adjusting medication use before starting a patient on the PSMF, it is logical to taper off or discontinue antihypertensive agents in patients with tightly controlled hypertension to avoid possible dehydration and hypotension during the first few diuresis-inducing weeks of the diet. In particular, diuretic agents should

TABLE 2

Effects of the protein-sparing modified fast in type 2 diabetes in clinical studies

Weight loss
- Average weight loss of 1–3 kg/week during intensive phase[8,9,23–27,29]
- Total weight loss between 8 and 40 kg depending on duration of diet and baseline weight[23–25]
- Partial regain of weight after 1 year[27]
- Return to baseline weight after 5 years[33]

Fat loss
- Fat loss from abdominal regions, leading to decrease in central obesity[25,29]
- Type 2 diabetic patients may lose less fat during weight loss than nondiabetic patients[26]

Fasting serum glucose
- Significant, immediate decreases in fasting serum glucose[24,30,32]
- Decreased glucose may last up to 1 year after intervention[27]
- Compared favorably against a control balanced, low-calorie diet[27]
- Discontinuation or decreased doses of oral hypoglycemic agents and insulin while on the diet; may remain medication-free for up to 1 year[28]

Hemoglobin A_{1c}
- Significant absolute reductions of 1%–3%[27,28,31]

Insulin resistance
- Decreased fasting serum insulin[25,27,28,30,31]
- Enhanced insulin output during glucose load[14,16,30]

Lipids
- Decreased triglycerides[8,23,24,26]
- Increased high-density lipoprotein cholesterol for up to 1 year[24,27,28]
- Shorter-term decrease in low-density lipoprotein cholesterol or total cholesterol[8,2427]

Blood pressure
- Discontinuation of diuretic agents, with discontinuation or reduction of other antihypertensive agents as needed[9]
- Lower systolic and diastolic blood pressure[23,24,28]

Kidney disease
- Lower serum creatinine and cystatin C levels in patients with diabetic nephropathy[31]
- Potential reduction in albuminuria[31]

be discontinued to prevent further electrolyte imbalance and fluid shifts.

Similarly, in patients with tightly controlled type 2 diabetes (hemoglobin A_{1c} < 7.0%), oral hypoglycemic agents and insulin therapy should be reduced before starting the diet to avoid potential hypoglycemia. During the course of the diet, providers should then adjust medication dosages based on follow-up vital signs and laboratory results and daily glucose monitoring.[8]

EFFECTS OF THE PSMF IN PATIENTS WITH TYPE 2 DIABETES

Though few formal studies have been done, the PSMF may have major effects on hyperglycemia, cardiovascular risk factors, and diabetic nephropathy in obese patients with type 2 diabetes, at least in the short term (TABLE 2).

Weight loss

In one of the first PSMF studies,[23] in 668 patients with or without type 2 diabetes (baseline weight 98 kg), the mean weight loss was 21 kg after the intensive phase and 19 kg by the end of the refeeding phase.

Patients on a food-based PSMF were less hungry and preoccupied with eating than those on a liquid formula diet

In another observational report,[25] 25% to 30% of patients lost even more weight, averaging 38.6 kg of weight loss. Typically, the higher the baseline weight, the greater the weight loss during the PSMF.[23]

Patients with type 2 diabetes lost a similar amount of weight (8.5 kg) compared with those without diabetes (9.4 kg, $P = .64$) in a study of meal-replacement PSMF (using OPTIFAST shakes and bars).[26] In a large meal-replacement study of 2,093 patients, Li et al[24] found that weight loss was similar between diabetic, prediabetic, and nondiabetic patients. Weight loss was also closely maintained in those patients who stayed on the diet for 12 months.

In a PSMF study in which all the participants had type 2 diabetes, the mean weight loss was 18.6 kg. Although the patients regained some of this weight, at 1 year they still weighed 8.6 kg less than at baseline. However, a conventional, balanced, low-calorie diet resulted in similar amounts of weight loss after 1 year.[27] Furthermore, a second round of the PSMF did not result in significant additional weight loss but rather weight maintenance.[28]

Fat loss and smaller waist circumference

Most of the weight lost during a PSMF is from fat tissue.[11,26] Abdominal (visceral) fat may be lost first, which is desirable for patients with type 2 diabetes, since a higher degree of abdominal fat is linked to insulin resistance.[2,29]

After a meal-replacement PSMF, waist circumference decreased significantly in patients both with and without type 2 diabetes.[24,26] However, in one study, less fat was lost per unit of change of BMI in the group with type 2 diabetes than in the nondiabetic group.[26] Since insulin inhibits lipolysis, it is possible that exogenous insulin use in diabetic patients may prevent greater reductions in fat mass, though this is likely not the only mechanism.[26]

Lower fasting serum glucose

Fasting serum glucose levels decreased significantly from baseline in patients with type 2 diabetes after a PSMF in all studies that measured this variable.[23–28,30,31] Changes in fasting glucose are immediate and are associated with caloric restriction rather than weight loss itself.[30,32] Furthermore, the observed decrease in serum glucose is even more impressive in view of the withdrawal or reduction of doses of insulin and oral hypoglycemic agents before starting the diet.

In a study that compared glycemic control in a PSMF diet vs a balanced low-calorie diet, the fasting serum glucose in the PSMF group declined 46%, from 255.9 mg/dL at baseline to 138.7 mg/dL at 20 weeks ($P = .001$). After 1 year, it had risen back to 187.4 mg/dL, which was still 27% lower than at baseline ($P = .023$). These results compared favorably with those in the low-calorie diet group ($P < .05$), which saw fasting serum glucose decline 27% after 20 weeks (from 230.6 mg/dL at baseline to 167.6 mg/dL) and then rise to 5% over baseline (243.2 mg/dL) after 1 year.[27]

In a later study, the decrease in fasting serum glucose was not maintained at 1 year, but a significantly higher percentage (55%) of participants in the PSMF group were still able to remain free of diabetic medications

compared with those who followed a balanced low-calorie diet (31%, $P = .01$).[28]

Decrease in hemoglobin A_{1c}

Declines in fasting serum glucose corresponded with short-term declines in hemoglobin A_{1c} in several reports.[27–31] Hemoglobin A_{1c} declined significantly from an average of 10.4% to 7.3% ($P = .001$) after PSMF intervention in patients with type 2 diabetes. In contrast, hemoglobin A_{1c} in the low-calorie diet control group declined from 10.4% to 8.6%.[27] One year later, hemoglobin A_{1c} remained lower than at baseline in the PSMF group (final 9.2%) and continued to compare favorably against the control group (final 11.8%, between-group $P = .001$). However, these 1-year post-intervention improvements were not seen in a second, more intensive study.[28]

Less insulin resistance

In several studies, fasting serum insulin levels declined along with serum glucose levels, implying decreased insulin resistance.[25,27,28,30,31] In addition, insulin output was enhanced during glucose challenge after completion of the PSMF, suggesting possible improved (though still impaired) pancreatic beta-cell capacity.[25,27,30]

Improved lipid profile

The most common effect of the PSMF on the lipid profile is a significant decrease in triglycerides in patients both with and without type 2 diabetes.[8,23,24,28] In addition, high-density lipoprotein cholesterol increased in two studies following PSMF intervention or after 1-year of follow-up.[24,27,28] Total cholesterol and low-density lipoprotein cholesterol levels also improved after the PSMF, but these changes were not always maintained at follow-up visits.[8,24,28]

Lower blood pressure

Improvements in both systolic and diastolic blood pressure were noted in two studies, with mean decreases of 6 mm Hg to 13 mm Hg systolic and 8 mm Hg diastolic after PSMF intervention.[23,28] In a third study, reductions in blood pressure were less dramatic, and only changes in diastolic but not systolic blood pressure remained significant at 12 months.[24] While improvements were not observed in a fourth study, patients in this study also had impaired kidney function caused by diabetic nephropathy, and changes in medication were not taken into account.[31]

Kidney function tests

In a small study, Friedman et al showed that 12 weeks of the PSMF in six patients with advanced diabetic nephropathy (stage 3B or stage 4 chronic kidney disease) led to a loss of 12% of body weight ($P = .03$) as well as significant reductions in serum creatinine and cystatin C levels ($P < .05$).[31] In addition, albuminuria decreased by 30% ($P = .08$). Side effects were minimal, and the diet was well tolerated despite its high protein content, which is a concern in patients with impaired kidney function.

Thus, weight loss via the PSMF may still be beneficial in type 2 diabetic patients with chronic kidney disease and may even improve the course of progression of diabetic nephropathy.

Long-term weight loss is elusive

Long-term weight loss has been an elusive goal for many diet programs. In a study using a very-low-calorie diet in obese patients with type 2 diabetes, substantial weight loss was maintained in half of the patients at 3 years after the intervention, but nearly all of the patients had regained most of their weight after 5 years.[33]

While commitment to behavior modification, maintenance of physical activity, and continued follow-up are all critical factors in sustaining weight loss, new and innovative approaches to battle weight regain are needed.[34]

Yet despite considerable weight regain in most patients, the Look AHEAD (Action for Health in Diabetes) study showed that participants in intensive lifestyle intervention programs still achieved greater weight loss after 4 years than those receiving standard care.[35] Whether this holds true for those in intensive PSMF programs is unknown. In addition, conclusive PSMF studies regarding glycemic control, lipids, and blood pressure beyond 1 year of follow-up are lacking.

Patients should not attempt the PSMF without medical supervision

A VIABLE OPTION FOR MANY

Adherence to a very-low-calorie, ketogenic PSMF program results in major short-term health benefits for obese patients with type 2 diabetes. These benefits include significant

weight loss, often more than 18 kg, within 6 months.[23–28] In addition, significant improvements in fasting glucose[23–28,30–32] and hemoglobin A_{1c} levels[27–31] are linked to the caloric and carbohydrate restriction of the PSMF. Insulin resistance was also attenuated, with possible partial restoration of pancreatic beta-cell capacity.[25,27,28,30,31] In some studies, the PSMF resulted in lower systolic and diastolic blood pressure[23,24,28] and triglyceride levels.[8,23,24,28] One small study also suggested a possible improvement of diabetic nephropathy.[31] Lastly, improvements in glycemia and hypertension were associated with a reduction in the need for antidiabetic and antihypertensive drugs.[36]

Still, weight loss and many of the associated improvements partially return to baseline levels 1 year after the intervention. Thus, more long-term studies are needed to explore factors for better weight maintenance after the PSMF.

Also, only a few studies have compared the effect of the PSMF between patients with or without type 2 diabetes. One study suggested that fat loss may be reduced in patients with type 2 diabetes.[26]

In conclusion, despite some risks and safety concerns, PSMF is a viable option for many obese, type 2 diabetic patients as a method of short-term weight loss, with evidence for improvement of glycemic control and cardiovascular risk factors for up to 1 year. To strengthen support for the PSMF, however, further research is warranted on the diet's long-term effects in patients with type 2 diabetes and also in nondiabetic patients.

***ACKNOWLEDGMENTS**: Many thanks to Cheryl Reitz, RD, LD, CDE, and Dawn Noe, RD, LD, CDE, for providing their expertise on the PSMF protocols carried out at Cleveland Clinic. Additional thanks to Tejas Kashyap for his initial assistance with this review.*

REFERENCES

1. **Smyth S, Heron A**. Diabetes and obesity: the twin epidemics. Nat Med 2006; 12:75–80.
2. **Kahn BB, Flier JS**. Obesity and insulin resistance. J Clin Invest 2000; 106:473–481.
3. **Hu FB, Manson JE, Stampfer MJ, et al**. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001; 345:790–797.
4. **Andrews RC, Cooper AR, Montgomery AA, et al**. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet 2011; 378:129–139.
5. **Lindström J, Louheranta A, Mannelin M, et al; Finnish Diabetes Prevention Study Group**. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 2003; 26:3230–3236.
6. **Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group**. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393–403.
7. **Gregg EW, Chen H, Wagenknecht LE, et al; Look AHEAD Research Group**. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012; 308:2489–2496.
8. **Henry RR, Gumbiner B**. Benefits and limitations of very-low-calorie diet therapy in obese NIDDM. Diabetes Care 1991; 14:802–823.
9. **Bistrian BR**. Clinical use of a protein-sparing modified fast. JAMA 1978; 240:2299–2302.
10. **Walters JK, Hoogwerf BJ, Reddy SS**. The protein-sparing modified fast for obesity-related medical problems. Cleve Clin J Med 1997; 64:242–244.
11. **Van Gaal LF, Snyders D, De Leeuw IH, Bekaert JL**. Anthropometric and calorimetric evidence for the protein sparing effects of a new protein supplemented low calorie preparation. Am J Clin Nutr 1985; 41:540–544.
12. **Baker S, Jerums G, Proietto J**. Effects and clinical potential of very-low-calorie diets (VLCDs) in type 2 diabetes. Diabetes Res Clin Pract 2009; 85:235–242.
13. **Shimazu T, Hirschey MD, Newman J, et al**. Suppression of oxidative stress by ß-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science 2013; 339:211–214.
14. **Johnstone AM, Horgan GW, Murison SD, Bremner DM, Lobley GE**. Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum. Am J Clin Nutr 2008; 87:44–55.
15. **Westerterp-Plantenga MS, Lemmens SG, Westerterp KR**. Dietary protein—its role in satiety, energetics, weight loss and health. Br J Nutr 2012; 108(suppl 2):S105–S112.
16. **Hemmingsson E, Johansson K, Eriksson J, Sundström J, Neovius M, Marcus C**. Weight loss and dropout during a commercial weight-loss program including a very-low-calorie diet, a low-calorie diet, or restricted normal food: observational cohort study. Am J Clin Nutr 2012; 96:953–961.
17. **Wadden TA, Stunkard AJ, Brownell KD, Day SC**. A comparison of two very-low-calorie diets: protein-sparing-modified fast versus protein-formula-liquid diet. Am J Clin Nutr 1985; 41:533–539.
18. **Isner JM, Sours HE, Paris AL, Ferrans VJ, Roberts WC**. Sudden, unexpected death in avid dieters using the liquid-protein-modified-fast diet. Observations in 17 patients and the role of the prolonged QT interval. Circulation 1979; 60:1401–1412.
19. **Henry RR, Wiest-Kent TA, Scheaffer L, Kolterman OG, Olefsky JM**. Metabolic consequences of very-low-calorie diet therapy in obese non-insulin-dependent diabetic and nondiabetic subjects. Diabetes 1986; 35:155–164.
20. **Seim HC, Mitchell JE, Pomeroy C, de Zwaan M**. Electrocardiographic findings associated with very low calorie dieting. Int J Obes Relat Metab Disord 1995; 19:817–819.
21. **Johansson K, Sundström J, Marcus C, Hemmingsson E, Neovius M**. Risk of symptomatic gallstones and cholecystectomy after a very-low-calorie diet or low-calorie diet in a commercial weight loss program: 1-year matched cohort study. Int J Obes (Lond) 2014; 38:279–284.
22. **Festi D, Colecchia A, Orsini M, et al**. Gallbladder motility and gallstone formation in obese patients following very low calorie diets. Use it (fat) to lose it (well). Int J Obes Relat Metab Disord 1998; 22:592–600.
23. **Palgi A, Read JL, Greenberg I, Hoefer MA, Bistrian BR, Blackburn GL**. Multidisciplinary treatment of obesity with a protein-sparing modified fast: results in 668 outpatients. Am J Public Health 1985; 75:1190–1194.
24. **Li Z, Tseng CH, Li Q, Deng ML, Wang M, Heber D**. Clinical efficacy of a medically supervised outpatient high-protein, low-calorie diet program is equivalent in prediabetic, diabetic and normoglycemic obese patients. Nutr Diabetes 2014 Feb 10; 4:e105.
25. **Genuth S**. Supplemented fasting in the treatment of obesity and diabetes. Am J Clin Nutr 1979; 32:2579–2586.
26. **Baker ST, Jerums G, Prendergast LA, Panagiotopoulos S, Strauss BJ, Proietto J**. Less fat reduction per unit weight loss in type 2 diabetic com-

pared with nondiabetic obese individuals completing a very-low-calorie diet program. Metabolism 2012; 61:873–882.
27. **Wing RR, Marcus MD, Salata R, Epstein LH, Miaskiewicz S, Blair EH**. Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. Arch Intern Med 1991; 151:1334–1340.
28. **Wing RR, Blair E, Marcus M, Epstein LH, Harvey J**. Year-long weight loss treatment for obese patients with type II diabetes: does including an intermittent very-low-calorie diet improve outcome? Am J Med 1994; 97:354–362.
29. **Kawamura I I, Chen CC, Yamazaki K, Miyazawa Y, Isono K**. A clinical study of protein sparing modified fast (PSMF) administered preoperatively to morbidly obese patients: comparison of PSMF with natural food products to originally prepared PSMF. Obes Surg 1992; 2:33–40.
30. **Hughes TA, Gwynne JT, Switzer BR, Herbst C, White G**. Effects of caloric restriction and weight loss on glycemic control, insulin release and resistance, and atherosclerotic risk in obese patients with type II diabetes mellitus. Am J Med 1984; 77:7–17.
31. **Friedman AN, Chambers M, Kamendulis LM, Temmerman J**. Short-term changes after a weight reduction intervention in advanced diabetic nephropathy. Clin J Am Soc Nephrol 2013; 8:1892–1898.
32. **Wing RR, Blair EH, Bononi P, Marcus MD, Watanabe R, Bergman RN**. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. Diabetes Care 1994; 17:30–36.
33. **Paisey RB, Frost J, Harvey P, et al**. Five year results of a prospective very low calorie diet or conventional weight loss programme in type 2 diabetes. J Hum Nutr Diet 2002; 15:121–127.
34. **Blackburn GL**. Weight of the nation: moving forward, reversing the trend using medical care. Am J Clin Nutr 2012; 96:949–950.
35. **Wadden TA, Neiberg RH, Wing RR, et al; Look AHEAD Research Group**. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. Obesity (Silver Spring) 2011; 19:1987–1998.
36. **Redmon JB, Bertoni AG, Connelly S, et al; Look AHEAD Research Group**. Effect of the Look AHEAD intervention on medication use and related cost to treat cardiovascular disease risk factors in individuals with type 2 diabetes. Diabetes Care 2010; 33:1153–1158.

***ADDRESS**: Sangeeta R. Kashyap, MD, Department of Endocrinology, Diabetes, and Metabolism, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail: kashyas@ccf.org*

Multidisciplinary Treatment of Obesity with a Protein-sparing Modified Fast: Results in 668 Outpatients

AVIVA PALGI, PHD, J. LEIGHTON READ, MD, ISAAC GREENBERG, PHD, MARTHA A. HOEFER, BA, BRUCE R. BISTRIAN, MD, PHD, AND GEORGE L. BLACKBURN, MD, PHD

Abstract: Six hundred sixty-eight obese outpatients, 71 per cent (± 34) in excess of ideal weight, were enrolled in a multidisciplinary weight control program. The major components of the program included nutrition, education, behavior modification, and exercise. Rapid weight loss was accomplished using a very low calorie (less than 800 kcal) ketogenic diet. Patients adhered to the protein sparing modified fast (PSMF) for 17 ± 12 weeks and averaged 9 ± 17 weeks in a refeeding/maintenance program. Mean weight loss was 47 ± 29 lb (21 ± 13 kg) at the point of minimum weight and 41 ± 29 lb (19 ± 13 kg) at the end of the maintenance period. Systolic and diastolic blood pressure and serum triglycerides fell significantly in men and women. Success in weight loss was greatest in the heaviest patients, those who adhered the longest to the PSMF, and those who stayed the longest in the maintenance program. (*Am J Public Health* 1985; 75:1190–1194.)

Introduction

Despite the unfortunate experiences caused by widespread, unsupervised use of low-quality liquid protein diets in the early 1970s,[1] responsible versions of very low calorie diets (VLCDs) are now recognized as a safe and appropriate therapy for high-risk obesity.[2] Safe use of VLCDs requires protein sources of high biologic value and supplementation with proper vitamins, minerals, and electrolytes. These diets must be supervised by medical personnel familiar with the metabolism of fasting, and limited to patients with "medically significant obesity."[3]

The threshold for defining medically significant obesity has been cited by various authors as ranging from 120 per cent to 160 per cent of ideal body weight (relative weight).[4–7] Since the risks of obesity appear to increase continuously with increasing weight, any attempt to distinguish between subgroups is necessarily arbitrary. It is helpful for treatment purposes, however, to divide the spectrum of obese states into the categories shown in the Appendix.

Methods

Patients and Program Description

A total of 668 outpatients enrolled in the Center for Nutrition Research (CNR) Clinic between 1973 and 1977. Many came on their physicians' advice but most were self-referred. Our approach emphasizes patients' responsibility for their own achievements. The major components are nutrition education, behavior modification, and exercise. These are described in detail elsewhere.[8,9]

Patients included in this report were those who spent at least one week on the protein sparing modified fast (PSMF).[10] This group does not include 60 patients enrolled in the CNR who had contraindications to supplemental fasting. We considered the following to be contraindications for the fast: pregnancy, age under 17 or greater than 75 years, Type I diabetes mellitus, myocardial infarction within six months, severe psychiatric disturbance (requiring drug therapy beyond minor tranquilizers), and severe hepatic or renal disease. With the exception of 62 patients in research protocols, the PSMF was restricted to patients with moderate or more severe obesity (≥ 130 per cent of ideal body weight). Almost all of the clinic population consisted of white, upper-middle class United States citizens. Other than a few patients whose diet was initiated in hospital because they were on higher doses of insulin or anti-hypertensive agents, all care was provided in an outpatient setting.

The initial stage of the program lasted approximately four weeks. In the first week, patients were asked to record their usual food intake and physical activities. Then they were placed on a 1,000 kcal balanced deficit diet (BDD) for three weeks and instructed to continue recording their food intake and activity. This record was reviewed with patients weekly. Initial medical evaluation included a medical history and physical examination by a physician, a complete blood count, blood chemistries, urinalysis, chest x-ray, electrocardiogram, and the Minnesota Multiphasic Personality Inventory.

If no contraindications had been noted during the initial weeks, patients were placed on the PSMF. This diet provides a daily intake of 1.5 gm of protein per kilogram of ideal body weight in the form of lean meat, fish, or fowl. Preweighed portions are divided over two to three meals per day. In addition, patients receive a supplement providing the RDA for all vitamins and essential minerals except calcium, magnesium and phosphorous, and 400 mg calcium. Patients were encouraged to drink a minimum of 1.5 L of fluid a day and to consume at least 5 gm of sodium chloride.

Weekly clinic visits were scheduled during which weight, blood pressure, and urine and breath ketone levels were monitored by a nurse. Patients then met with a counselor to review their progress, gain support, and set realistic goals for coping with specific food-related problems. The clinic counselors were individuals with training in psychology at the undergraduate or master's level who worked under the supervision of a clinical psychologist. Patients also had weekly educational lectures, discussions, or readings. Topics included nutrition, methods of behavior change, and exercise physiology.

When patients neared their target weight, a refeeding and maintenance program was initiated. This was prescribed as a 12-week program in which carbohydrate was gradually added until a balanced maintenance diet was established. During this period patients met weekly with their counselor where techniques for maintaining weight while coping with everyday food cues were discussed.

Information for this report was abstracted from the medical record of every patient treated with the PSMF for at

Address reprint requests to J. Leighton Read, MD, Nutrition/Metabolism Lab, New England Deaconess Hospital, 194 Pilgrim Road, Boston, MA 02215.
This paper, submitted to the Journal August 17, 1984, was revised and accepted for publication April 19, 1985.

TABLE 1—Patient Characteristics at Time of Enrollment

	All Patients	Women	Men
Number of patients	668	564	104
Age (yrs)	38 ± 11*	38	41
Entry Weight (lb)	216 ± 49	207	264
Entry Weight (kg)	98 ± 22	94	120
Height (cm)	165 ± 6	163	177
Ideal Body Weight (kg)	57 ± 7	55	69
Per Cent Excess Weight	71 ± 34	70	74
Body Mass Index	36 ± 7	35	38
Age of Obesity Onset	16 ± 12	16	16
Years of School	15 ± 2	15	16
% Who are Married (N = 319)	67	66	74
% Who had Obese Father (N = 122)	63	57	91
% Who had Obese Mother (N = 123)	73	71	82

*mean ± standard deviation.

least seven days during the years 1973–77. Data on physiological parameters (blood pressure and blood chemistries) and family history were obtained on half of the population, selected by choosing every other chart from an alphabetical file.

Definition of Variables

Most patients in our program participated in a maintenance phase following the PSMF. As a result, their final weight on completing the program was often different from the lowest weight reached while on the fast. The latter value is termed minimum weight and is reported along with the final weight measured in our program. Excess weight is based on the 1959 Metropolitan Life Insurance Company weight for height standard.[4] Body frame was not taken into account, except in the extreme cases of a very small frame. The mid-point of the ideal weight for each height was selected as a reference point.

We also report an additional measure, *Feinstein's Weight Loss Index,* because it takes into account both height, weight, and the initial excess weight.[11,12] This index is calculated as the per cent excess weight lost times (initial weight/ideal weight). Statistical comparisons between groups are based on the Student's t-test, Pearson product moment correlations, and step-wise multiple regression.

Results

Table 1 describes the characteristics of our patients on entry to the program.

Adherence to Program and Weight Loss Results

Table 2 shows measures of weight change from entry to the minimum weight in the program and to the final weight recorded. The minimum and final values shown in these Tables are all significantly different from entry values. Final weights indicated that the average patient had regained only 6.2 ± 12.1 lbs. during the refeeding/maintenance period. While weight loss averaged one-fifth of total body weight, it represented almost half of the patients' weight above ideal.

Each patient was classified as a success or failure according to different criteria to allow comparison with other weight loss studies. Table 3 shows the result of using differing criteria of weight loss success. Some criteria are easier for the heaviest patients to reach and some are more difficult. For example, 70 per cent of the heaviest half of our population had lost 40 lbs. at their minimum weight but only 25 per cent reached ≤ 130 per cent ideal body weight.

TABLE 2—Weight Loss Results

	Total (mean ± SD)	Women (mean)	Men (mean)
From Entry to Minimum Weight			
Weeks from entry to minimum weight	21.20 ± 11.80	20.6	22.19
Weeks on PSMF	17.42 ± 11.72	17.8	15.4
Kilograms lost	21.44 ± 13.27	20.5	26.7
% Excess body weight lost	56.54 ± 26.23	57	53
Weight reduction index	93.90 ± 41.75	94	92
From Entry to Final Weight			
Weeks in from entry to final weight	31.29 ± 21.95	32.1	26.7
Kilograms lost	18.60 ± 13.00	12.0	23.9
% Excess body weight lost	48.30 ± 25.86	48	48
Weight reduction index	80.69 ± 42.75	80	83

TABLE 3—Alternative Measures of Success for Short-term Weight Loss

	All	Women	Men
Entry to minimum weight			
N	668	564	104
% Patients losing 40 lbs	50	47	63
% Patients reaching ≤130% IBW	53	53	54
% Patients losing half excess weight	57	57	54
% Patients reaching Reduction Index of 60	76	77	76
Entry to final weight			
% Patients losing 40 lbs	42	38	60
% Patients losing ≤130% IBW	47	46	47
% Patients losing half excess weight	46	46	47
% Patients reaching Reduction Index of 60	66	64	73

Changes in Physiological Parameters

As shown in Table 4, systolic blood pressure fell an average of 13 mm Hg and diastolic blood pressure fell 8 mm Hg. Mean fasting blood sugar fell by 15 mg/dl and serum triglicerides by 37 mg/dl. All of these changes are highly significant by paired t-test ($p < .0001$).

Serum cholesterol changes were variable, and sex-related. Despite an increase in mean cholesterol for women, the per cent of women who had a cholesterol level ≥ 200 mg/dl fell from 64 per cent at entry to the program to 40 per cent at the final measurement. While 28 per cent of women had a serum cholesterol of ≥ 250 at entry, only 23 per cent did at the final measurement. Average uric acid levels rose slightly, by 0.4 mg/dl.

Predictors for Weight Loss

Other than measures of excess weight, few of the variables available to describe patient characteristics on entry to the clinic were correlated with eventual weight loss. The per cent excess weight at entry was strongly correlated with both pounds lost at minimum ($r = .58$) and per cent of excess weight lost at minimum ($r = .30$). Although age at entry and reported age of onset of obesity showed small, significant correlations with weight loss, these relationships did not persist in a multiple regression using the maximum R-square improvement technique in which weight at entry was included. Marital status, years of education, family history of obesity, and entry blood pressure, triglycerides, and cholesterol were not correlated with weight loss success.

Table 5 illustrates the strong relationship between the time patients remained on the PSMF and their weight loss. Time on the PSMF is also strongly related to the degree of patient weight problem at entry.

TABLE 4—Changes in Physiological Parameters from Entry to Final Assessment

	N	All Patients	Female	Male
Systolic Blood Pressure (mm/Hg)				
Entry	335	135	133	144
Entry—final	334	12.99	12.76	14.34
95% confidence intervals on change value		(11.02, 14.96)	(10.65, 14.87)	(9.12, 19.49)
Diastolic Blood Pressure (mm/Hg)				
Entry	335	87	86	93
Entry—final	334	8.37	7.87	11.2
95% confidence intervals on change value		(7.07, 9.67)	(6.53, 9.21)	(7.21, 15.19)
Blood sugar (mg/dl)				
Entry	296	97	97	97
Entry—final	170	14.77	15.07	12.73
95% confidence intervals on change value		(11.96, 17.58)	(8.87, 21.27)	(4.43, 21.03)
Triglycerides (mg/dl)				
Entry	301	133	127	170
Entry—final	154	36.75	28.24	101.06
95% confidence intervals on change value		(31.04, 42.45)	(17.63, 38.85)	(62.47, 139.65)
Cholesterol (mg/dl)				
Entry	327	225	225	225
Entry—final	181	−6.53*	−10.85*	23.13
95% confidence intervals on change value		(−11.04, 2.02)	(−20.44, −1.26)	(4.69, 41.57)
Uric Acid (mg/dl)				
Entry	327	5.9	5.6	7.6
Entry—final	180	−0.40*	−0.50*	−0.30*
95% confidence intervals on change value		(−0.82, 0.02)	(−0.73, −0.27)	(−0.71, 0.11)

*negative values indicate increase in parameter from entry to final measurement.

TABLE 5—Entry Characteristics, Outcomes, and Compliance with PSMF

	Time Patient Remained on PSMF (weeks)			
	0–6	7–12	13–24	≥25
Entry Characteristics				
N	119	156	227	166
Age	35 ± 11	38 ± 11	39 ± 11	40 ± 10
Age of obesity onset	17 ± 12	17 ± 12	16 ± 12	13 ± 12
Weight (kg)	91 ± 23	93 ± 21	97 ± 21	109 ± 22
Weight (lb)	199 ± 51	205 ± 45	214 ± 46	239 ± 48
Outcomes				
Kilograms lost	9.39 ± 6.98	14.70 ± 5.10	22.75 ± 9.37	34.62 ± 14.41
Pounds lost	20.66 ± 15.37	32.35 ± 11.23	50.05 ± 20.62	76.17 ± 31.70
% Excess body weight lost	35 ± 23	51 ± 28	62 ± 24	69 ± 19
Weight Reduction Index	51 ± 28	77 ± 30	102 ± 31	129 ± 37

Side Effects and Mortality

The principal symptom experienced by patients on the PSMF was mild postural lightheadedness occurring in a minority of patients in the first two weeks. This was usually relieved by increasing salt intake. All patients noticed a decrease in the quantity and frequency of bowel movements but only a few required laxative therapy. A small number of patients experienced generalized hair loss after many weeks on the fast. This transient phenomenon has been described elsewhere as "telogen effluvium."[13] There were no deaths among patients while undergoing the PSMF. We are aware of five deaths in the patients described in this report, all of which occurred at least one year after leaving the program. This mortality rate is consistent with that expected in this population.

Other weight loss studies have reported emotional disturbances in a significant number of obese patients, including onset or intensification of depression and anxiety.[14,15] Very few of these symptoms were observed in our program. Most patients felt well on the PSMF and were encouraged by their ability to lose weight. Emotional problems may occur once the patient is off the diet struggling to maintain weight loss: feelings of failure and frustration were noted in patients who were unsuccessful in maintaining the weight loss at the maintenance stage.

Discussion

Our results are better than those seen in programs using primarily behavior therapy[12] and compare favorably with 14 other major studies using very low calorie diets.[16–29] Since all of the patients described here were offered the same multidisciplinary program of diet, exercise, behavior modification, and nutrition education, it is not possible to assess the relative contribution of each component to the program's success.

In many of the very low calorie diet studies cited above, patients were treated with formula diets containing various combinations of milk or egg protein and carbohydrates. No added carbohydrate is provided on the PSMF, in contrast to most of the studies cited above. We believe that the pronounced ketosis seen when carbohydrate is absent enhances

the anorectic effects of the diet. Although early empirical evidence on this effect was conflicting,[3,30–31] a recent randomized trial found that patients on a PSMF reported significantly less hunger and preoccupation with eating when compared to patients on a formula diet with carbohydrate included.[32]

Carbohydrate apparently does not improve protein sparing in very low calorie diets.[33–35] Contaldo has shown that obese patients on a 180-Kcal diet containing 40 grams of protein experienced significantly better nitrogen balance than patients on an isocaloric diet in which 26 grams of carbohydrate replaced some of the protein.[36]

On the other hand, two studies using a small number of subjects were unable to show a difference in protein sparing between protein and protein plus carbohydrate,[37,38] but both studies had a number of methodologic problems.[39]

There is another theoretical advantage to omitting carbohydrate from a very low calorie diet. If a diet contains the minimum amount of protein needed to prevent loss of lean body mass, addition of carbohydrate adds calories and will therefore decrease the rate of weight loss.

In a recent randomized trial in 17 healthy obese women, a diet containing 1.5 gm protein/kg ideal body weight was found to result in significantly better protein sparing than an isocaloric diet providing only .8 gm protein/kg ideal body weight.[40] Patients lost weight at the same rate on the two diets, but since there was less nitrogen loss on the diet without carbohydrate, it can be assumed that more fat loss occurred than on the diet where carbohydrate replaced some of the protein.

Reports of weight loss typically show that absolute weight loss and per cent excess are correlated with starting weight.[11,24,25,29] The magnitude of our patients' average systolic and diastolic blood pressure reductions are consistent with the 7 mmHg per 10 per cent reduction of relative weight noted in the Framingham Study.[41] The hypotensive effect of weight loss has been shown to be due to factors other than changes in sodium balance. Hypothesized mechanisms include changes in sympathomimetic hormone activity, adjustments in the renin-angiotensin system, and reduction and redistribution of blood volume.[16,42,43] The potential efficacy of this approach is supported by our finding that 108 of our 160 patients who initially had diastolic blood pressures >90 mmHg were normotensive following weight loss.

Our finding that serum triglycerides fell significantly in both men and women is also consistent with those of many previous studies.[9,20] Clinical studies of weight loss programs have reported variable effects on cholesterol and high density lipoprotein.[2,44,45] Observed changes in serum cholesterol with weight loss may have been due to the fact that cholesterol rises transiently in some individuals following about 40 lbs of weight loss.

Serum uric acid is known to rise in individuals on ketogenic regimens providing less than 900 calories per day. Uric acid also follows a biphasic course on the PSMF, rising slightly over the first 6–8 weeks and then falling during maintenance of a new, lower weight. Attacks of acute gouty arthritis, however, occurred in less than 1 per cent of our subjects.

For most patients with moderate or more severe obesity (≥ 130 per cent ideal body weight), very low calorie diets provide a safe opportunity to lose a large fraction of their excess weight. Unfortunately, this weight loss does not always constitute a cure because many patients eventually gain back much or all of the lost weight.[2]

The fact that only a minority of the patients maintain long-term weight reduction should not be an excuse for therapeutic nihilism. All obese patients deserve an opportunity to achieve long-term weight reduction. Even for those who fail to maintain their losses, weight regain is often not immediate. It is not known to what extent a few years of weight reduction provides some reduction in cardiovascular risk. Other approaches to control of cardiovascular risk are also subject to long-term compliance problems. For example, at five year follow-up in the Hypertension Detection and Follow-up Program, 20–36 per cent of patients in the Stepped Care group (treatment arm) had diastolic blood pressures above the target level.[46]

Relatively short duration of weight reduction may confer other benefits. For example, decreases in medications for hypertension and diabetes could reduce side effects, drug costs, and physician visits for a few months or years. Symptoms of breathlessness and osteoarthritis are likely to be ameliorated when weight is down. Moreover, patients who undergo major elective surgical procedures during the time their weight is reduced could have lower risk of complications.[47–49]

Weight loss followed by rapid regain, on the other hand, may be harmful. We have observed, along with others, that patients seem to have a more difficult time on VLCD programs which follow previous weight loss and regain [Kelly Brownell, PhD, personal communication]. Until more is known about the benefits and risks of transient weight reduction, very low calorie diets should only be conducted under the supervision of experienced clinicians and in conjunction with behavior modification programs to maximize the chance of long-term weight maintenance.

ACKNOWLEDGMENTS

Supported in part by grants RR-05591, awarded by the Research Resources Division, GM-22691, awarded by the National Institute of General Medical Science, AM-26349, awarded by the National Institute of Arthritis, Metabolism, Digestive and Kidney Disease, DHHS, and HL-31389, funded by the National Heart, Lung and Blood Institute. Dr. Palgi was supported in part by a grant from the Center for Nutritional Research Charitable Trust.

REFERENCES

1. Wadden T, Stunkard A, Brownell K, VanItallie T: The Cambridge diet—more mayhem? JAMA 1983; 250:2833–2834.
2. Wadden T, Stunkard A, Brownell K: VLCDs: their efficacy, safety and future. Ann Int Med 1983; 99:675–684.
3. Felig P: Very-low-calorie diets (editorial retrospective). N Engl J Med 1984; 310:589–591.
4. Society of Actuaries, Committee on Mortality: Build and Blood Pressure Study. Chicago: The Society, 1959.
5. Lew EA, Garfinkel L: Variations in mortality by weight among 750,000 men and women. J Chronic Dis 1979; 32:563–576.
6. Kannel WB, Gordon T: Physiological and medical concomitant of obesity: the Framingham Study. *In:* Bray GA (ed): Obesity in America, NIH Pub. No. 79-359. Washington, DC: Govt Printing Office, 1979.
7. VanItallie T: Morbid obesity: a hazardous disorder that resists conservative treatment. Am J Clin Nutr 1980; 33:358–363.
8. Blackburn GL, Greenberg I: Multidisciplinary approach to adult obesity therapy. Int J Obesity 1978; 2:133–142.
9. Lindner PG, Blackburn GL: Multidisciplinary approach to obesity utilizing fasting modified by protein-sparing therapy. Obesity/Bariatric Medicine 1976; 5:198–216.
10. Bistrian BR: Clinical use of a protein-sparing modified fast. JAMA 1978; 2401:2299–2302.
11. Feinstein AR: The measurement of success in weight reduction. J Chronic Dis 1959; 10:439–456.
12. Wing RR, Jeffrey RW: Outpatient treatments of obesity: review of the literature and report of a series. Int J Obesity 1979; 103:79–85.
13. Blackburn GL, Bistrian BR, Hoag C: Hair loss with rapid weight loss. JAMA 1976; 236:252.
14. Volkmar FR, Stunkard AJ, Mason ER: Emotional responses to weight

reduction by three methods: gastric bypass, jejunoileal bypass, and diet. Am J Clin Nutr 1980; 33:446–451.
15. Stunkard AJ, Rush J: Diet and depression re-examined: a critical review of untoward responses during weight reduction for obesity. Ann Intern Med 1974; 81:526–533.
16. Tuck ML, Sowers J, Dornfield L, Kledzik G, Maxwell M: The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. N Engl J Med 1981; 304:930–933.
17. Coronas R, Duran S, Gomez P, Romero H, Sastre A: Modified total fasting and obesity: results of a multicentric study. Int J Obesity 1982; 6:463–471.
18. Kirshner MA, Schneider G, Ertel N, Cortes G: Supplemented starvation: a successful method for control of major obesity. J Med Soc NJ 1979; 76:175–179.
19. Mancini M, DiBiase G, Contaldo F, Fischetti A, Grasso L, Mattioli PL: Medical complications of severe obesity: importance of treatment by very-low-calorie diets: intermediate and long-term effects. Int J Obesity 1981; 5:341–352.
20. Howard AN, Baird M: A long term evaluation of very-low-calorie semi-synthetic diets: an inpatient/outpatient study with egg albumin as the protein source. Int J Obesity 1977; 1:63–78.
21. McLean Baird I, Howard AN: A double blind trial of mazindol using a very-low-calorie formula diet. Int J Obesity 1977; 1:271–278.
22. Atkinson RL, Kaiser DL: Nonphysician supervision of a very-low calorie diet. Results in over 200 cases. Int J Obesity 1981; 5:237–241.
23. Vertes V, Genuth SM, Hazelton IM: Supplemented fasting as a large scale outpatient program. JAMA 1977; 238:2151–2153.
24. Genuth SM, Vertes V, Hazelton IM: Supplemented fasting in the treatment of obesity. *In:* Bray GA (ed): Recent Advances in Obesity Research II. London: John Libbey and Co, 1978; 370–378.
25. Iselin HU, Burckhardt P: Balanced hypocaloric diet versus protein sparing modified fast in the treatment of obesity: a comparative study. Int J Obesity 1982; 6:175–181.
26. Quaade F, Backer O, Stokholm KH, Anderson T: The Copenhagen PLAFA project: a randomized trial of gastroplasty versus very-low-calorie diet in the treatment of severe obesity (preliminary results). Int J Obesity 1981; 5:257–261.
27. Stokholm KH, Jensen GF, Hansen BB, Quaade F: VLCD in the treatment of massive obesity: preliminary experience. Int J Obesity 1980; 4:213–220.
28. Miller PM, Sims KL: Evaluation and component analysis of a comprehensive weight control program. Int J Obesity 1981; 5:57–65.
29. Clausen JD, Silfen M, Coombs J, Ayers W, Altschul AM: Relationship of dietary regimens to success, efficacy, and cost of weight loss. J Am Dietet Assoc 1980; 77:249–257.
30. Silverstone JT, Stark JE, Buckle PM: Hunger during total starvation. Lancet 1966; 1:343–344.
31. Rosen JC, Hunt DA, Sims EAH, Bogardus C: Comparison of carbohydrate-containing and carbohydrate-restricted hypocaloric diets in the treatment of obesity: effect on appetite and mood. Am J Clin Nutr 1982; 36:463–469.
32. Wadden TA, Stunkard AJ, Brownell KD, Day SC: A comparison of two very-low-calorie diets: protein-sparing-modified fast versus protein-formula-liquid diet. Am J Clin Nutr 1985; 41:533–539.
33. Flatt JP, Blackburn GL: The metabolic fuel regulatory system: implications for protein sparing therapies during caloric deprivation and disease. Am J Clin Nutr 1974; 27:175–187.
34. Blackburn GL, Flatt JP, Clowes GHA, O'Donnell TF, Hensle TE: Protein sparing therapy during periods of starvation with sepsis or trauma. Ann Surg 1973; 177:588–594.
35. Blackburn GL, Flatt JP, Clowes GHA: Peripheral intravenous feeding with isotonic amino acid solutions. Am J Surg 1973; 125:447–454.
36. Contaldo F, DiBiase G, Fischetti A, Mancini M: Evaluation of the safety of very-low-calorie diets in the treatment of severely obese patients in a metabolic ward. Int J Obesity 1981; 5:221–226.
37. Yang M-U, Barbosa-Saldivar JL, PiSunyer FX, VanItallie TB: Metabolic effects of substituting carbohydrate for protein in a low-calorie diet: a prolonged study in obese outpatients. Int J Obesity 1981; 5:231–236.
38. DeHaven J, Sherwin R, Hendler R, Felig P: Nitrogen and sodium balance and sympathetic nervous system activity in obese subjects treated with a low-calorie protein or mixed diet. N Engl J Med 1980; 302:477–482.
39. Phinney SD: Low-calorie protein versus mixed diet (letter). N Engl J Med 1980; 303:158–159.
40. Bistrian BR, Hoffer J, Young VR, Blackburn GL, Matthews DE: Metabolic effects of very-low-calorie weight reduction diets. J Clin Invest 1984; 73:750–758.
41. Ashley FW, Kannel WB: Relationship of weight change to changes in atherogenic traits: the Framingham Study. J Chronic Dis 1974; 27:103–114.
42. Reisin ER, Abel R, Modan M: Effect of weight loss without salt restriction on reduction of blood pressure in overweight hypertensive patients. N Engl J Med 1978; 298:1–10.
43. Stokholm KH, Nielson PE, Quaade F: Correlation between initial blood pressure and blood pressure decrease after weight loss. Int J Obesity 1982; 6:307–312.
44. Brownell KD, Stunkard AJ: Differential changes in plasma high density lipoprotein-cholesterol levels in obese men and women during weight reduction. Arch Int Med 1981; 141:1142–1146.
45. Wechsler HG, Hutt V, Wenzel H, Klor HU, Ditschuneit H: Lipids and lipoproteins during very-low-calorie diets. Int J Obesity 1981; 5:325–331.
46. Hypertension Detection and Follow-up Program: Five year findings of the Hypertension Detection and Follow-up Program II: Mortality by race, sex and age. JAMA 1979; 242:2572–2577.
47. Fisher A, Waterhouse TD, Adams AP: Obesity: its relationship to anaesthesia. Anesthesia 1975; 30:633–647.
48. Glaser B, Vertes V: Supplemented fasting in preparation for surgical treatment. Ohio St Med J 1979; 75:79–81.
49. Vaughn RW: What you should know about obesity and anesthesia. Resident Staff Physician 1980;64–79.
50. National Center for Health Statistics, Abraham S: Obese and Overweight adults in the United States. Vital and Health Statistics. Series 11, No. 230. DHHS Pub. No. 83-1680. Public Health Service. Washington, DC: Govt Printing Office, January 1983.
51. Dublin LI, Marks HH: Mortality among insured overweights in recent years. Trans Assoc Life Insur Med Dir Amer 1951; 35:235–263.
52. Drenick EJ, Bale GS, Seltzer F: Excessive mortality and causes of death in morbidly obese men. JAMA 1980; 243:443–445.

APPENDIX
Classification, Incidence, and Risk of Obesity

Category	Per Cent Relative Weight	Incidence per 1000[a]		Relative Risk of Mortality
		Male	Female	
Normal	100–110	263	184	1
Mild Overweight	110–120	181	127	1.16[b]
Mild Obesity	120–130	81	106	1.28[b]
Moderate Obesity	130–160	53	119	1.46[b]
Severe Obesity	160–200	7	34	3–5[b]
Morbid Obesity	200–250			6–13[c,d]
Super-morbid Obesity	>250		8	>15[d]

a) NCHS Study.[50]
b) Lew and Garfinkel's American Cancer Society Study.[3]
c) Dublin and Marks, Metropolitan Life Study.[51]
d) Drenick, Bales, Seltzer Study.[52]

European Food Safety Authority

EFSA Journal 2011;9(6):2271

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to very low calorie diets (VLCDs) and reduction in body weight (ID 1410), reduction in the sense of hunger (ID 1411), reduction in body fat mass while maintaining lean body mass (ID 1412), reduction of post-prandial glycaemic responses (ID 1414), and maintenance of normal blood lipid profile (1421) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. This opinion addresses the scientific substantiation of health claims in relation to very low calorie diets (VLCDs) and reduction in body weight, reduction in the sense of hunger, reduction in body fat mass while maintaining lean body mass, reduction of post-prandial glycaemic responses, and maintenance of normal blood lipid profile. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The diet that is the subject of the claims is "very low calorie diet (VLCD) program". The Panel considers that whereas the diet that is the subject of the claim, very low calorie diet, is sufficiently characterised in relation to the following claimed effects: reduction in body weight (ID 1410), reduction in the sense of hunger (ID 1411), and reduction in body fat mass while maintaining lean body mass (ID 1412), very low calorie diet is not sufficiently characterised in relation to: reduction of post-prandial glycaemic responses (ID 1414) and maintenance of normal blood lipid profile

[1] On request from the European Commission, Question No EFSA-Q-2008-2147, EFSA-Q-2008-2148, EFSA-Q-2008-2149, EFSA-Q-2008-2151, EFSA-Q-2008-2158, adopted on 08 April 2011.

[2] Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank for the preparatory work on this scientific opinion: The members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen. The members of the Claims Sub-Working Group on Weight Management/Satiety/Glucose and Insulin Control/Physical Performance: Kees de Graaf, Joanne Harrold, Mette Hansen, Mette Kristensen, Anders Sjödin and Inge Tetens.

Suggested citation: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to very low calorie diets (VLCDs) and reduction in body weight (ID 1410), reduction in the sense of hunger (ID 1411), reduction in body fat mass while maintaining lean body mass (ID 1412), reduction of post-prandial glycaemic responses (ID 1414), and maintenance of a normal blood lipid profile (1421) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(6):2271. [22 pp.]. doi:10.2903/j.efsa.2011.2271. Available online: www.efsa.europa.eu/efsajournal

(ID 1421), mainly owing to the lack of standardisation of the type of available carbohydrates and of most of the fatty acids that formula foods for use in very low calorie diets should contain.

The Panel concludes that a cause and effect relationship cannot be established between the consumption of a very low calorie diet and reduction of post-prandial glycaemic responses (ID 1414) and maintenance of normal blood lipid profile (ID 1421).

Reduction in body weight

The claimed effect is "safe and effective weight loss, long term weight maintenance". The target population is assumed to be obese adults who wish to reduce their body weight. The Panel considers that reduction in body weight is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that the evidence provided consistently showed a greater reduction of body weight in obese subjects on very low calorie diets compared to other dietary interventions aimed at weight loss.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the consumption of a very low calorie diet and reduction in body weight.

The Panel considers that in order to bear the claim, a diet should comply with the specifications and conditions of use laid down in CODEX STAN 203-1995. The target population is obese adults who wish to reduce their body weight.

Reduction in the sense of hunger

The claimed effect is "reduced hunger". The target population is assumed to be obese adults in the general population. In the context of the proposed wordings, the Panel assumes that the claimed effect refers to a reduction in sense of hunger mediated by the induction of ketogenesis during a sustained energy deficit. The Panel considers that reduction in the sense of hunger during a sustained energy deficit is a beneficial physiological effect.

No references were provided which addressed the effects of very low calorie diets on sense of hunger.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of a very low calorie diet and reduction in the sense of hunger during a sustained energy deficit.

Reduction in body fat mass while maintaining lean body mass

The claimed effect is "burning fat for energy, preserving lean tissue". The target population is assumed to be obese adults in the general population. In the context of the proposed wordings, the Panel assumes that the claimed effect refers to the loss of fat mass while maintaining lean body mass during weight loss. The Panel considers that reduction in body fat mass while maintaining lean body mass is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that the evidence provided does not consistently show a greater reduction in body fat mass relative to lean body mass in obese subjects on very low calorie diets compared to other dietary interventions aimed at weight loss.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of a very low calorie diet and reduction in body fat mass while maintaining lean body mass.

KEY WORDS

Very low calorie diets, VLCD, weight loss, hunger, body fat mass, lean body mass, post-prandial glycaemic response, lipid profile, health claims.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

EFSA DISCLAIMER

See Appendix B

INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006[4] submitted by Member States contains main entry claims with corresponding conditions of use and literature for similar health claims. EFSA has screened all health claims contained in the original consolidated list of Article 13 health claims which was received by EFSA in 2008 using six criteria established by the NDA Panel to identify claims for which EFSA considered sufficient information had been provided for evaluation and those for which more information or clarification was needed before evaluation could be carried out[5]. The clarifications which were received by EFSA through the screening process have been included in the consolidated list. This additional information will serve as clarification to the originally provided information. The information provided in the consolidated list for the health claims which are the subject of this opinion is tabulated in Appendix C.

ASSESSMENT

1. Characterisation of the food/constituent

The diet that is the subject of the claims is "very low calorie diet (VLCD) program".

Very low calorie diets (VLCDs) or very low energy diets are diets which contain energy levels between 450 and 800 kcal per day, and 100 % of the recommended daily intakes for vitamins and minerals. They should contain not less than 50 g of high-quality protein (protein-digestibility-corrected amino acid score of 1), should provide not less than 3 g of linoleic acid and not less than 0.5 g alpha-linolenic acid with a linoleic acid/alpha-linolenic acid ratio between 5 and 15, and should provide not less than 50 g of available carbohydrates (CODEX STAN 203-1995[6]). VLCDs are typically used for 8-16 weeks.

The Panel notes that the nutritional composition and use of VLCDs is not regulated in the European Union.

Additional components or interventions included in a "very low calorie diet (VLCD) program", however, are not sufficiently characterised; these may vary between programs and may affect both initial weight loss and long term weight maintenance. Similarly, the types of available carbohydrates (e.g. their chemical composition and physical properties) which formula foods for use in VLCDs should contain, are not specified. The Panel also notes that the fatty acid composition of formula foods for use in VLCDs is only partially specified (CODEX STAN 203-1995).

The Panel considers that whereas the diet which is the subject of the claim, VLCD, is sufficiently characterised in relation to the following claimed effects: reduction in body weight (ID 1410), reduction in the sense of hunger (ID 1411), and reduction in body fat mass while maintaining lean body mass (ID 1412), VLCD is not sufficiently characterised in relation to: reduction of post-prandial glycaemic responses (ID 1414) and maintenance of normal blood lipid profile (ID 1421), mainly owing to the lack of standardisation of the type of available carbohydrates and of most of the fatty acids that formula foods for use in VLCDs should contain.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

[5] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal, 9(4):2135, 24 pp.

[6] CODEX STAN 203-1995. CODEX STANDARD for Formula Foods for Use in Very Low Energy Diets for Weight Reduction

The Panel concludes that a cause and effect relationship cannot be established between the consumption of a VLCD and reduction of post-prandial glycaemic responses (ID 1414) and maintenance of normal blood lipid profile (ID 1421).

The Panel considers that the diet which is the subject of the claim, VLCD, is sufficiently characterised in relation to the following claimed effects: reduction in body weight (ID 1410), reduction in the sense of hunger (ID 1411) and reduction in body fat mass while maintaining lean body mass (ID 1412).

2. Relevance of the claimed effect to human health

2.1. Reduction in body weight (ID 1410)

The claimed effect is "safe and effective weight loss, long term weight maintenance". The Panel assumes that the target population is obese adults who wish to reduce their body weight.

In the context of the proposed wordings, the Panel assumes that the claimed effect refers to a reduction in body weight.

Weight loss can be interpreted as the achievement of a normal body weight in previously obese subjects. In this context, weight loss in obese subjects without the achievement of a normal body weight is considered a beneficial physiological effect.

The Panel considers that reduction in body weight is a beneficial physiological effect.

2.2. Reduction in the sense of hunger (ID 1411)

The claimed effect is "reduced hunger". The Panel assumes that the target population is obese adults in the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effect refers to a reduction in sense of hunger mediated by the induction of ketogenesis during a sustained energy deficit.

The Panel considers that reduction in the sense of hunger during a sustained energy deficit is a beneficial physiological effect.

2.3. Reduction in body fat mass while maintaining lean body mass (ID 1412)

The claimed effect is "burning fat for energy, preserving lean tissue". The Panel assumes that the target population is obese adults in the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effect refers to the loss of fat mass while maintaining lean body mass during weight loss.

The Panel considers that reduction in body fat mass while maintaining lean body mass is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

3.1. Reduction in body weight (ID 1410)

The references provided for the scientific substantiation of the claim included abstracts with insufficient information for a scientific evaluation, narrative reviews, and human intervention studies on diets other than VLCDs (e.g. low carbohydrate diets and low fat diets) and/or effects other than body weight changes (e.g. body composition and snoring). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Four reviews (Ayyad and Andersen, 2000; Jebb and Goldberg, 1998; Miura et al., 1989; Mustajoki and Pekkarinen, 2001) and two meta-analyses (Anderson et al., 2004; Gilden Tsai and Wadden, 2006) including most of the original human intervention studies presented on the effects of VLCDs on body weight loss were provided.

The two meta-analyses were based on 19 individual studies including more than 2,500 overweight or obese subjects (the majority of whom were obese) of both sexes (the majority of whom were females) treated with VLCDs for between eight and 28 weeks (median 22 weeks), and with a follow-up period of between one and five years.

The meta-analysis by Anderson et al. (2004) was based on 47 intervention studies conducted in obese but otherwise healthy adult subjects (BMI at least 30 kg/m^2 at baseline) which assessed the effects of meal replacements (at least two meal replacements per day, four studies), energy restricted diets (providing >1,500 kcal per day, six studies), low-energy diets (providing 800-1500 kcal per day, 10 studies), VLCDs (providing up to 800 kcal per day, 19 studies), and soy diets (providing up to 800 kcal per day, eight studies), and reported weight loss data after 24 weeks of treatment. Participants in the 19 studies on VLCDs were 1,968 obese subjects of both sexes with an average initial BMI of 39.6 kg/m^2 (range 36.1 to 41.9 kg/m^2). The mean drop-out rate in these studies was 35.3 %. Data were reported for 1,347 women and 396 men. Subjects lost an average of 22.6 % of their initial body weight over the 24 weeks of intervention; such weight loss was significantly higher than the weight loss achieved with any other weight loss strategy considered, and this significant difference with respect to other weight loss strategies was maintained after one year. However, no significant differences in body weight loss were observed between weight loss strategies at longer follow-ups. Subjects on VLCDs maintained an average weight loss of 16.1 %, 9.7 %, 7.8 %, 7.0 % and 6.2 % of their initial body weight at follow-up after one, two, three, four and five years, respectively. Large individual differences were observed in long-term effectiveness depending on the initial amount of weight loss, additional (behavioural) interventions, and level of physical activity. VLCDs and low-energy-diet programs were the weight loss strategies which required more aggregated medical visits, clinic visits and class hours (e.g. intensity score about four times higher than meal replacements). The Panel notes that the majority of studies presented data on completers only, and not on the intention-to-treat population.

The meta-analysis by Gilden Tsai and Wadden (2006) included only randomised controlled trials (RCTs) comparing the efficacy of low calorie diets (LCDs) *vs.* VLCDs, and which included follow-up data of at least one year after maximum weight loss. Six RCTs including 233 subjects met the inclusion criteria. Initial VLCD treatment for 8-12 weeks followed by an LCD containing 1,000 to 1,600 kcal/day and behavioural treatment for additional 12 to 104 weeks was compared to LCD and behavioural treatment of similar durations. Maximal weight loss for subjects in the VLCD group ranged between 13.4 and 19.9 % of initial body weight, which was approximately 6.5 % more than that observed for subjects in the LCD group. Body weight at 1.5-2 years of follow-up in the VLCD group was -12.3 to -7.6 % of initial body weight, which was slightly but still significantly (1.5 % difference) lower than in the LCD group.

The remaining references and reviews, which addressed the effects of VLCDs on weight loss compared to other dietary strategies aimed at weight loss, are in agreement with these two meta-analyses. Compared with other non-surgical interventions for weight loss, VLCDs in the context of intense supervision (e.g. by physicians and other health professionals) lead to greater weight loss (ranging from 12 to 20 % of initial body weight or about 12 to 35 kg) after 8-16 weeks of treatment, although considerable weight regain occurs when follow-up is extended for a number of years, particularly in the absence of behavioural modifications at follow-up. However, about one third of women and about 28 % of men still had 10 % lower body weight after five years. Those subjects had generally been more successful during the weight loss phase (Jebb and Goldberg, 1998; Mustajoki and Pekkarinen, 2001; Pekkarinen et al., 1996).

Although VLCDs appear to be superior in producing large initial weight loss compared with other dietary interventions, long-term success is highly dependent on additional interventions including long-term life-style changes and active follow-up (Ayyad and Andersen, 2000). Miura et al. (1989) assessed the effects of combining VLCDs and behavioural modifications *vs.* the effects of either VLCD alone or behavioural modification alone in 70 obese subjects refractory to other weight loss interventions. VLCD alone or in combination with behavioural modifications showed no significant differences in initial weight loss (7.5±2.1 *vs.* 8.3±2.3 kg/month). However, after 2 years, the group on VLCD only had regained on average 4.3±3.5 kg (>50% of their initial weight loss) while the group receiving the combination of VLCD plus behavioural modification had lost one additional kg (-1.0±0.7 kg) and the group on behavioural therapy only had lost an additional 1.3±2.2 kg. Compared to the group receiving behavioural therapy only, the total weight loss at two years was not significantly different in the group on VLCD only (approximately -5 kg in both groups).

In weighing the evidence, the Panel took into account that the evidence provided consistently showed a greater reduction of body weight in obese subjects on VLCDs compared to other dietary interventions aimed at weight loss.

The Panel concludes that a cause and effect relationship has been established between the consumption of a VLCD and reduction in body weight.

3.2. Reduction in the sense of hunger (ID 1411)

The references provided for the scientific substantiation of the claim included narrative reviews, and human intervention studies on diets other than VLCDs (e.g. low carbohydrate diets and low fat diets) and/or effects other than sense of hunger (e.g. body weight changes, body composition and snoring). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

No references were provided which addressed the effects of VLCDs on sense of hunger.

The Panel concludes that a cause and effect relationship has not been established between the consumption of a VLCD and reduction in the sense of hunger during a sustained energy deficit.

3.3. Reduction in body fat mass while maintaining lean body mass (ID 1412)

The references provided for the scientific substantiation of the claim included narrative reviews, and human intervention studies on the effects of diets other than VLCDs (e.g. low carbohydrate diets, and low fat diets) on body composition. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Ryttig and Rossner (1995) assessed body composition changes in 60 obese subjects on a diet providing 330 kcal/day for 12 weeks using tetra polar bioelectrical impedance analysis. The Panel

notes that this diet does not comply with the minimum requirement of 450 kcal/day for VLCDs, and considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

Zahouani et al. (2003) reported on a study in 1,389 obese subjects who lost on average 10.3±5.5 kg fat mass and 2.2±2.05 kg fat free mass after 90 days on a VLCD. Body composition was assessed by leg-to-leg bioelectrical impedance analysis. Burgess (1991) found that fat mass contributed 75 % to total weight loss after 12 weeks of VLCD treatment assessed by hydro-densitometry as well as by bio-impedance analysis in 17 obese subjects (9 women). Coxon et al. (1989) randomised obese females to consume either a VLCD providing 405 kcal/day (n=12) or a VLCD providing 800 kcal/day (n=14) for eight weeks, each aimed at obtaining different rates of weight loss. Body composition was assessed by bioelectrical impedance analysis and by infrared interactance. A ratio of just over 0.4 between loss of fat free mass and total weight loss regardless of the rate of weight loss was observed. Hoie et al. (1993) assessed the quality of weight loss by near-infra-red interactance in 127 obese subjects on a VLCD for eight weeks. Mean weight reduction was 12.7 kg (12.6 % of initial weight) and mean body fat loss was 9.5 kg, which constitutes about 75 % of the weight loss. Mean reduction in lean body mass was 3.2 kg. No correlation was found between initial body mass index (BMI) and loss of lean body mass, or between initial body composition and weight loss. Morgan et al. (1992) assessed changes in body composition using total body nitrogen measured by *in vivo* neutron activation analysis in 11 females on a VLCD for 11 weeks. The mean loss of total body nitrogen was 125±57 g, equivalent to 781±356 g protein. The fat-free mass component of the weight loss was calculated by two different methods as 23.5 % (±3 % SEM) and 22.8 % (±2.7 % SEM), respectively.

The Panel notes that none of the studies provided assessed the effects of VLCDs on body composition compared to other dietary strategies for weight loss, that most of the studies provided used bioelectrical impedance analysis or infrared interactance for body composition analysis, both of which are not considered as reliable methods to assess changes in body composition in obese subjects during rapid weight loss, and that in most of the studies provided body fat accounted for about 70-78 %, and fat-free mass for about 22-30 %, of the total weight lost, which is, respectively, the approximate composition of the excess body weight in obese subjects and the approximate composition of the weight loss which could be expected by the use of other weight loss strategies.

In weighing the evidence, the Panel took into account that the evidence provided did not consistently show a greater reduction in body fat mass relative to lean body mass in obese subjects on VLCDs compared to other dietary interventions aimed at weight loss.

The Panel concludes that a cause and effect relationship has not been established between the consumption of a VLCD and reduction in body fat mass while maintaining lean body mass.

4. Panel's comments on the proposed wording

4.1. Reduction in body weight (ID 1410)

The Panel considers that the following wording reflects the scientific evidence: "Replacing the usual diet with a very low calorie diet helps to lose weight".

5. Conditions and possible restrictions of use

5.1. Reduction in body weight (ID 1410)

The Panel considers that in order to bear the claim, a diet should comply with the specifications and conditions of use laid down in CODEX STAN 203-1995. The target population is obese adults who wish to reduce their body weight.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- Whereas the diet, very low calorie diet (VLCD), which is the subject of the claims is sufficiently characterised in relation to the following claimed effects: reduction in body weight (ID 1410), reduction in the sense of hunger (ID 1411), and reduction in body fat mass while maintaining lean body mass (ID 1412), VLCD is not sufficiently characterised in relation to: reduction of post-prandial glycaemic responses (ID 1414) and maintenance of normal blood lipid profile (ID 1421), mainly owing to the lack of standardisation of the type of available carbohydrates and of most of the fatty acids that formula foods for use in VLCDs should contain.

- A cause and effect relationship cannot be established between the consumption of a VLCD and reduction of post-prandial glycaemic responses (ID 1414) and maintenance of normal blood lipid profile (ID 1421).

Reduction in body weight (ID 1410)

- The claimed effect is "safe and effective weight loss, long term weight maintenance". The target population is assumed to be obese adults who wish to reduce their body weight. Reduction in body weight is a beneficial physiological effect.

- A cause and effect relationship has been established between the consumption of a VLCD and reduction in body weight.

- The following wording reflects the scientific evidence: "Replacing the usual diet with a very low calorie diet helps to lose weight".

- In order to bear the claim, a diet should comply with the specifications and conditions of use laid down in CODEX STAN 203-1995. The target population is obese adults who wish to reduce their body weight.

Reduction in the sense of hunger (ID 1411)

- The claimed effect is "reduced hunger". The target population is assumed to be obese adults in the general population. In the context of the proposed wordings, it is assumed that the claimed effect refers to a reduction in sense of hunger mediated by the induction of ketogenesis during a sustained energy deficit. Reduction in the sense of hunger during a sustained energy deficit is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of a VLCD and reduction in the sense of hunger during a sustained energy deficit.

Reduction in body fat mass while maintaining lean body mass (ID 1412)

- The claimed effect is "burning fat for energy, preserving lean tissue". The target population is assumed to be obese adults in the general population. In the context of the proposed wordings, it is assumed that the claimed effect refers to the loss of fat mass while maintaining lean body mass during weight loss. Reduction in body fat mass while maintaining lean body mass is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of a VLCD and reduction in body fat mass while maintaining lean body mass.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-2147, EFSA-Q-2008-2148, EFSA-Q-2008-2149, EFSA-Q-2008-2151, EFSA-Q-2008-2158). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The full list of supporting references as provided to EFSA is available on: http://www.efsa.europa.eu/panels/nda/claims/article13.htm.

REFERENCES

Anderson JW, Luan J and Hoie LH, 2004. Structured weight-loss programs: meta-analysis of weight loss at 24 weeks and assessment of effects of intervention intensity. Advances in Therapy, 21, 61-75.

Ayyad C and Andersen T, 2000. Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. Obesity Reviews, 1, 113-119.

Burgess NS, 1991. Effect of a very-low-calorie diet on body composition and resting metabolic rate in obese men and women. Journal of the American Dietetic Association, 91, 430-434.

Coxon A, Kreitzman S, Brodie D and Howard A, 1989. Rapid weight loss and lean tissue: evidence for comparable body composition and metabolic rate in differing rates of weight loss. International Journal of Obesity, 13 Suppl 2, 179-181.

Gilden Tsai A and Wadden TA, 2006. The evolution of very-low-calorie diets: an update and meta-analysis. Obesity (Silver Spring), 14, 1283-1293.

Hoie LH, Bruusgaard D and Thom E, 1993. Reduction of body mass and change in body composition on a very low calorie diet. International Journal of Obesity and Related Metabolic Disorders, 17, 17-20.

Jebb SA and Goldberg GR, 1998. Efficacy of very low-energy diets and meal replacements in the treatment of obesity. Journal of Human Nutrition & Dietetics, 11, 219.

Miura J, Arai K, Tsukahara S, Ohno M and Ikeda Y, 1989. The long term effectiveness of combined therapy by behavior modification and very low calorie diet: 2 years follow-up. International Journal of Obesity, 13 Suppl 2, 73-77.

Morgan WD, Ryde SJ, Birks JL, Thomas DW and Kreitzman SN, 1992. Changes in total body nitrogen during weight reduction by very-low-calorie diets. American Journal of Clinical Nutrition, 56, 262S-264S.

Mustajoki P and Pekkarinen T, 2001. Very low energy diets in the treatment of obesity. Obesity Reviews, 2, 61-72.

Pekkarinen T, Takala I and Mustajoki P, 1996. Two year maintenance of weight loss after a VLCD and behavioural therapy for obesity: correlation to the scores of questionnaires measuring eating behaviour. International Journal of Obesity and Related Metabolic Disorders, 20, 332-337.

Ryttig KR and Rossner S, 1995. Weight maintenance after a very low calorie diet (VLCD) weight reduction period and the effects of VLCD supplementation. A prospective, randomized, comparative, controlled long-term trial. Journal of Internal Medicine, 238, 299-306.

Zahouani A, Boulier A and Hespel JP, 2003. Short- and long-term evolution of body composition in 1389 obese outpatients following a very low calorie diet (Pro'gram18 VLCD). Acta Diabetologica, 40 Suppl 1, S149-150.

APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation 1924/2006 on nutrition and health claims made on foods[7] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or

b) psychological and behavioural functions; or

c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and

(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD[8]

Foods are commonly involved in many different functions[9] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

[7] OJ L12, 18/01/2007
[8] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.
[9] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to

describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.
- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.
- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.
- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity

consumed.

- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.
- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

APPENDIX C

Table 1. Main entry health claims related to very low calorie diet (VLCD) including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
1410	Very low calorie diet (VLCD) Programme	1) Safe and effective weight loss 2) long term weight maintenance	which ensures a rapid, yet controlled way of reaching a healthier weight The programme allows thousands of clients to lose their excess weight (VLCD is a ...) way of reaching a healthier weight (Foodpacks allow...) effective weight loss This is a unique opportunity for you to reshape your waist, your weight A fast safe and effective way to slim down to your target weight For fast weight loss as the sole source of nutrition For more gradual weight loss with additional food for long term weight maintenance Produces excellent weight loss in the desired timescale Will help you lose weight in a scientifically proven safe and healthy way A healthy way to reduce weight and keep it off Shrink your waist Lose weight from your waist 'Weight care' Scientific research confirms credibility and efficacy The low calorie levels of the diet mean that everyone will lose weight on the programme/sole source programme Nutritionally complete VLCD formula, which enables fast,

			safe and effective weight loss Lose weight safely and comfortably/shed weight quickly and safely/Look forward to a slimmer you/The low calorie levels of the diet mean that everyone will lose weight/You will re-shape waist/ lose inches off your waist
	Conditions of use - Nutritionally complete formula VLCD providing <800 kcal/day - Programme using initial nutritionally complete formula VLCD providing <800kcal/day. Weight management Programme providing counsellor support and/or behaviour modification		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1411	Very low calorie diet (VLCD) Programme	Reduced hunger	The composition of the Food packs means you wont be starving – once you're in ketosis your physical hunger is suppressed. With such formula food, clients experience little, if any hunger – as after around 3-4 days the body goes into a state of ketosis.
	Conditions of use - Nutritionally complete, ketogenic VLCD formula providing <800kcal/day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1412	Very low calorie diet (VLCD) Programme	Burning fat for energy, preserving lean tissue	when you are on Food packs - your body uses its stored fat to make up the difference (of energy) ..evidence suggests that VLCDs do not accelerate the loss of lean tissue weight loss is 3 parts fat and 1 part lean during weight loss. the body breaks down fat to make up the deficit. When you lose weight it comes off in the ratio 3 parts fat to 1 part lean tissue – and that's true of any diet.
	Conditions of use - Nutritionally complete very low calorie diet formula providing <800kcal/day		

ID	Food or Food constituent	Health Relationship	Proposed wording
1414	Very low calorie diet (VLCD) Programme	Low glycaemic index	Low glycaemic index formula food Low glycamic index products
	Conditions of use - Nutritionally complete VLCD formula food providing <800kcal/day with GI measured to <55		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1421	Very low calorie diet (VLCD) Programme	VLCD/low carbohydrate diets helps to the maintenance of normal blood lipid profile	VLCD/low carbohydrate diets helps to the maintenance of normal blood lipid profile
	Conditions of use - Nutritionally complete VLCD formula <800kcal		

GLOSSARY AND ABBREVIATIONS

BMI	Body mass index
LCD	Low calorie diet
RCT	Randomised controlled trial
VLCD	Very low calorie diet

Current Opinion On Dietary Advice In Order To Preserve Fat Free Mass During A Low-Calorie Diet

Mariangela Rondanelli , Milena Anna Faliva , Clara Gasparri , Gabriella Peroni , Daniele Spadaccini , Roberto Maugeri , Mara Nichetti , Vittoria Infantino , Simone Perna

PII: S0899-9007(19)30250-3
DOI: https://doi.org/10.1016/j.nut.2019.110667
Reference: NUT 110667

To appear in: *Nutrition*

Received date: 19 December 2018
Revised date: 27 November 2019
Accepted date: 1 December 2019

Please cite this article as: Mariangela Rondanelli , Milena Anna Faliva , Clara Gasparri , Gabriella Peroni , Daniele Spadaccini , Roberto Maugeri , Mara Nichetti , Vittoria Infantino , Simone Perna , Current Opinion On Dietary Advice In Order To Preserve Fat Free Mass During A Low-Calorie Diet, *Nutrition* (2019), doi: https://doi.org/10.1016/j.nut.2019.110667

Highlights

- The assessment of obese subjects must consider the analysis of body composition.

- Very low calorie ketogenic diet preserves the fat free mass during weight loss.

- Branched chain amino acids and whey protein are useful in maintaining fat free mass.

- The assessment of vitamin D blood concentration is required for obese patients.

Current Opinion On Dietary Advice In Order To Preserve Fat Free Mass During A Low-Calorie Diet

Mariangela Rondanelli[1,2], Milena Anna Faliva[3], Clara Gasparri[3], Gabriella Peroni[3], Daniele Spadaccini[3], Roberto Maugeri[4], Mara Nichetti[3], Vittoria Infantino[5], Simone Perna[6]

[1]IRCCS Mondino Foundation, Pavia

[2] Department of Public Health, Experimental and Forensic Medicine, Unit of Human and Clinical Nutrition, University of Pavia, Pavia, Italy

[3]Department of Public Health, Experimental and Forensic Medicine, Section of Human Nutrition, Endocrinology and Nutrition Unit, Azienda di Servizi alla Persona (ASP), University of Pavia, Pavia, Italy

[4]Research and Clinical Investigation Department, Company Medical Dietetics, Savigliano, Italy

[5]Department of Biomedical Science and Human Oncology, University of Bari Aldo Moro, Bari, Italy

[6]Department of Biology, College of Science, University of Bahrain, Sakhir Campus P. O. Box 32038 Kingdom of Bahrain

EMAIL ADDRESSES: mariangela.rondanelli@unipv.it; milena.faliva@gmail.com; clara.gasparri01@universitadipavia.it; gabriella.peroni01@universitadipavia.it; daniele.spadaccini01@universitadipavia.it; r.maugeri@kalibragroup.com; dietista.mara.nichetti@gmail.com; viriainfantino@hotmail.it; sperna@uob.edu.bh

Corresponding author: Dr. Clara Gasparri. Department of Public Health, Experimental and Forensic Medicine, Section of Human Nutrition, Endocrinology and Nutrition Unit, Azienda di Servizi alla Persona, University of Pavia, 27100 Pavia, Italy. E-mail: clara.gasparri01@universitadipavia.it; tel: 00390382381739.

Abbreviations

FFM: FAT FREE MASS
VLCKD: VERY LOW CARBOYDRATE KETOGENIC DIET
IGF-I-GH: INSULIN LIKE GROW FACTOR-I – GROWTH HORMONE
IL6: INTERLEUKIN 6
IL8: INTERLEUKIN 8
IL15: INTERLEUKIN 15
BDNF: BRAIN DERIVED NEUROTROPHIC FACTOR
LFD : LOW-FAT DIET
LIF: LEUKEMIA INHIBITORY FACTOR
BCAA: BRANCHED CHAIN AMINO ACIDS
VDR: VITAMIN D RECEPTOR

ABSTRACT

The loss of fat free mass (FFM) that occurs during a weight loss secondary to low-calorie diet can lead to numerous and deleterious consequences. We performed a review in order to evaluate the till-now evidence regarding the optimum treatment for maintaining FFM during low-calorie diet. This review included eligible studies. In order to maintain FFM during a low-calorie diet, there are various diet strategies: adopt a very-low carbohydrates ketogenic diets (VLCKD) and take an adequate amount of specific nutrients (vitamin D, leucine, whey protein). As regard the numerous and various low-calorie diet proposals for achieving weight loss, the comparison of VLCKD with prudent low-calorie diet demonstrated that FFM was practically unaffected by VLCKD. This is possible for numerous mechanisms, involving insulin and insulin like grow factor-I – growth hormone (IGF-I-GH) axis, and which acts by stimulating protein synthesis. Considering protein and amino acids intake, an adequate daily intake of leucine (4 grams/day), and whey protein (20 grams/day) is recommended.

Regarding vitamin D, if the blood vitamin D has low values (<30 ng/ml), it is mandatory that an adequate supplementation is provided, specifically calcifediol because in the obese subject, this form is recommended to avoid seizure in the adipose tissue: 3–4 drops/day or 20–30 drops/week of calcifediol are generally adequate to restore normal 25(OH)D plasma levels in obese subjects.

KEYWORDS: VLCKD; leucine; fat free mass; whey protein; branched chain amino acid; vitamin D

Introduction

The decrease in body weight, which takes place during a low-calorie diet (protein intake equal to 15% of total energy intake), physiologically involves a loss of both fat and fat free mass (FFM): the physiology shows that about 75% of the weight loss consists of a loss of fat mass, while the remaining 25% consists of a loss in fat free mass [1]. The loss of fat free mass that occurs during a weight loss can lead to numerous and deleterious short and long term consequences which can frustrate some of the benefits related to weight loss [2]. In fact, fat free mass, in addition to its role in locomotion, plays a key role in various metabolic pathways, such as glucose regulation [3] and lipid control [4]. A loss of fat free mass can then determine significant adverse effects on the body's metabolic health, as well as leads to a significant decrease in basal metabolic rate, contributing to the recovery of body weight [5]. The muscle is then a real endocrine organ that produces substances, defined by miokin, such as interleukin 6 (IL6), IL 8, IL15, Brain-Derived Neurotrophic Factor (BDNF), and Leukemia Inhibitory Factor (LIF), which have autocrine, paracrine and endocrine activities [6]. In addition, the muscle in return, has receptors for numerous molecules that have significant activities, such as the Insulin like growth factor -I, and vitamin D [7] that control the function of the muscle itself.

The aim of this study is to evaluate the specific factors that play a pivotal role in allowing to preserve fat free mass during a weight loss due to low-calorie diet.

Materials and Methods

The present narrative review was performed following the steps by Egger et al which are as follows [8]: configuration of a working group: three operators skilled in endocrinology and clinical nutrition, of whom one is acting as a methodological operator and two participating as clinical operators. 2. Formulation of the revision question on the basis of considerations made in the abstract: “the state of the art on metabolic and nutritional correlates of loss of fat free mass during low calorie diet and treatment for maintaining fat free mass”. 3. Identification of relevant studies: a research strategy

was planned, on PubMed [Public MedIine run by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of Bathesda (USA)], as follows: a) definition of the key words (fat free mass, low calorie diet), allowing the definition of the interest field of the documents to be searched, grouped in inverted commas ("…") and used separately or in combination; b) use of: the Boolean AND operator, that allows the establishments of logical relations among concepts; c) research modalities: advanced search; d) limits: time limits: papers published in the last 20 years; humans; languages: English; e) manual search performed by the senior researchers experienced in clinical nutrition through the revision of reviews and individual articles on metabolic and nutritional correlates of loss of fat free mass during low calorie diet and treatment for maintaining fat free mass published in journals qualified in the Index Medicus. 4. The analysis was carried out in the form of a narrative review of the reports. Figure 1 shows the flow-chart of the studies evaluated.

Results and Discussion

Very - Low carbohydrates ketogenic diet (VLCKD)

Among low-calorie diets, the role of the very-low-carbohydrate ketogenic diets (VLCKD) in the management of obesity is now well established [9]. Comparing VLCKD with other diets, such as paleo and vegan diets, commonalities included weight loss while major differences included time frame of weight loss, blood pressure changes, elimination patterns, musculoskeletal effects, psychosocial responses, and environmental and economic impact [10]. A meta-analysis [9] demonstrated that individuals assigned to a VLCKD (i.e. a diet with no more than 50 g carbohydrates/d) achieve better long-term body weight and cardiovascular risk factor management when compared with individuals assigned to a conventional low-fat diet (LFD; i.e. a restricted-energy diet with less than 30% of energy from fat).

Very recently numerous double-blind studies confirmed that a VLCKD was highly effective in terms of body weight reduction without inducing lean body mass loss [11–13].

Further than in obesity, the literature demonstrated that there are good effect of ketogenic diet on muscle mass in various disease states: such as epilepsy [14,15], Parkinson's disease [16], Alzheimer's disease [17], multiple sclerosis [18] .

In particular, very recently a study has been demonstrated that a ketogenic diet increases lean mass and decreases inflammation and oxidation possibly as a consequence of an increase in satiety and decrease in hunger in Multiple Sclerosis patients [18].

VLCKD appears to be protective against muscle catabolism [19,20] for several reasons, such as: the adrenergic stimulation by the protein and by low levels of sugar in the blood inhibits the proteolysis of skeletal muscle; the formation of ketone bodies suppresses the use of protein-derived amino acids by muscle; in addition, the beta-hydroxybutyrate decreases leucine oxidation and promotes protein synthesis; increased availability of dietary protein causes an increase in IGF-1 in muscle; the increased protein intake leads to increased protein synthesis, thanks to the presence of amino acids available. It has been suggested that branched-chain amino acids (BCAA) leucine especially interacts with the metabolic pathways that regulate insulin signaling, decreasing hormone levels and simultaneously increasing protein synthesis in skeletal muscle.

Moreover, VLCKD induces a particular metabolic condition that activates fasting pathways during a high or normal energy state and it can also be argued that the transcription of autophagy related genes (fundamental for the anabolic/catabolic equilibrium and hence for whole muscle health) can be activated by ketogenic diet, mediated by FoxO3 [21–23].

Molecular effects of ketogenic diet on muscle preservation were investigated in animal model [24]. In slow-twitch soleus muscle, administration of ketogenic diet for four weeks can increase skeletal muscle mTOR signaling in old adults rats (28 mo.), while decrease its signalling in young adults muscles (5 mo.). Phosphorylation of p70 ribosomal protein S6 kinase (p70S6k) was increased by 400% by ketogenic diet versus standard diet in old rats, and soleus muscles (assessed for muscle size and effects on p70S6k) from old rats receiving ketogenic diet were 6% larger than old rats who received standard diet [24].

Finally, the observed preservation of fat free mass brought by during a VKLCD is possible at least by four other possible mechanisms [19]. It be involved as the surge of low levels of blood sugar which are a stimulus for its secretion and it could be that the protein mass of skeletal muscle is affected by adrenergic influences. The liver produces ketone bodies during a VKLCD and they flow from the liver to extra-hepatic tissues (e.g., brain, muscle) for use as a fuel. As low blood sugar increases GH is secreted, one could speculate that a VKLCD increases GH levels. A VKLCD is almost always relatively high in protein and there is evidence that high protein intake increases protein synthesis by increasing systemic amino acid availability [25], which is a potent stimulus of muscle protein synthesis [26]. During weight loss, higher protein intake reduces loss of fat free mass and increases loss of body fat [27], which can interact with the insulin to regulate the control of protein synthesis to support the fat free mass during periods of reduced caloric intake [28].

Regarding the effects of long-term VLCKDs the results are in contrast: despite some studies have documented the safety of VLCKD in the long-term period, other studies demonstrated that intake of KD has been linked to renal stones, gallstones and elevated liver enzymes, given that dietary intervention included approximately 70% of energy as fat [29]. Moreover, the assessment of the effects of VLCKD on bone health, insulin resistance and beta-cell function in the long term is still lacking. Given this background, it is important to considerate that VLCKD requires proper medical supervision, along with the routine measurement of urine and/or blood ketones according to clinical judgment [29]. Considering the limitations of VLCKDs, these included increased LDL levels, arterial stiffening, reduction in REM sleep, interference with endothelial function and renal stones [10]. As far as mood, it was found that in the first 8 weeks participants experienced mood improvement. But, after the 8 weeks, the mood improvement was shown to plateau due to lower concentration of serotonin in the brain from limited consumption of carbohydrates over a period of 12 months [30].

In conclusion, the comparison of VKLCD with a prudent standard low-calorie diet demonstrated that fat free mass was practically unaffected. The observed preservation of fat free mass brought by

during a VKLCD is possible for numerous factors predominantly of hormonal mechanisms involving the insulin and the IGF-I GH axis which acts by stimulating protein synthesis.

Branched chain amino acids and leucine

Unlike other amino acids, the branched-chain amino acids (BCAAs) are metabolised in skeletal muscle. The BCAAs (leucine, isoleucine and valine) represent 14-18% of the total amino acids present in skeletal muscle [31]. At the resting state, BCAAs, and particularly leucine, have an anabolic effect by increasing protein synthesis and/or a reducing the rate of protein degradation, resulting in a positive net muscle protein balance [32]. Leucine, whose average requirement is 40 mg / kg / day, is critical to maintaining a healthy muscle tissue and the leucine content in meals is an important regulator of muscle protein synthesis and produces different results on the long-term body composition [33].

Further research has compared the intake of 10 grams of protein with 18% of leucine with a similar beverage containing 35% of leucine, concluding that the beverage with the highest concentration of leucine (4 grams) determines a greater stimulus to the muscle protein synthesis, resulting in an inferior muscle catabolism by the action of cortisol [34].

Even if isoleucine and valine haven't shown the same potential, they play a key role as part of the "construction". In fact, the hypertrophy induced by leucine drops to zero as soon as the presence of the other two BCAAs is poor: no matter how much leucine is made available for the muscles, since muscle growth does not occur if the other two BCAAs fall below a certain level [35]. Leucine is capable of interacting with the metabolic insulin pathway with apparent modulation of protein synthesis and consequent maintenance of fat free mass during a period of caloric restriction and since the same amino acid also modulates the use of glucose by the skeletal muscle, through stimulation of the glucose-alanine cycle, which allows reuse of glucose, the assumption of adequate amounts of leucine is considered as a potential strategy for the treatment of obese patients, being of an assistance in maintaining the lean body mass [28].

In conclusion, an adequate daily intake of the amino acid leucine (4 grams/day), along with other amino acids isoleucine, valine (BCAA 2:1:1, Leucine:Isoleucine:Valine), is essential to maintain fat free mass during weight loss induced by low calorie diet.

Whey Protein

Approximately 300-600 grams of muscle proteins are degraded and resynthesized daily over 24 hours. Food intake stimulates the degree of muscle protein synthesis, resulting in a positive protein balance. After the intake of a meal containing protein, the degree of protein synthesis remains elevated for over 5 hours, with a peak 2-3 hours after intake. It has been shown that in an adult subject to a dose of approximately 15-20 grams of protein (or 7.5 grams of essential amino acids) is sufficient to stimulate the maximization of the degree of muscle protein synthesis [36].

Probably in the elderly to obtain the same maximization of protein synthesis compared to the young, a greater amount of protein is needed, probably 30 grams [37].

In the elderly, the breakdown of the protein requirement is spread over more meals throughout the day, it is not enough to determine a peak plasma amino acid capable of inducing a protein-synthetic stimulus in a muscle tissue that has significantly reduced its sensitivity to that stimulus. Not all food proteins possess the same properties in terms of kinetics: the speed of assimilation of dietary amino acids and their effect on the protein metabolism regulation are a function of the molecular characteristics of the protein [38].

This feature has led to the distinction of food proteins in fast and slow. The intake of fast absorbing proteins may represent an advantage over slowly digesting proteins. Dietary proteins are those in fast absorption of whey protein, which are the beta-globulin fraction, characterized by good digestibility, low lactose content and high biological value.

Hydrolysed proteins are more easily assimilated than intact proteins, hydrolysed proteins obtained from whey (β-globulin fraction) have the highest rate of assimilation [39].

In conclusion, a daily intake of adequate amount of whey protein (average at least 20 grams/day) is beneficial in maintaining fat free mass.

Vitamin D

Vitamin D, by which the muscle has receptors for it [7], plays a key role in muscle activity [40], because it causes an increase in the accumulation of calcium in the sarcoplasmic reticulum by increasing number of receptors that bind calcium and by increasing the efficiency of sites to bind calcium and stimulating the transport across cell membranes phosphate.

A study in animal models [41] has shown that 1,25(OH)2D3 is able to enhance protein synthesis: it enhances the stimulatory effects of insulin and leucine on protein synthesis in myotubes C2C12 cells, it increases the stimulation of the insulin receptor in skeletal muscle cells and stimulates the expression of insulin receptors and the receptor of the same vitamin D (VDR) in skeletal muscle cells ensuring, therefore, a greater sensitivity on the part of C2C12 myotubes to vitamin D and insulin. Following, a further in vitro study confirmed that treatment of C2C12 cells with 25-hydroxyvitamin D (25OHD) and 1,25 dihydroxyvitamin D (1,25 (OH) 2D) alters gene expression with consequent positive effects on the proliferation, differentiation and size of myotubes [42]. In clinical situations the important relationship between Vitamin D and muscle function has been demonstrated in various studies, extremely significant in terms of number of subjects evaluated [43–46], which reported as blood levels of vitamin D are related to the muscle strength, assessed by the hand grip force (using dynamometry). Particularly the Pro.Va study (Veneto project elderly) has been shown, through a follow-up lasted three years, that the subjects who had lower values of vitamin D, had a greater loss of fat free mass and muscle strength [46].

A recent review has shown how low levels of vitamin D are present in many diseases including obesity [47]. In obese subjects there are many reasons that can determine these low serum levels of vitamin D. The vitamin D intake is due for the most part (80-90%) to the skin synthesis of cholecalciferol following exposure to sunlight and so we know how obese subjects barely expose themselves to the sun. Furthermore, although the amount of vitamin D contained in the food is equal to 10-20%, it is completely insufficient, alone, to cover the needs, and in any case the maximum content of vitamin D is present in foods that frequently obese subjects consume in small

quantities due to food habits, tradition and costs [48,49]. Vitamin D is found in good quantities in fish, especially herring (19 mcg / 100 g), fresh tuna (16.3 mcg / 100 g), swordfish, grouper, and anchovies (11 mcg / 100 g).

A recent review [50] showed that daily supplementation with at least 400 IU of vitamin D increases skeletal muscle force an average of 17%. If there is excess fat mass part of it may be sequestered as Vitamin D in this tissue [51].

For this reason, oral supplementation with vitamin D should be recommended in the activated form, calcifediol: it has an elective indication in obesity [52–54]. Calcifediol is available in drops (0.15 mg/mL, where 1 drop contains 5 g). 3–4 drops/day or 20–30 drops/week of calcifediol are generally adequate to restore normal 25(OH)D plasma levels in obese subjects [55,56].

An assessment of blood concentrations of vitamin D is required in the obese patients. In the case of low values of blood vitamin D, less than 30 ng / ml [57], it is mandatory an adequate oral supplementation with calcifediol (3–4 drops/day or 20–30 drops/week) in order to maintain fat free mass.

Conclusion

It is necessary to consider that assessment of obese subjects must necessarily pass through the analysis of body composition [53], which takes into account adipose mass (with quantifying the amount of visceral fat), fat free mass, mineral compartment and fluids.

The results of this review demonstrated that, in order to maintain fat free mass during a low-calorie diet, there are various diet strategies. The comparison of VLCKD with standard low-calorie diet demonstrated that fat free mass was practically unaffected; this is possible for numerous factors, predominantly of hormonal mechanisms, involving the insulin and the IGF-I GH axis which acts by stimulating protein synthesis.

An adequate daily intake of the amino acid leucine (4 grams/day), along with other amino acids isoleucine and valine (BCAA 2:1:1, Leucine:Isoleucine:Valine), and daily intake of adequate

amount of whey protein (average 20 grams/day) is beneficial in maintaining fat free mass during weight loss induced by low calorie diet.

An assessment of blood concentrations of this vitamin is required in the obese patient. In the case of low values of blood vitamin D, less than 30 ng / ml [52], it is mandatory for an adequate supplementation, specifically calcifediol because in the obese subject, this form is recommended to avoid seizure in the adipose tissue.

Table 1 showed the diet strategies useful to maintain the fat free mass during low calorie diet together with the various mechanisms behind these strategies.

Declaration of Interest: None.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Statement of Authorship: SP, MR, VI and MAF equally contributed to the conception and design of the research; MR and RM contributed to the design of the research; GP, GC, DS and MN contributed to the acquisition and analysis of the data; SP contributed to the analysis of the data; VI contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

References

1. Weinheimer EM, Sands LP, Campbell WW. A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. Nutr Rev [Internet]. 2010 [cited 2019 Nov 19];68:375–88. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20591106

2. Wolfe RR. The underappreciated role of muscle in health and disease. Am. J. Clin. Nutr. 2006. p. 475–82.

3. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet (London, England) [Internet]. 2010 [cited 2019 Nov 19];375:2267–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20609972

4. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr. Rev. Endocrine Society; 2002. p. 201–29.

5. Stiegler P, Cunliffe A. The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. Sports Med. 2006. p. 239–62.

6. Pratesi A, Tarantini F, Di Bari M. Skeletal muscle: an endocrine organ. Clin Cases Miner Bone Metab [Internet]. 2013 [cited 2019 Nov 19];10:11–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23858303

7. Bouillon R, Okamura WH, Norman AW, Bouillon R. Structure-Function Relationships in the Vitamin D Endocrine System. Endocr Rev. 1995;16:200–57.

8. Egger M, Smith GD, Altman DG. Systematic reviews in health care : meta-analysis in context [Internet]. BMJ Books; 2001 [cited 2019 Apr 29]. Available from: https://books.google.it/books?hl=it&lr=&id=ErhNdafPCrQC&oi=fnd&pg=PR5&dq=77.%09Egger,+M.%3B+Dickersin,+K.%3B+Smith,+G.+D.+Problems+and+limitations+in+conducting+systematic+reviews.+In+Systematic+Reviews+in+Health+Care:+Meta-Analysis+in+Context,+2nd+edition%3B+M.+Egger,+M.,+Smith,+G.D.,+Altman,+D.G.+BMJ+Publishing+Groups,+London,+UK,+20&ots=2B9YwJWijR&sig=CvrWRWt4o8nOxElrSJwUE5gK-Tk#v=onepage&q&f=false

9. Bueno NB, de Melo ISV, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr [Internet]. 2013 [cited 2019 Nov 19];110:1178–87. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/23651522

10. Bahr M, Chrisostom K, Chrisostom S, Peters N, Thomas P, Patricia Catts, APRN P. A comparative analysis of the ketogenic, paleolithic, and vegan diets. Nurs Undergrad Work [Internet]. 2019 [cited 2019 Nov 20]; Available from: https://digitalshowcase.oru.edu/nurs_undergrad_work/9

11. Merra G, Costa De Miranda R, Fa T, Chang M, De Lorenzo A. Very-low-calorie ketogenic diet with aminoacid supplement versus very low restricted-calorie diet for preserving muscle mass during weight loss: a pilot double-blind study CONSUMPTION OF ULTRA-PROCESSED FOODS AND INDICATORS OF DIET QUALITY IN PORTUGAL View project [Internet]. 2016. Available from: https://www.researchgate.net/publication/305041153

12. Moreno B, Bellido D, Sajoux I, Goday A, Saavedra D, Crujeiras AB, et al. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. Endocrine [Internet]. 2014 [cited 2019 Nov 19];47:793–805. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24584583

13. Moreno B, Crujeiras AB, Bellido D, Sajoux I, Casanueva FF. Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. Endocrine [Internet]. 2016 [cited 2019 Nov 19];54:681–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27623967

14. Stafstrom CE, Rho JM. The ketogenic diet as a treatment paradigm for diverse neurological disorders. Front Pharmacol. 2012;3 APR.

15. Deng-Bryant Y, Prins ML, Hovda DA, Harris NG. Ketogenic Diet Prevents Alterations in Brain Metabolism in Young but not Adult Rats after Traumatic Brain Injury. J Neurotrauma [Internet]. 2011 [cited 2019 Nov 20];28:1813–25. Available from: http://www.liebertpub.com/doi/10.1089/neu.2011.1822

16. Cheng B, Yang X, An L, Gao B, Liu X, Liu S. Ketogenic diet protects dopaminergic neurons against 6-OHDA neurotoxicity via up-regulating glutathione in a rat model of Parkinson's disease. Brain Res. 2009;1286:25–31.

17. de la Rubia Ortí JE, García-Pardo MP, Drehmer E, Sancho Cantus D, Julián Rochina M, Aguilar MA, et al. Improvement of Main Cognitive Functions in Patients with Alzheimer's Disease after Treatment with Coconut Oil Enriched Mediterranean Diet: A Pilot Study. J Alzheimers Dis. NLM (Medline); 2018;65:577–87.

18. Benlloch M, López-Rodríguez MM, Cuerda-Ballester M, Drehmer E, Carrera S, Ceron JJ, et al. Satiating effect of a ketogenic diet and its impact on muscle improvement and oxidation state in multiple sclerosis patients. Nutrients. 2019;11:1–14.

19. Manninen AH. Very-low-carbohydrate diets and preservation of muscle mass. Nutr Metab (Lond) [Internet]. 2006 [cited 2019 Nov 19];3:9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16448570

20. Paoli A, Canato M, Toniolo L, Bargossi AM, Neri M, Mediati M, et al. [The ketogenic diet: an underappreciated therapeutic option?]. Clin. Ter. 2011.

21. Mammucari C, Schiaffino S, Sandri M. Downstream of Akt: FoxO3 and mTOR in the regulation of autophagy in skeletal muscle. Autophagy [Internet]. 2008 [cited 2019 Nov 19];4:524–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18367868

22. Sandri M. Signaling in muscle atrophy and hypertrophy. Physiology. 2008. p. 160–70.

23. Sandri M, Barberi L, Bijlsma AY, Blaauw B, Dyar KA, Milan G, et al. Signalling pathways regulating muscle mass in ageing skeletal muscle. the role of the IGF1-Akt-mTOR-FoxO pathway. Biogerontology. 2013;14:303–23.

24. Bennett SL, Smith AH, Ramirez L, Thomson DM. Effects of ketogenic diet on p70s6k phosphorylation in young adult and old soleus muscle. FASEB J. 2019;33.

25. Motil KJ, Matthews DE, Bier DM. Whole-body leucine and lysine metabolism: Response to dietary protein intake in young men. Am J Physiol - Endocrinol Metab. 1981;3.

26. Paddon-Jones D, Sheffield-Moore M, Zhang X-J, Volpi E, Wolf SE, Aarsland A, et al. Amino acid ingestion improves muscle protein synthesis in the young and elderly. Am J Physiol Endocrinol Metab [Internet]. 2004 [cited 2019 Nov 19];286:E321-8. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/14583440

27. Layman DK, Evans E, Baum JI, Seyler J, Erickson DJ, Boileau RA. Dietary Protein and Exercise Have Additive Effects on Body Composition during Weight Loss in Adult Women. J Nutr. Oxford University Press (OUP); 2005;135:1903–10.

28. Layman DK, Walker DA. Potential Importance of Leucine in Treatment of Obesity and the Metabolic Syndrome. J Nutr. Oxford University Press (OUP); 2006;136:319S–323S.

29. Caprio M, Infante M, Moriconi E, Armani A, Fabbri A, Mantovani G, et al. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE). J Endocrinol Invest. 2019;1365–86.

30. Brinkworth GD, Buckley JD, Noakes M, Clifton PM, Wilson CJ. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. Arch Intern Med. 2009;169:1873–80.

31. Riazi R, Wykes LJ, Ball RO, Pencharz PB. The Total Branched-Chain Amino Acid Requirement in Young Healthy Adult Men Determined by Indicator Amino Acid Oxidation by Use of l-[1-13C]Phenylalanine. J Nutr [Internet]. 2003 [cited 2019 Nov 20];133:1383–9. Available from: https://academic.oup.com/jn/article/133/5/1383/4558602

32. Kimball SR, Jefferson LS. Signaling Pathways and Molecular Mechanisms through which Branched-Chain Amino Acids Mediate Translational Control of Protein Synthesis. J Nutr. Oxford University Press (OUP); 2006;136:227S–231S.

33. Northon LE. Leucine is a critical factor determining protein quantity and quality of a complete meal to initiate muscle protein synthesis: University of Illinois Dissertations and Theses. 2010.

34. Glynn EL, Fry CS, Drummond MJ, Timmerman KL, Dhanani S, Volpi E, et al. Excess Leucine Intake Enhances Muscle Anabolic Signaling but Not Net Protein Anabolism in Young Men and Women. J Nutr [Internet]. 2010 [cited 2019 Nov 20];140:1970–6. Available from: https://academic.oup.com/jn/article/140/11/1970/4630508

35. Layman DK. The Role of Leucine in Weight Loss Diets and Glucose Homeostasis. J Nutr. Oxford University Press (OUP); 2003;133:261S–267S.

36. Phillips SM, Tang JE, Moore DR. The role of milk- and soy-based protein in support of muscle protein synthesis and muscle protein accretion in young and elderly persons. J Am Coll Nutr. 2009;28:343–54.

37. Pennings B, Groen B, de Lange A, Gijsen AP, Zorenc AH, Senden JMG, et al. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. Am J Physiol - Endocrinol Metab. 2012;302.

38. Tang JE, Phillips SM. Maximizing muscle protein anabolism: The role of protein quality. Curr. Opin. Clin. Nutr. Metab. Care. 2009. p. 66–71.

39. Etzel MR. Manufacture and Use of Dairy Protein Fractions. J Nutr. Oxford University Press (OUP); 2004;134:996S–1002S.

40. Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. Calcif Tissue Int [Internet]. 2013 [cited 2019 Nov 20];92:151–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22968766

41. Salles J, Chanet A, Giraudet C, Patrac V, Pierre P, Jourdan M, et al. 1,25(OH)2-vitamin D3 enhances the stimulating effect of leucine and insulin on protein synthesis rate through Akt/PKB and mTOR mediated pathways in murine C2C12 skeletal myotubes. Mol Nutr Food Res [Internet]. 2013 [cited 2019 Nov 20];57:2137–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23929734

42. Girgis CM, Clifton-Bligh RJ, Mokbel N, Cheng K, Gunton JE. Vitamin D signaling regulates proliferation, differentiation, and myotube size in C2C12 skeletal muscle cells. Endocrinology [Internet]. 2014 [cited 2019 Nov 20];155:347–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24280059

43. Houston DK, Tooze JA, Davis CC, Chaves PHM, Hirsch CH, Robbins JA, et al. Serum 25-hydroxyvitamin D and physical function in older adults: the Cardiovascular Health Study All Stars. J Am Geriatr Soc [Internet]. 2011 [cited 2019 Nov 20];59:1793–801. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/22091492

44. Houston DK, Cesari M, Ferrucci L, Cherubini A, Maggio D, Bartali B, et al. Association between vitamin D status and physical performance: The inCHIANTI study. Journals Gerontol - Ser A Biol Sci Med Sci. Gerontological Society of America; 2007;62:440–6.

45. Hirani V, Naganathan V, Cumming RG, Blyth F, Le Couteur DG, Handelsman DJ, et al. Associations between frailty and serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations in older Australian men: the Concord Health and Ageing in Men Project. J Gerontol A Biol Sci Med Sci [Internet]. 2013 [cited 2019 Nov 20];68:1112–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23657973

46. Toffanello ED, Perissinotto E, Sergi G, Zambon S, Musacchio E, Maggi S, et al. Vitamin D and physical performance in elderly subjects: the Pro.V.A study. PLoS One [Internet]. 2012 [cited 2019 Nov 20];7:e34950. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22539952

47. Matysiak-Luśnia K. Vitamin D in critically ill patients. Anaesthesiol Intensive Ther [Internet]. 2016 [cited 2019 Nov 20];48:201–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27444873

48. Gil JM, Takourabt S. Socio-economics, food habits and the prevalence of childhood obesity in Spain. Child Care Health Dev [Internet]. 2017 [cited 2019 Nov 20];43:250–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27676318

49. Andreeva VA, Allès B, Feron G, Gonzalez R, Sulmont-Rossé C, Galan P, et al. Sex-Specific Sociodemographic Correlates of Dietary Patterns in a Large Sample of French Elderly Individuals. Nutrients [Internet]. 2016 [cited 2019 Nov 20];8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27509523

50. Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, et al. The Effects of Vitamin D on Skeletal Muscle Strength, Muscle Mass, and Muscle Power: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Endocrinol Metab [Internet]. 2014 [cited 2019 Nov 20];99:4336–45. Available from:

https://academic.oup.com/jcem/article/99/11/4336/2836764

51. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr [Internet]. 2008 [cited 2019 Aug 20];88:491S–499S. Available from: https://academic.oup.com/ajcn/article/88/2/491S/4649916

52. Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, et al. The urgent need to recommend an intake of vitamin D that is effective. Am J Clin Nutr. United States; 2007. p. 649–50.

53. Di Nisio A, De Toni L, Sabovic I, Rocca MS, De Filippis V, Opocher G, et al. Impaired Release of Vitamin D in Dysfunctional Adipose Tissue: New Cues on Vitamin D Supplementation in Obesity. J Clin Endocrinol Metab [Internet]. 2017 [cited 2019 Nov 20];102:2564–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28187222

54. Cesareo R, Attanasio R, Caputo M, Castello R, Chiodini I, Falchetti A, et al. Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE) Position Statement: Clinical Management of Vitamin D Deficiency in Adults. Nutrients [Internet]. 2018 [cited 2019 Nov 20];10:546. Available from: http://www.mdpi.com/2072-6643/10/5/546

55. Cashman KD, Seamans KM, Lucey AJ, Stöcklin E, Weber P, Kiely M, et al. Relative effectiveness of oral 25-hydroxyvitamin D3 and vitamin D3 in raising wintertime serum 25-hydroxyvitamin D in older adults. Am J Clin Nutr [Internet]. 2012 [cited 2019 Nov 20];95:1350–6. Available from: https://academic.oup.com/ajcn/article/95/6/1350/4568381

56. Shieh A, Ma C, Chun RF, Witzel S, Rafison B, Contreras HTM, et al. Effects of Cholecalciferol vs Calcifediol on Total and Free 25-Hydroxyvitamin D and Parathyroid Hormone. J Clin Endocrinol Metab [Internet]. 2017 [cited 2019 Nov 20];102:1133–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28187226

57. Tanamas SK, Lean MEJ, Combet E, Vlassopoulos A, Zimmet PZ, Peeters A. Changing guards: time to move beyond body mass index for population monitoring of excess adiposity. QJM

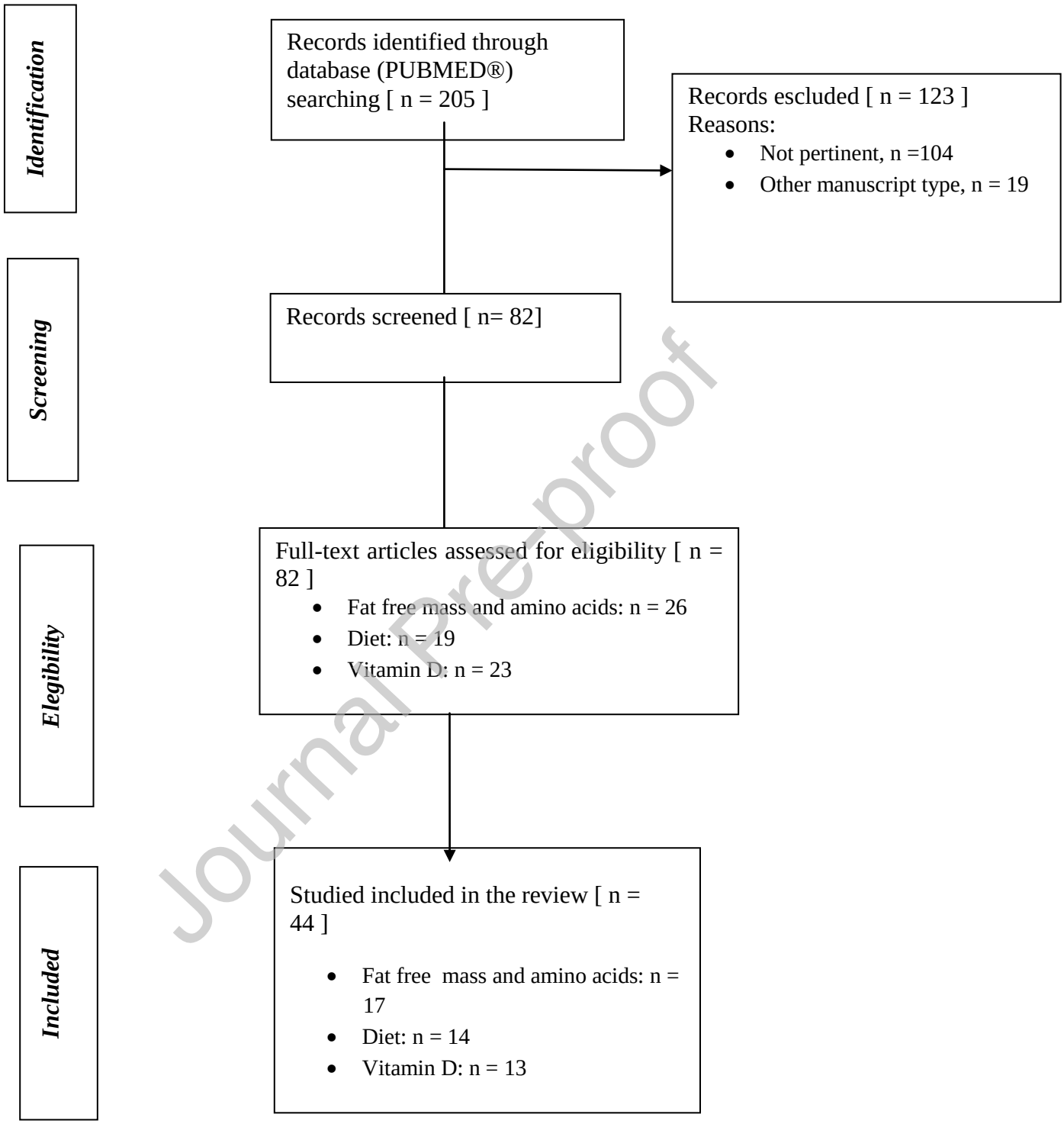
[Internet]. 2016 [cited 2019 Nov 20];109:443–6. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/26527773

Table 1. Strategies useful to maintain the fat free mass during low calorie diet together with the various mechanisms behind these strategies

Pivotal strategies	Mechanisms
Adopt a Very-Low carbohydrates ketogenic diet (VLCKD)	- the adrenergic stimulation by the protein and by low levels of sugar in the blood inhibits the proteolysis of skeletal muscle; - the formation of ketone bodies suppresses the use of protein-derived amino acids by muscle; - the beta-hydroxybutyrate decreases leucine oxidation and promotes protein synthesis; - increased availability of dietary protein causes an increase in IGF-1 in muscle;
Vitamin D	- causes an increase in the accumulation of calcium in the sarcoplasmic reticulum by increasing number of receptors that bind calcium and by increasing the efficiency of sites to bind calcium and stimulating the transport across cell membranes phosphate. This activity leads to muscle cell proliferation and differentiation;
Leucine	- has an anabolic effect by increasing protein synthesis and/or a reducing the rate of protein degradation, resulting in a positive net muscle protein balance;
Whey proteins	- are characterized by good digestibility, low lactose content and high biological value; - have the highest rate of assimilation;

Figure 1. Flow chart of the studies evaluated.



Very-Low-Calorie Ketogenic Diets With Whey, Vegetable, or Animal Protein in Patients With Obesity: A Randomized Pilot Study

Sabrina Basciani,[1] Elisabetta Camajani,[1,*] Savina Contini,[1,*] Agnese Persichetti,[2,*] Renata Risi,[1] Loris Bertoldi,[3] Lidia Strigari,[4] Giancarlo Prossomariti,[1] Mikiko Watanabe,[1] Stefania Mariani,[1] Carla Lubrano,[1] Alfredo Genco,[5] Giovanni Spera,[1] and Lucio Gnessi[1]

[1]Department of Experimental Medicine, University of Rome "La Sapienza," Rome, Italy; [2]Service of Pharmacovigilance, IRCCS-Regina Elena National Cancer Institute, Rome, Italy; [3]BMR Genomics s.r.l., Padova, Italy; [4]Department of Medical Physics, Policlinico S. Orsola-Malpighi, Bologna, Italy; and [5]Department of Surgical Sciences, Surgical Endoscopy Unit, University of Rome "La Sapienza," Rome, Italy

ORCiD numbers: 0000-0003-2225-8814 (M. Watanabe); 0000-0001-8217-2372 (L. Gnessi).

Context. We compared the efficacy, safety, and effect of 45-day isocaloric very-low-calorie ketogenic diets (VLCKDs) incorporating whey, vegetable, or animal protein on the microbiota in patients with obesity and insulin resistance to test the hypothesis that protein source may modulate the response to VLCKD interventions.

Subjects and Methods. Forty-eight patients with obesity (19 males and 29 females, homeostatic model assessment (HOMA) index ≥ 2.5, aged 56.2 ± 6.1 years, body mass index [BMI] 35.9 ± 4.1 kg/m^2) were randomly assigned to three 45-day isocaloric VLCKD regimens (≤800 kcal/day) containing whey, plant, or animal protein. Anthropometric indexes; blood and urine chemistry, including parameters of kidney, liver, glucose, and lipid metabolism; body composition; muscle strength; and taxonomic composition of the gut microbiome were assessed. Adverse events were also recorded.

Results. Body weight, BMI, blood pressure, waist circumference, HOMA index, insulin, and total and low-density lipoprotein cholesterol decreased in all patients. Patients who consumed whey protein had a more pronounced improvement in muscle strength. The markers of renal function worsened slightly in the animal protein group. A decrease in the relative abundance of Firmicutes and an increase in Bacteroidetes were observed after the consumption of VLCKDs. This pattern was less pronounced in patients consuming animal protein.

Conclusions. VLCKDs led to significant weight loss and a striking improvement in metabolic parameters over a 45-day period. VLCKDs based on whey or vegetable protein have a safer profile and result in a healthier microbiota composition than those containing animal proteins. VLCKDs incorporating whey protein are more effective in maintaining muscle performance. **(*J Clin Endocrinol Metab* 105: 2939–2949, 2020)**

Key Words: very low calorie ketogenic diet, VLCKD, obesity, whey proteins, vegetable proteins, animal proteins, intestinal microbiota, therapy

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 16 January 2020. Accepted 26 May 2020.
First Published Online 2 June 2020.
Corrected and Typeset 16 July 2020.

Obesity is strongly related to comorbidities, such as type 2 diabetes (T2D), inflammation, excess fat within the liver and pancreas, hypertension, and certain

*These authors contributed equally to this work.

types of cancer (1,2). Obesity management can delay the progression from prediabetes to T2D and result in sustained remission of T2D (3).

For many individuals with obesity and prediabetes, weight loss produces beneficial outcomes in regard to glycemic control, lipids, and blood pressure (BP), and more intensive weight loss maximizes these benefits (3,4). Despite the agreement on the important role of diet in treating insulin resistance and T2D, there is little consensus about the optimal diet and ideal dietary macronutrient ratio (5). Weight loss and improvement in glucose homeostasis, including diabetes remission, were seen both after the consumption of a low-energy diet (825-853 kcal/day) with a carbohydrate content that exceeded 50% of total calories (3) and after the consumption of very-low-calorie diets (≤800 kcal/day) containing less than 30% carbohydrates/day (6). Recently, very-low-calorie ketogenic diets (VLCKDs) with <50 g of carbohydrates/day were found to be associated with greater weight loss along with amelioration of glycemic control in subjects with T2D compared with the effects of a standard care nutritional intervention (7-11). In patients with obesity who did not have diabetes, the effects of VLCKDs were found to be powerful in reducing plasma insulin levels (5). Furthermore, the source of dietary protein while following an energy-restricted diet was associated with benefits in body weight (BW) maintenance, BP, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) (12). Epidemiological studies indicate that diets containing whey proteins and vegetable proteins protect against obesity, whereas diets characterized by increased meat consumption are associated with greater weight gain (13). The mechanisms underlying these effects are not known. Interactions with the intestinal microbiota (14), appetite regulation (15,16), effects on insulin and incretin secretion (17-20), and palatability (19,21) have been suggested as contributing factors that deserve in-depth analysis (22). We conducted a prospective pilot study comparing the efficacy and safety of VLCKDs incorporating either whey, plant, or animal protein on metabolic and body composition parameters and on the composition of the gut microbiota in a population of patients with obesity and insulin resistance.

Materials and Methods

Study design and participants

This was a prospective, open, nutritional intervention pilot study that enrolled patients with obesity and pharmacologically naïve insulin resistance among those attending the Center for the Study of Eating Disorders and Obesity, Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology of the University of Rome "La Sapienza," Italy. We compared VLCKDs based on whey protein (16 patients, whey protein group [WPG]), vegetable protein (16 patients, vegetable protein group [VPG]), or animal protein (16 patients, animal protein group [APG]). Eligible patients were randomly assigned (in a 1:1:1 ratio) through automated allocation. The primary outcome measure was change in body mass index (BMI). Key secondary outcomes were changes in lipids, glucose, insulin resistance as estimated by HOMA-IR, IGF-1, body composition, muscle strength, and composition of the gut microbiota. Male and postmenopausal female outpatients were eligible. The inclusion criteria were as follows: stable BW in the previous 3 months, age between 50 and 70 years, BMI between 30 and 40 kg/m2, and HOMA-IR ≥ 2.5. The exclusion criteria were the following conditions either self-reported or derived from medical records or examination: hypersensitivity to components used in the protocol products; renal, cardiac, cerebrovascular, or gastrointestinal diseases; psychiatric disturbances; hydroelectrolytic alterations; type 1 diabetes; lack of informed consent; and bariatric surgery. Adverse events (AEs) were monitored throughout the treatment. This trial was registered at clinicaltrials.gov (NCT04019431).

Dietary interventions

All patients followed a VLCKD (780 kcal/day) for 45 days, with the following composition in macronutrients, percentage of caloric intake, and g/kg of ideal BW of proteins (derived by the BMI set at 25 kg/m^2): carbohydrates, 26 g (13.5%); olive oil, 20 g plus 15 g of lipids from other sources (40.4%); protein, 90 g (46.1%, 1.2-1.4 g/kg). The amount of protein was within the proposed essential composition of total diet replacements for weight control and was adjusted for the patients with overweight or obesity (23). WPG and VPG patients were given 5 meals/day (timing was at main meals [8:00 AM, 1:00 PM, and 8:00 PM], mid-morning, and mid-afternoon) containing whey protein (WPG) or vegetable protein derived from soya, green peas, or cereals and 1 serving of vegetables with a low glycemic index at lunch and dinner (VPG). Patients in the APG were given 5 meals/day containing natural animal protein (meat, fish, eggs). Supplements containing vitamins, minerals, and omega-3 fatty acids were provided in accordance with international recommendations (24). The diets were prepared by New Penta s.r.l. (Cuneo, Italy) following the indications of nutritionists and were delivered in preassembled boxes.

Participants received counseling by physicians and nutrition experts at baseline (T0) and every 2 weeks up to day 45 (T45); dietary compliance was also assessed. Participants were encouraged to exercise for 30 min at least 3 times weekly, but no formal exercise program or incentives were provided.

Anthropometric assessment

BW, height, systolic and diastolic BP, waist circumference (WC), thigh circumference (TC), and hip circumference (HC) were measured at T0 and every 2 weeks. Anthropometric measurements were recorded after an overnight fast under resting conditions using calibrated equipment. BW was measured using a balance-beam scale (Seca GmbH & Co). Systolic and diastolic BP were measured using a mercury-gravity manometer. Height was rounded to the closest 0.5 cm. BMI was calculated as weight divided by squared height in meters (kg/

m^2). WC was measured midway between the costal arch and the iliac crest, HC was measured at the symphysis-greater trochanter level to the closest 1 cm, and TC was measured directly below the gluteal fold of the right thigh.

Blood and urine chemistry

Blood count (ADVIA 2120i Hematology System, Siemens Healthcare s.r.l., Italy), electrolytes (chloride, potassium, and sodium: indirect ion-selective electrode potentiometry; calcium, and magnesium: colorimetric assay]), glucose (enzymatic colorimetric assay), insulin (electrochemiluminescence immunoassay), lipids (triglycerides, total, high-density lipoprotein, and low-density lipoprotein cholesterol; enzymatic colorimetric assay), total protein and albumin (capillary system), C-reactive protein (immunoturbidimetric assay), erythrocyte sedimentation rate (capillary photometric assay), plasma creatinine (kinetic colorimetric compensated Jaffé method), blood urea nitrogen (BUN), uric acid, alanine transferase, and aspartate transaminase (enzymatic colorimetric assay), and estimated glomerular filtration rate (eGFR) were determined at baseline and T45. All analyses were performed on a COBAS 6000 (Roche Diagnostics, Risch-Rotkreuz, Switzerland) and on CapillarysR Systems (Sebia, Evry, France).

The hepatic steatosis index, a noninvasive screening tool for hepatic steatosis, was calculated according to Lee et al (25). Insulin-like growth factor 1 (IGF-1) plasma levels were measured after an overnight fast using commercial enzyme-linked immunosorbent assay kits (R&D Systems, Inc., Minneapolis, MN, US). Insulin resistance was determined using HOMA-IR (26). The semiquantitative concentration of acetoacetic acid was measured in the first morning urine at baseline and every week until the end of the study by the patients (Ketur-Test, Accu-Chek, Roche Diagnostics, Italy).

Dual-energy X-ray absorptiometry measurement

Body composition, total and regional body fat mass, and fat-free mass were measured by dual-energy X-ray absorptiometry (Hologic 4500, Bedford, MA, US) at baseline and at the end of the trial. Trunk fat was defined as the adipose tissue localized within the region below the chin, delineated by vertical lines within the left and right glenoid fossae bordering laterally to the ribs and by the oblique lines that cross the femoral necks and converge below the pubic symphysis.

Muscular strength

Handgrip strength (HG) was measured with a digital dynamometer (DynEx, Akern, Pontassieve, FI, Italy) at T0 and T45 with the patients seated, shoulder adducted, and forearms resting flat on the chair arms. Before starting, patients were asked to squeeze the dynamometer as hard as possible for at least 3 s. Three measurements were repeated with both the dominant and nondominant arms. The highest value measured was recorded.

Taxonomic composition of the gut microbiome

Fecal sampling was performed using a sterile swab (FLmedical, Italy) and tubes (Starlab Group, Italy) in the morning of the day of initiating the VLCKD and at T45; the samples were put on ice immediately after collection, brought to the hospital within 2 h, and stored at −80°C. The samples were transferred to the laboratory on dry ice within 24 h of collection and stored at −80°C until deoxyribonucleic acid extraction. Deoxyribonucleic acid was extracted using the Cador Pathogen 96 QIAcube HT Kit (Qiagen s.r.l., Italy) with lysis step modification according to the Mobio PowerFecal kit (Qiagen). The V3-V4 regions of the 16S ribosomal ribonucleic acid gene were amplified using the Illumina tailed primers Pro341F (5'-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAG-CCTACGGG AGGCAGCA-3′) and Pro805R (5'-GTCTCGTGGGCTCGGAGATGTGTATAAGAGA CAGGACTACNVGGGTATCTAATCC-3′) using Platinum Taq (Thermo Fisher Scientific Inc, US) to conduct PCR (94°C for 2 min, followed by 25 cycles at 94°C for 30 s, 55°C for 30 s, and 68°C for 30 s, and a final extension at 68°C for 7 min). Polymerase chain reaction amplicons were purified with Agencourt AMPure XP Beads 0.8X (Beckman Coulter, Inc., CA, US) and amplified following the Nextera XT Index protocol (Illumina, Inc., CA, US). The purified amplicons were normalized by SequalPrep™ Normalization Plate Kit (Thermo Fisher Scientific Inc.) and multiplexed. The pool was purified with 1X Magnetic Beads Agencourt XP (Beckman Coulter, Inc.) loaded on the MiSeq System (Illumina, Inc.) and sequenced following the V3-300PE strategy. The bioinformatic analysis was performed by Qiime2 (27). Raw reads were first trimmed by applying Cutadapt to remove residual primer sequences and then processed with DADA2 plug-in to perform the denoising step (28,29). DADA2 was run with default parameters except for the truncation length: forward and reverse reads were truncated at 270 and 260 nucleotides, respectively. The resulting amplicon sequence variant sequences were filtered out by applying a 0.005% frequency threshold to discard singletons and very rare sequences. Greengeens v0.13–8 and Silva v0.132 databases were used to associate the taxonomy to the remaining amplicon sequence variants.

Questionnaires

Adherence to the dietary interventions was evaluated through a daily food diary. Safety was monitored throughout the trial based on the reported AEs either collected spontaneously or actively assessed by the investigators. Quality of life was assessed through the SF-36 questionnaire every 2 weeks. Vivacity, agitation, sadness, calmness, energy, discouragement, happiness, and satiety were evaluated using a 5-point scale.

Data management and statistical methods

Data are expressed as the mean values ± standard deviations or percentages where appropriate. Comparisons between groups were evaluated using Student's *t* test. Differences between groups were tested by analysis of variance, and for differences 0-45, an analysis of covariance model was used when a significant group effect was observed. A Tukey post hoc test was used for multiple-comparison purposes in the case of *F* significant values. The number of subjects was identified considering the number of subjects generally included in similar published pilot studies (30-33). Assuming a power of 0.80 and alpha of 0.05, 48 participants (total sample size, 16 participants in each of 3 groups) were considered appropriate to highlight an effect size of 0.46 (high). Differences were considered statistically significant when P was ≤0.05. Since this was a pilot study, we also reported values with $P < 0.1$ as

"trending toward significance." Statistical analysis was carried out using R-package version 3.6.3.

Ethical aspects

The study protocol was approved by the Ethics Committee of the University of Rome "La Sapienza" (code 3920) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients were informed about the possible risks and benefits of the proposed interventions and provided written consent.

Results

We screened 350 patients with obesity for eligibility from January 2019 to June 2019. We enrolled and randomized 48 participants. Sixteen patients were allocated to the VLCKD with whey protein (WPG), 16 to the VLCKD with vegetable protein (VPG), and 16 to the VLCKD with animal protein (APG) (Fig. 1). All the participants were followed up to the completion of the study. The baseline characteristics of the patients were similar between groups and are summarized in Table 1. Compliance was comparable in all groups. Urine acetoacetic acid, reflecting ketosis, increased significantly from baseline to the end of the VLCKD interventions (Table 1), and a plateau value was reached after 7 days in all groups (data not shown).

We recorded a significant reduction in initial BW both in the WPG and the VPG at T45. A reduction in BW was also observed in the APG (−6.4 ± 2.4 kg compared to baseline; range: −2.0 to −11.1 kg; average percentage BW loss: −6.5%), although it did not reach statistical significance. BMI followed the same pattern, with the exception that the improvement in BMI was statistically significant in the APG as well. Significant reductions in WC and systolic and diastolic BP were recorded in all groups. HC and TC reductions were observed in all groups and reached significance in the VPG and APG and in the WPG and VPG, respectively.

A significant reduction in fasting glycemia, fasting insulin, and HOMA-IR was observed in all groups, with the exception of fasting glycemia in the VPG. Circulating IGF-1 levels increased in the WPG and decreased in the VPG. The increase in IGF-1 seen in the APG was not statistically significant.

A decreasing trend in total fat and trunk fat mass was consistently recorded, although the significance was seen only for trunk fat mass in the WPG and the VPG. A relative increase in the percentage of lean mass was also seen consistently. Electrolytes (data not shown) and liver function tests did not change during the study within groups. Small, nonsignificant variations in plasma creatinine values were observed in all groups. Of note, in the APG, BUN and uric acid increased while eGFR decreased significantly compared with baseline. Urinary pH values varied within the normal reference intervals (data not shown). At the baseline visit, no ketosis was recorded. The mean values of urinary acetoacetic acid increased from T0 to T45 in all groups (Table 1).

The hepatic steatosis index was slightly reduced at T45; however, the difference was significant only for VPG. All groups experienced a profound reduction in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Despite a strong improvement in the inflammatory markers erythrocyte sedimentation rate and C-reactive protein, changes in these measures did not show statistical significance. HG did not change during the observation period in any of the groups.

The *P* values of multiple comparisons of delta percentage variations in the measured parameters between groups that were statistically significant are shown in Table 2. No differences were seen for the majority of parameters, with the exception of IGF-1, creatinine, eGFR, blood urea, uric acid, and HG, whose variations differed between groups. Fig. 2 shows the box plot of the within-group percentage change values from baseline. Although the variations remained within the

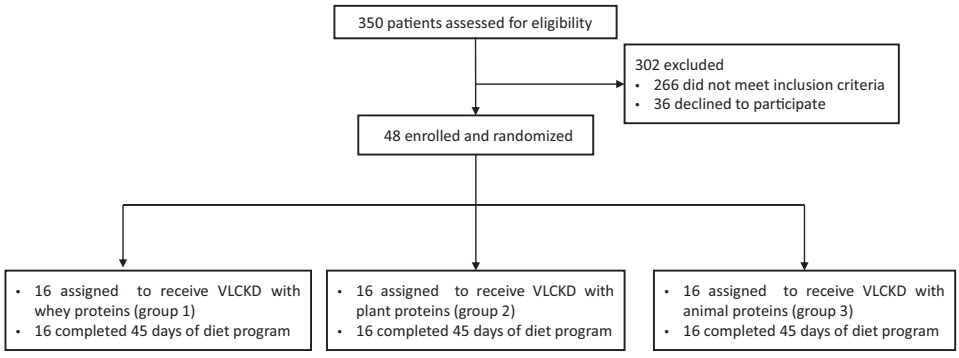


Figure 1. Flow diagram of the study. A total of 350 individuals were screened. The subjects enrolled were randomized to either a VLCKD dietary intervention group with whey protein, a VLCKD dietary intervention group with vegetable protein, or a VLCKD dietary intervention group with animal protein.

Table 1. Participant characteristics at baseline (T0) and after 45 days (T45) of VLCKD consumption

	WPG			VPG			APG		
	T0	T45	*P*	T0	T45	*P*	T0	T45	*P*
BW (kg)	102.02 ± 12.04	94.05 ± 11.43	**0.032**	102.10 ± 12.36	94.08 ± 11.92	**0.041**	98.36 ± 14.49	91.72 ± 14.48	0.106
BMI (kg/m^2)	35.8 ± 5.0	32.6 ± 4.8	**0.035**	36.1 ± 4.3	32.9 ± 4.0	**0.020**	35.7 ± 3.7	32.8 ± 3.7	**0.016**
WC (cm)	110.0 ± 9.4	102.8 ± 8.4	**0.014**	108.2 ± 8.5	102.5 ± 7.6	**0.031**	105.3 ± 9.1	99.1 ± 10.2	**0.040**
HC (cm)	123.6 ± 12.1	117.9 ± 12.2	0.098	123.3 ± 9.3	117.9 ± 8.4	**0.049**	122.5 ± 10.6	116.1 ± 10.3	**0.047**
TC (cm)	63.6 ± 5.3	59.7 ± 5.2	**0.022**	64.1 ± 5.3	60.5 ± 5.9	**0.043**	65.4 ± 7.2	62.1 ± 6.6	0.091
Arm circumference (cm)	36.6 ± 3.9	34.6 ± 3.7	0.072	36.3 ± 3.7	34.5 ± 3.4	0.083	37.7 ± 3.0	35.6 ± 2.9	**0.029**
Systolic BP (mmHg)	132 ± 10	124 ± 13	**0.032**	131 ± 8	121 ± 10	**0.005**	129 ± 9	121 ± 16	**0.036**
Diastolic BP (mmHg)	78 ± 11	70 ± 9	**0.020**	78 ± 10	72 ± 10	**0.030**	78 ± 10	71 ± 9	**0.014**
Fasting glycemia mg/dL	108.1 ± 22.3	94.1 ± 11.4	**0.017**	106.5 ± 17.6	100.9 ± 17.6	0.193	99.7 ± 12.9	92.6 ± 9.2	**0.042**
Fasting insulin (μIU/ml)	25.0 ± 18.9	8.5 ± 4.1	**0.001**	19.4 ± 7.4	8.3 ± 4.7	**0.000**	17.7 ± 8.7	6.8 ± 4.1	**0.000**
HOMA-IR (ng/ml)	4.15 ± 1.34	2.1 ± 1.2	**0.004**	5.1 ± 2.0	2.1 ± 1.2	**0.000**	4.05 ± 1.72	1.6 ± 1.1	**0.000**
IGF-1 (ng/ml)	141.4 ± 15.91	167.46 ± 43.15	**0.018**	159.82 ± 19.25	116.52 ± 22.05	**0.000**	132.88 ± 26.92	148.86 ± 32.15	0.160
Creatinine (mg/dl)	0.90 ± 0.30	0.79 ± 0.22	0.12	0.78 ± 0.17	0.78 ± 0.15	0.465	0.80 ± 0.16	0.86 ± 0.19	0.163
BUN (mg/dl)	39.0 ± 12.5	38.5 ± 13.9	0.466	40.0 ± 13.1	37.4 ± 12.1	0.281	39.3 ± 6.8	48.0 ± 14.4	**0.019**
eGFR (ml/min)	131.9 ± 42.9	136.6 ± 56.1	0.395	146.4 ± 33.3	131.4 ± 26.8	0.091	134.8 ± 33.2	115.6 ± 30.2	**0.049**
Proteins (g/L)	74.3 ± 4.0	71.8 ± 2.9	**0.028**	75.0 ± 3.5	74.0 ± 4.1	0.237	74.3 ± 4.4	72.2 ± 3.5	0.070
Albumin (g/L)	44.13 ± 2.43	43.71 ± 2.90	0.328	44.55 ± 2.76	43.98 ± 2.69	0.283	44.68 ± 2.71	44.22 ± 1.91	0.293
AST (U/L)	23.8 ± 13.0	19.9 ± 5.8	0.146	25.3 ± 13.2	26.8 ± 14.0	0.385	19.8 ± 4.7	19.9 ± 3.7	0.450
ALT (U/L)	31.1 ± 15.4	24.0 ± 9.3	0.062	35.0 ± 24.0	35.5 ± 26.9	0.479	23.8 ± 7.0	21.6 ± 4.9	0.151
HSI	44.0 ± 5.1	41.6 ± 5.4	0.101	44.1 ± 5.4	40.9 ± 5.2	0.049	44.3 ± 4.4	42.1 ± 4.1	0.077
Uric acid (mg/dl)	5.4 ± 1.1	5.1 ± 1.4	0.257	5.2 ± 1.0	5.8 ± 1.1	0.072	4.9 ± 1.0	5.6 ± 0.8	**0.021**
CRP (μg/L)	4700 ± 6740	2662 ± 2414	0.132	7050 ± 5959	5913 ± 6435	0.307	5156 ± 4820	4087 ± 3383	0.237
ESR (mm/h)	26.8 ± 16.0	28.5 ± 15.8	0.379	28.0 ± 17.9	25.7 ± 17.1	0.357	28.8 ± 15.8	26.1 ± 12.1	0.292
Total cholesterol (mg/dl)	214.8 ± 31.5	166.2 ± 43.6	**0.001**	220.9 ± 51.6	170.7 ± 36.3	**0.002**	226.9 ± 32.7	191.2 ± 34.2	**0.003**
LDL cholesterol (mg/dl)	132.8 ± 30.8	100.8 ± 38.4	**0.008**	136.1 ± 41.3	97.5 ± 32.3	**0.004**	143.9 ± 25.8	118.5 ± 23.1	**0.003**
Triglycerides (mg/dl)	131.0 ± 44.9	94.6 ± 32.0	**0.007**	170.1 ± 126.9	117.6 ± 42.7	0.069	124.25 ± 58	82.25 ± 33.32	**0.009**
HDL cholesterol (mg/dl)	51.7 ± 12.3	46.1 ± 7.5	0.072	51.2 ± 12.8	49.0 ± 9.5	0.298	57.9 ± 23.7	56.2 ± 18.0	0.408
Urine acetoacetic acid (mg/dL)	1.8 ± 0.8	56.3 ± 31.3	**0.000**	1.8 ± 0.7	41.1 ± 15.4	**0.000**	1.6 ± 0.7	44.8 ± 15.3	**0.000**
Total fat (kg)	36.74 ± 10.83	31.92 ± 10.19	0.102	37.40 ± 7.77	32.00 ± 7.51	0.081	37.00 ± 8.23	32.85 ± 8.88	0.094
Total lean (kg)	62.95 ± 9.04	59.93 ± 7.66	0.158	62.32 ± 1.04	59.70 ± 10.02	0.246	57.24 ± 9.21	56.59 ± 12.18	0.434
Total fat (%)	35.71 ± 8.38	33.33 ± 8.33	0.213	36.69 ± 6.46	34.06 ± 6.82	0.144	37.75 ± 6.87	35.89 ± 8.04	0.247
Total lean (%)	62.01 ± 8.01	64.13 ± 7.88	0.438	60.96 ± 6.29	63.41 ± 6.59	0.072	58.57 ± 7.60	61.63 ± 7.99	**0.026**
Trunk fat (kg)	18.40 ± 5.54	15.43 ± 5.01	**0.022**	18.69 ± 3.36	15.96 ± 3.24	**0.016**	17.43 ± 3.27	15.46 ± 3.80	0.065
HG (kg)	32.47 ± 7.73	34.45 ± 7.34	0.23	30.13 ± 6.99	31.01 ± 6.92	0.36	32.64 ± 9.04	34.03 ± 9.25	0.33

Values in bold indicate statistically significant results ($P \leq 0.05$).

Abbreviations: ALT, alanine transferase; APG, animal protein group; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; BW, body weight; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; HC, hip circumference; HDL, high-density lipoprotein; HG, handgrip strength. HOMA-IR, homeostasis model assessment-insulin resistance; HSI, hepatic steatosis index; LDL, low-density lipoprotein; TC, thigh circumference; VPG, vegetable protein group; WC, waist circumference; WPG, whey protein group.

Table 2. Between-group (analysis of covariance) and within-group (analysis of variance) *P* values of the percentage change from baseline of the parameters with a significant group effect measured after 45 days of VLCKD consumption

	Between Groups	WPG vs VPG	WPG vs APG	A PG vs VPG
IGF-1	**0.0000**	**0.0000**	0.5697	**0.0011**
Creatinine	**0.0010**	**0.0696**	**0.0006**	0.2004
BUN	**0.0019**	0.2281	**0.0973**	**0.0013**
eGFR	**0.0016**	**0.0334**	**0.0013**	0.4690
Uric acid	**0.0112**	**0.0533**	**0.0128**	0.8316
HG	**0.0040**	**0.0027**	0.1351	0.2652

Values in bold indicate statistically significant results ($P \leq 0.05$) and values "trending toward significance" ($P < 0.1$).
Abbreviations: ALM, appendicular lean mass; APG, animal protein group; BUN, blood urea nitrogen; DALM, dominant arm lean mass; eGFR, estimated glomerular filtration rate; HG, handgrip strength; VPG, vegetable protein group; WPG, whey protein group.

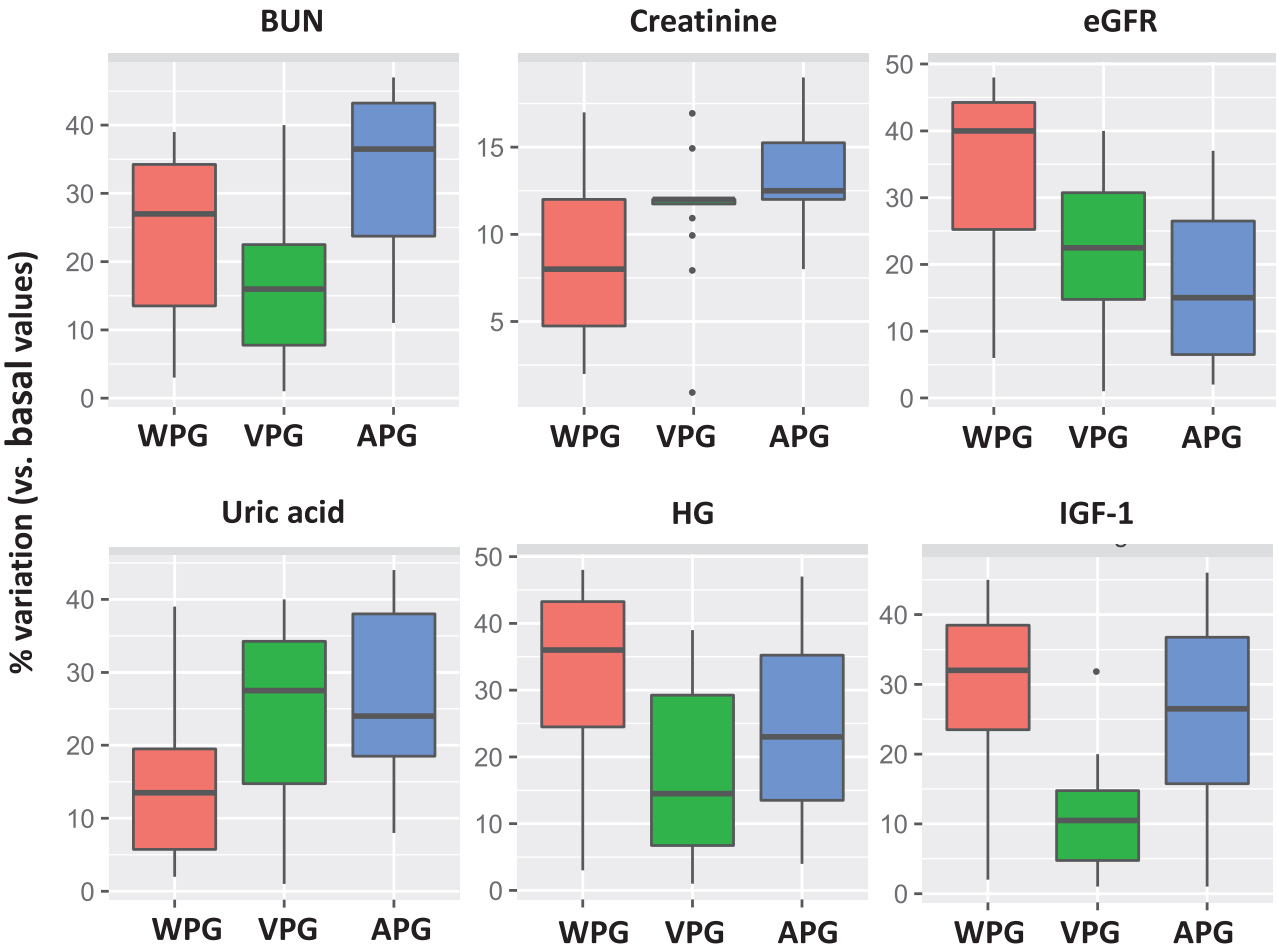


Figure 2. Box plot of pooled ranking of all observed relative differences (% variation vs basal values) from day 0 to day 45 in BUN, creatinine, eGFR, uric acid, HG, and IGF-1 values in the WPG, the VPG, and the APG. *P* values of the parameters plotted are shown in Table 2.

normal range, the group of patients who consumed a VLCKD containing animal protein (APG) showed an increase in creatinine levels and a significant reduction in eGFR compared to the same parameters of the other 2 treatment groups. The delta percentage increase in BUN was more pronounced in the WPG and APG, while uric acid increased more in the VPG. HG was maintained to a greater extent in the WPG than in the VPG. The delta percentage increase in IGF-1 values was more pronounced in the WPG and APG than in the VPG.

The dominant phyla in the fecal samples of the patients at T0 were Firmicutes, Bacteroidetes, Proteobacteria, Verrucomicrobia, Fusobacteria, and Actinobacteria (Fig. 3A). The relative abundance of Firmicutes was significantly diminished and that of Bacteroidetes increased proportionally 45 days after the initiation of the VLCKDs (Fig. 3B). The mean relative abundance of Proteobacteria also increased, while that of Actinobacteria decreased (data not shown). The abundance of the 2 predominant bacterial divisions

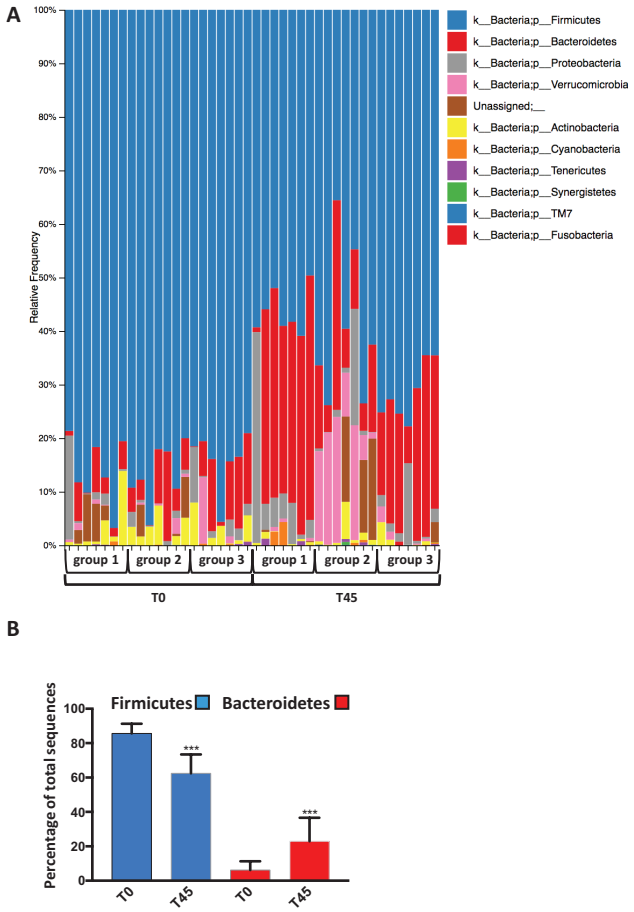


Figure 3. Correlation between VLCK dietary interventions and gut microbial ecology. (A) Relative abundance of bacterial phyla in each sample among each treatment group (n = 7) at time 0 and after 45 days of VLCKD dietary intervention (Group 1, VLCKD with whey protein; Group 2, VLCKD with vegetable protein; Group 3, VLCKD with animal protein). (B) Relative abundance of Bacteroidetes and Firmicutes. For each time point, values from all available samples were averaged (n = 21 per time point). Mean values ± standard deviations are plotted. ***$P < 0.0001$

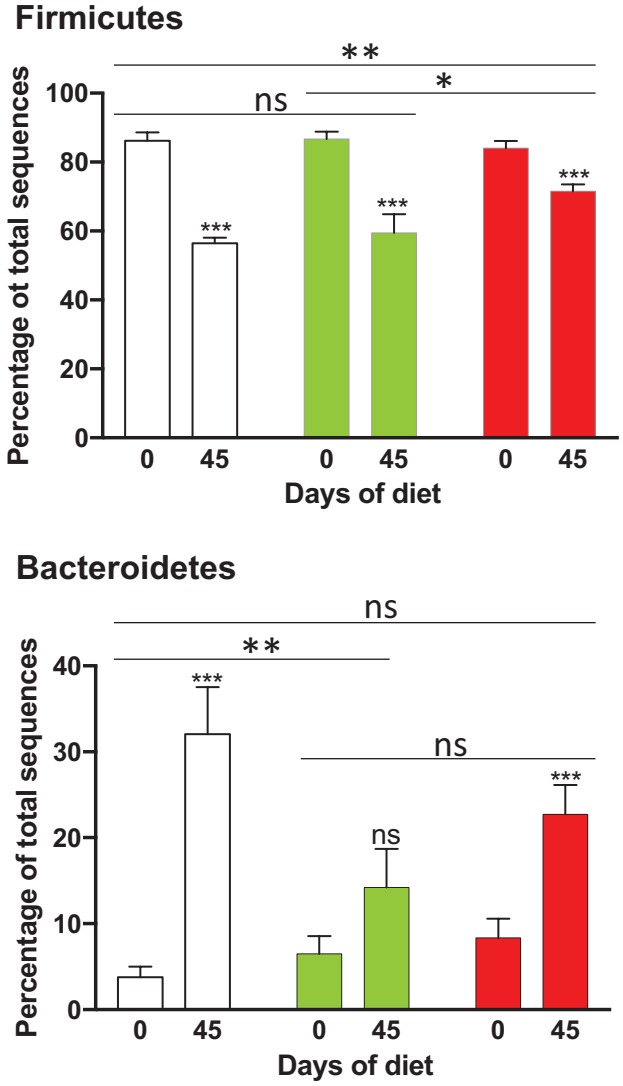


Figure 4. Effect of 45-day VLCKD dietary interventions with whey protein (white bars), vegetable protein (green bars), and animal protein (red bars) on the relative abundance of Firmicutes and Bacteroidetes. For each time point, values from all available samples were averaged (n = 7 per time point). Mean values ± standard deviations are plotted. *$P < 0.017$; **$P < 0.0023$; ***$P < 0.001$.

(Firmicutes and Bacteroidetes) was almost superimposable in the 3 dietary intervention groups of patients at baseline, with no differences according to multiple comparison (Fig. 4). Over time, the relative abundance of Bacteroidetes increased, and the abundance of Firmicutes significantly decreased, irrespective of diet type, with the only exception in the VPG, in which the increase in Bacteroidetes did not reach statistical significance (Fig. 4). To verify whether the different protein sources in the VLCKDs could influence the variation in the abundance of Firmicutes and Bacteroidetes, a 2-way analysis of variance test was performed. The increase in Bacteroidetes and the decrease in Firmicutes were influenced by the protein composition of the diets. In particular, whey protein and vegetable protein were more potent in reducing the percentage of Firmicutes than the dietary intervention incorporating animal protein. Regarding the Bacteroidetes gut microbiota content, a significant difference was only observed between the individuals exposed to the diets incorporating whey protein and vegetable protein, with the VLCKD containing whey protein exhibiting a more potent ability to increase the percentage of total sequences of Bacteroidetes.

The AEs were mild; in fact, none of the patients dropped out of the study, and the differences between the diet interventions were negligible (Table 3 shows the most frequent side effects and the number of participants reporting them). During ketosis, the intragroup variation as well as the intergroup variation in the quality-of-life scores did not change (data not shown).

Table 3. Adverse events during the nutritional interventions recorded 15 days (T15) and 45 days (T45) after the start of the diets

	WPG		VPG		APG	
	T15	T45	T15	T45	T15	T45
Constipation	2 (12.5)	4 (25)	2 (12.5)	4 (25)	2 (12.5)	6 (37.5)
Diarrhea	1 (0.6)	1 (0.6)	3 (18.7)	2 (12.5)	1 (0.6)	2 (12.5)
Cramps	1 (0.6)	1 (0.6)	2 (12.5)	1 (0.6)	1 (0.6)	1 (0.6)
Nausea	2 (12.5)	2 (12.5)	2 (12.5)	1 (0.6)	1 (0.6)	1 (0.6)
Fatigue	1 (0.6)	1 (0.6)	3 (18.7)	2 (12.5)	2 (12.5)	1 (0.6)
Hunger	3 (18.7)	3 (18.7)	2 (12.5)	2 (12.5)	3 (18.7)	2 (12.5)
Headache	4 (25)	1 (0.6)	2 (12.5)	1 (0.6)	2 (12.5)	2 (12.5)
dizziness	2 (12.5)	2 (12.5)	2 (12.5)	1 (0.6)	1 (0.6)	1 (0.6)
Insomnia	1 (0.6)	1 (0.6)	1 (0.6)	2 (12.5)	2 (12.5)	2 (12.5)

Results are given as number (percentage) of participants reporting an adverse event.
Abbreviations: APG, VLCKD incorporating animal protein; VPG, VLCKD incorporating vegetable protein; WPG, VLCKD incorporating whey protein.

Discussion

Our data show that a 45-day-long VLCKD causes a profound reduction in BW and improves glycemic control, lipid metabolism, and arterial pressure in patients with obesity and insulin resistance. The VLCKD is safe and well tolerated; the gut microbiota composition is influenced by the VLCKD, and the source of dietary protein modulates the variation in the gut microbiota caused by the VLCKD. Whey protein intake contributes more substantially to the preservation of muscle performance.

These results provide important implications. First, VLCKDs may hold promise as a strategy to simultaneously improve glycemic control while facilitating profound weight loss in patients with insulin resistance. All individuals who consumed VLCKDs showed a decrease in fasting plasma glucose, insulin, and HOMA-IR. Of note, no episodes of hypoglycemia were observed. Numerous studies on VLCKDs have shown diabetes improvement and remission (8,9,11,34). Here, we show that this pattern applies to individuals with insulin resistance as well. We hypothesize that the improvement in carbohydrate metabolism might correlate with both weight loss and low sugar content, although additional mechanisms cannot be excluded (35). The short duration of our intervention prevents the assessment of the durability of the effect.

An important concern with low carbohydrate diets is the potential negative impact on lipid metabolism due to the increased proportion of calories coming from fat. Clearly, this does not apply to a 45-day VLCKD, for which the daily lipid intake is still low, as can be inferred by the profound reduction in the circulating cholesterol and triglyceride levels measured in our patients. Many other mechanisms may contribute to the reduction in circulating lipids, such as the improvement in insulin resistance with positive effects on lipid metabolism through the action on 3-hydroxy-3-methylglutaryl coenzyme A reductase and striking effects on lipoprotein size and subclass particle concentrations (36). Moreover, it has been reported that even high-fat ketogenic diets are capable of ameliorating nonalcoholic fatty liver disease through de novo lipogenesis inhibition and fatty acid oxidation induction, leading to weight loss and reduced hepatic fat content. It is therefore unsurprising that serum triglycerides, well-established markers of liver fat, are almost invariably reduced upon the adoption of any kind of ketogenic diet (37).

Many studies have shown that dietary protein content may play a role in weight management (38-40). Much less is known about the importance of the sources from which these proteins are derived (41). In the face of significant variations in the anthropometric measures between T0 and T45 within each group, the intake of different kinds of protein was not associated with meaningful changes in BW, WC, BMI, or the remaining anthropometric parameters among groups. Some differences that might have clinical significance reflect the proportion of lean and fat mass in different body regions. The loss of trunk fat mass was less pronounced in the group of patients who consumed animal protein. However, the between-group comparison of trunk fat content did not reveal a significant difference.

Analogous to a previous report (33), crude HG did not vary significantly during our dietary intervention. This is notable due to the well-known cardiovascular advantages of maintaining muscle strength (42,43). Interestingly, the individuals fed whey protein preserved their HG strength to a greater extent than in the vegetable protein-fed group. Whether this is due to the higher relative increase in IGF-1 levels associated with whey protein consumption is unclear. Our data are in line with the reported association between protein intake, largely attributable to milk intake, and circulating IGF-1 levels, an association that has been related to muscle strength (44,45). Our evidence is purely

associative, and many other mechanisms, including neural mechanisms, learning effects, and improvement in the actin-myosin machinery, among others, may explain this finding. Furthermore, our measurements, although accurately conducted, suffer from the variation in current methods of assessing grip strength (46); thus, an analysis of a larger sample is warranted.

The intestinal microbiota is relatively stable throughout adult life (47-49). Each individual has his or her own unique microbial community whose profile is stable over time. However, much is still unknown regarding how stable the microbiota is to perturbations, such as those arising from antibiotics, diet, and the immune system. Ketogenic diets influence the taxonomic and functional composition of the gut microbiota with mixed contradictory results (50). We observed a pattern in the variation in the microbiota that resembled that in children affected by refractory epilepsy treated with ketogenic diets, with increased amounts of Bacteroides and decreased amounts in Firmicutes (51,52). Moreover, we found divergent responses to VLCKDs containing protein from different sources with substantial effects on the Firmicutes-to-Bacteroidetes ratio. Recent evidence suggests that the quality of dietary protein may impact the gut environment, shaping the microbiota and the host-microbe (co)metabolic pathways and products and linking protein-dependent changes in the obese gut microbiota (53,54). The gut microbiota composition in mice (55), rats (56), and piglets (57) revealed divergent responses to diets containing protein from different sources. Although the prospect of health-interpretable microbiota data is exciting (58,59), and despite a decade of research establishing a strong association between the gut microbiota and various diseases, including obesity and diabetes, in humans a causal relationship and the underlying mechanism remain unknown (60-62). The strongest effect of the VLCKD containing whey protein in reducing Firmicutes and increasing Bacteroidetes compared with the vegetable- and animal-containing VLCKDs observed here warrants further investigation.

The profound metabolic effects associated with VLCKDs were observed in the absence of serious AEs that were previously associated with VLCKD interventions (8,50,63,64). Quality-of-life score variations were negligible.

Regarding the potential issues of our pilot study, the number of subjects enrolled was small, although sufficient, to appreciate the variations induced by VLCKDs. The short duration is a further limitation, together with the lack of follow-up. Moreover, the measurement of capillary blood concentration of beta hydroxybutyrate would have been a more accurate method of ketosis assessment than the urinary acetoacetate semiquantitative determination used in this study for technical reasons. However, the fundamental objectives that our study had set were achieved, and the additional information obtained will certainly lead to further investigation. In summary, these data show that a 45-day-long VLCKD is safe and quickly reduces weight and fasting glycemia in patients with obesity and insulin resistance. The investigated protein sources did not differentially impact anthropometric or metabolic parameters under the acute conditions of the intervention in our experimental design. However, whey proteins and vegetable proteins showed a safer profile and directed the intestinal microbiota toward a healthier composition.

Acknowledgments

The authors would like to thank Settimia Di Bernardo and Maria Faro for their contribution in the management of the patients.

Financial Support: Financial support as well as meal replacement protein preparations were kindly provided by New Penta s.r.l. (Cuneo, Italy). The funding source had no involvement in the study design, recruitment of patients, study interventions, data collection, or interpretation of the results.

Author Contributions: The author contributions to the paper were as follows. Study concept: SB and GS; design: SB, GS, and LG; acquisition of data: SB, SC, AP, EC, LB, RR, GP, and MW; interpretation of the data: SM, CL, AG, MW, and LS; analysis: LS, LB, and AP; and writing of the manuscript: SB, EC, AP, and LG. All authors approved the final version of the manuscript.

Clinical Trial Information: This study was registered under ClinicalTrials.gov NCT04019431.

Additional Information

Correspondence and Reprint Requests: Lucio Gnessi, MD, PhD, Department of Experimental Medicine, Viale Regina Elena 324, University of Rome "La Sapienza," 00161 Rome, Italy. E-mail: lucio.gnessi@uniroma1.it.

Disclosure Summary: The authors declare no conflicts of interest.

Data Availability: The data sets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Afshin A, Forouzanfar MH, Reitsma MB, et al.; GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;**377**(1):13-27.

2. Apovian CM. Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care*. 2016;**22**(7 Suppl):s176-s185.
3. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;**391**(10120):541-551.
4. Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review. *Am J Prev Med*. 2005;**28**(1):126-139.
5. Caprio M, Infante M, Moriconi E, et al.; Cardiovascular Endocrinology Club of the Italian Society of Endocrinology. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE). *J Endocrinol Invest*. 2019;**42**(11):1365-1386.
6. Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition*. 2015;**31**(1):1-13.
7. Willi SM, Martin K, Datko FM, Brant BP. Treatment of type 2 diabetes in childhood using a very-low-calorie diet. *Diabetes Care*. 2004;**27**(2):348-353.
8. Goday A, Bellido D, Sajoux I, et al. Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. *Nutr Diabetes*. 2016;**6**(9):e230.
9. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition*. 2012;**28**(10):1016-1021.
10. Westman EC, Yancy WS Jr, Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutr Metab (Lond)*. 2008;**5**:36.
11. Romano L, Marchetti M, Gualtieri P, et al. Effects of a personalized VLCKD on body composition and resting energy expenditure in the reversal of diabetes to prevent complications. *Nutrients*. 2019;**11**: E1526.
12. van Baak MA, Larsen TM, Jebb SA, et al. Dietary intake of protein from different sources and weight regain, changes in body composition and cardiometabolic risk factors after weight loss: the DIOGenes study. *Nutrients*. 2017;**9**:E1326.
13. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation*. 2016;**133**(2):187-225.
14. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;**23**:559-563.
15. Bendtsen LQ, Lorenzen JK, Bendsen NT, Rasmussen C, Astrup A. Effect of dairy proteins on appetite, energy expenditure, body weight, and composition: a review of the evidence from controlled clinical trials. *Adv Nutr*. 2013;**4**(4):418-438.
16. Neacsu M, Fyfe C, Horgan G, Johnstone AM. Appetite control and biomarkers of satiety with vegetarian (soy) and meat-based high-protein diets for weight loss in obese men: a randomized crossover trial. *Am J Clin Nutr*. 2014;**100**(2):548-558.
17. Jakubowicz D, Froy O, Ahrén B, et al. Incretin, insulinotropic and glucose-lowering effects of whey protein pre-load in type 2 diabetes: a randomised clinical trial. *Diabetologia*. 2014;**57**(9):1807-1811.
18. Viguiliouk E, Stewart SE, Jayalath VH, et al. Effect of replacing animal protein with plant protein on glycemic control in diabetes: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2015;**7**(12):9804-9824.
19. Hutchison AT, Piscitelli D, Horowitz M, et al. Acute load-dependent effects of oral whey protein on gastric emptying, gut hormone release, glycemia, appetite, and energy intake in healthy men. *Am J Clin Nutr*. 2015;**102**(6):1574-1584.
20. Klementova M, Thieme L, Haluzik M, Pavlovicova R, Hill M, Pelikanova T, Kahleova H. A plant-based meal increases gastrointestinal hormones and satiety more than an energy- and macronutrient-matched processed-meat meal in T2D, obese, and healthy men: a three-group randomized crossover study. *Nutrients*. 2019;**11**:E157.
21. Flaim C, Kob M, Di Pierro AM, Herrmann M, Lucchin L. Effects of a whey protein supplementation on oxidative stress, body composition and glucose metabolism among overweight people affected by diabetes mellitus or impaired fasting glucose: a pilot study. *J Nutr Biochem*. 2017;**50**:95-102.
22. Comerford KB, Pasin G. Emerging evidence for the importance of dietary protein source on glucoregulatory markers and type 2 diabetes: different effects of dairy, meat, fish, egg, and plant protein foods. *Nutrients*. 2016;**8**:E446.
23. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific opinion on the essential composition of total diet replacements for weight control. *EFSA J*. 2015;**13**:3957.
24. European Food Safety Authority. Dietary reference values for nutrients summary report. *EFSA Supporting Publication*. 2017;**14**(12):e15121.
25. Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis*. 2010;**42**(7):503-508.
26. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;**28**(7):412-419.
27. Bolyen E, Rideout JR, Dillon MR, et al. Reproducible, interactive, scalable and extensible microbiome data science using QIIME 2. *Nat Biotechnol*. 2019;**37**(8):852-857.
28. Martin M. Cutadapt removes adapter sequences from high-throughput sequencing reads. *EMBnet J*. 2011;**17**:10-12.
29. Callahan BJ, McMurdie PJ, Rosen MJ, Han AW, Johnson AJ, Holmes SP. DADA2: high-resolution sample inference from Illumina amplicon data. *Nat Methods*. 2016;**13**(7):581-583.
30. Sajoux I, Lorenzo PM, Gomez-Arbelaez D, et al. Effect of a very-low-calorie ketogenic diet on circulating myokine levels compared with the effect of bariatric surgery or a low-calorie diet in patients with obesity. *Nutrients*. 2019;**11**:E2368.
31. Gomez-Arbelaez D, Crujeiras AB, Castro AI, et al. Acid-base safety during the course of a very low-calorie-ketogenic diet. *Endocrine*. 2017;**58**(1):81-90.
32. Basciani S, Costantini D, Contini S, et al. Safety and efficacy of a multiphase dietetic protocol with meal replacements including a step with very low calorie diet. *Endocrine*. 2015;**48**(3):863-870.
33. Gomez-Arbelaez D, Bellido D, Castro AI, et al. Body composition changes after very-low-calorie ketogenic diet in obesity evaluated by 3 standardized methods. *J Clin Endocrinol Metab*. 2017;**102**(2):488-498.
34. Westman EC, Tondt J, Maguire E, Yancy WS Jr. Implementing a low-carbohydrate, ketogenic diet to manage type 2 diabetes mellitus. *Expert Rev Endocrinol Metab*. 2018;**13**(5):263-272.
35. Bolla AM, Caretto A, Laurenzi A, Scavini M, Piemonti L. Low-carb and ketogenic diets in type 1 and type 2 diabetes. *Nutrients*. 2019;**11**:962.
36. Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? *Diabetologia*. 2015;**58**(5):886-899.
37. Watanabe M, Tozzi R, Risi R, et al. Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: A comprehensive review of the literature. *Obes Rev*. 2020. doi:10.1111/obr.13024. [Online ahead of print]
38. Wadden TA, Hollander P, Klein S, et al.; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)*. 2013;**37**(11):1443-1451.
39. Larsen TM, Dalskov SM, van Baak M, et al.; Diet, Obesity, and Genes (Diogenes) Project. Diets with high or low protein content and glycemic index for weight-loss maintenance. *N Engl J Med*. 2010;**363**(22):2102-2113.

40. Aller EE, Larsen TM, Claus H, et al. Weight loss maintenance in overweight subjects on ad libitum diets with high or low protein content and glycemic index: the DIOGENES trial 12-month results. *Int J Obes (Lond)*. 2014;**38**(12):1511-1517.
41. Gilbert JA, Bendsen NT, Tremblay A, Astrup A. Effect of proteins from different sources on body composition. *Nutr Metab Cardiovasc Dis*. 2011;**21 Suppl 2**:B16-B31.
42. Leong DP, Teo KK, Rangarajan S, et al.; Prospective Urban Rural Epidemiology (PURE) Study investigators. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet*. 2015;**386**(9990):266-273.
43. Lopez-Jaramillo P, Cohen DD, Gómez-Arbeláez D, et al.; ORIGIN Trial Investigators. Association of handgrip strength to cardiovascular mortality in pre-diabetic and diabetic patients: a subanalysis of the ORIGIN trial. *Int J Cardiol*. 2014;**174**(2):458-461.
44. Holmes MD, Pollak MN, Willett WC, Hankinson SE. Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. *Cancer Epidemiol Biomarkers Prev*. 2002;**11**(9):852-861.
45. Taekema DG, Ling CH, Blauw GJ, et al. Circulating levels of IGF1 are associated with muscle strength in middle-aged- and oldest-old women. *Eur J Endocrinol*. 2011;**164**(2):189-196.
46. Roberts HC, Denison HJ, Martin HJ, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing*. 2011;**40**(4):423-429.
47. Mehta RS, Abu-Ali GS, Drew DA, et al. Stability of the human faecal microbiome in a cohort of adult men. *Nat Microbiol*. 2018;**3**(3):347-355.
48. Faith JJ, Guruge JL, Charbonneau M, et al. The long-term stability of the human gut microbiota. *Science*. 2013;**341**(6141):1237439.
49. Rinninella E, Raoul P, Cintoni M, et al. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. *Microorganisms*. 2019;**7**:E14
50. Paoli A, Mancin L, Bianco A, Thomas E, Mota JF, Piccini F. Ketogenic diet and microbiota: friends or enemies? *Genes (Basel)*. 2019;**15**:E534.
51. Zhang Y, Zhou S, Zhou Y, Yu L, Zhang L, Wang Y. Altered gut microbiome composition in children with refractory epilepsy after ketogenic diet. *Epilepsy Res*. 2018;**145**:163-168.
52. Xie G, Zhou Q, Qiu CZ, et al. Ketogenic diet poses a significant effect on imbalanced gut microbiota in infants with refractory epilepsy. *World J Gastroenterol*. 2017;**23**(33):6164-6171.
53. Madsen L, Myrmel LS, Fjære E, Liaset B, Kristiansen K. Links between dietary protein sources, the gut microbiota, and obesity. *Front Physiol*. 2017;**8**:1047.
54. Blachier F, Beaumont M, Portune KJ, et al. High-protein diets for weight management: Interactions with the intestinal microbiota and consequences for gut health. A position paper by the my new gut study group. *Clin Nutr*. 2019;**38**(3):1012-1022.
55. Kar SK, Jansman AJM, Benis N, et al. Dietary protein sources differentially affect microbiota, mTOR activity and transcription of mTOR signaling pathways in the small intestine. *PloS One*. 2017;**12**(11):e0188282.
56. Zhu Y, Lin X, Zhao F, et al. Meat, dairy and plant proteins alter bacterial composition of rat gut bacteria. *Sci Rep*. 2015;**5**:15220.
57. Li R, Chang L, Hou G, et al. Colonic microbiota and metabolites response to different dietary protein sources in a piglet model. *Front Nutr*. 2019;**6**:151.
58. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell*. 2012;**148**(6):1258-1270.
59. Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. *Genome Med*. 2016;**8**(1):51.
60. Maruvada P, Leone V, Kaplan LM, Chang EB. The human microbiome and obesity: moving beyond associations. *Cell Host Microbe*. 2017;**22**:589-599.
61. Brunkwall L, Orho-Melander M. The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities. *Diabetologia*. 2017;**60**(6):943-951.
62. Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. *Nat Med*. 2018;**24**(4):392-400.
63. Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr*. 2013;**67**(8):789-796.
64. Bruci A, Tuccinardi D, Tozzi R, et al. Very low-calorie ketogenic diet: a safe and effective tool for weight loss in patients with obesity and mild kidney failure. *Nutrients*. 2020;**12**(2):E333.

nutrients

MDPI

Article

Reduction of Cardio-Metabolic Risk and Body Weight through a Multiphasic Very-Low Calorie Ketogenic Diet Program in Women with Overweight/Obesity: A Study in a Real-World Setting

Elena Tragni [1], Luisella Vigna [2], Massimiliano Ruscica [1], Chiara Macchi [1], Manuela Casula [1,3], Alfonso Santelia [1], Alberico L. Catapano [1,3] and Paolo Magni [1,3,*]

[1] Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, 20133 Milan, Italy; elena.tragni@unimi.it (E.T.); massimiliano.ruscica@unimi.it (M.R.); chiara.macchi@unimi.it (C.M.); manuela.casula@unimi.it (M.C.); the.alfsan@gmail.com (A.S.); alberico.catapano@unimi.it (A.L.C.)
[2] Center of Obesity and Work EASO Collaborating Centers for Obesity Management, Occupational Health Unit, Fondazione Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy; luisella.vigna@policlinico.mi.it
[3] IRCCS MultiMedica, Sesto S. Giovanni, 20099 Milan, Italy
* Correspondence: paolo.magni@unimi.it; Tel.: +39-02-50318229

Abstract: Background: The prevention and treatment of obesity and its cardio-metabolic complications are relevant issues worldwide. Among lifestyle approaches, very low-calorie ketogenic diets (VLCKD) have been shown to lead to rapid initial weight loss, resulting in better long-term weight loss maintenance. As no information on VLCKD studies carried on in a real-world setting are available, we conducted this multi-centre study in a real-world setting, aiming at assessing the efficacy and the safety of a specific multiphasic VLCKD program in women with overweight or obesity. Methods: A multi-center, prospective, uncontrolled trial was conducted in 33 outpatient women (age range 27–60 y) with overweight or obesity (BMI: 30.9 ± 2.7 kg/m^2; waist circumference: 96.0 ± 9.4 cm) who started a VLCKD dietary program (duration: 24 weeks), divided into four phases. The efficacy of VLCKD was assessed by evaluating anthropometric measures and cardiometabolic markers; liver and kidney function biomarkers were assessed as safety parameters. Results: The VLCKD program resulted in a significant decrease of body weight and BMI (−14.6%) and waist circumference (−12.4%). At the end of the protocol, 33.3% of the participants reached a normal weight and the subjects in the obesity range were reduced from 70% to 16.7%. HOMA-IR was markedly reduced from 3.17 ± 2.67 to 1.73 ± 1.23 already after phase 2 and was unchanged thereafter. Systolic blood pressure decreased after phase 1 (−3.5 mmHg) and remained unchanged until the end of the program. Total and LDL cholesterol and triglycerides were significantly reduced by VLCKD along with a significant HDL cholesterol increase. Liver, kidney and thyroid function markers did not change and remained within the reference range. Conclusions: The findings of a multi-center VLCKD program conducted in a real-world setting in a cohort of overweight/obese women indicate that it is safe and effective, as it results in a major improvement of cardiometabolic parameters, thus leading to benefits that span well beyond the mere body weight/adiposity reduction.

Keywords: very-low calorie ketogenic diet; obesity; cardiovascular risk; insulin resistance; nutraceutical

Citation: Tragni, E.; Vigna, L.; Ruscica, M.; Macchi, C.; Casula, M.; Santelia, A.; Catapano, A.L.; Magni, P. Reduction of Cardio-Metabolic Risk and Body Weight through a Multiphasic Very-Low Calorie Ketogenic Diet Program in Women with Overweight/Obesity: A Study in a Real-World Setting. *Nutrients* **2021**, *13*, 1804. https://doi.org/10.3390/nu13061804

Academic Editor: Rosa Casas

Received: 9 April 2021
Accepted: 22 May 2021
Published: 26 May 2021

1. Introduction

Prevention and treatment of obesity and its cardio-metabolic complications are growing public health problems worldwide since this condition affects a relevant part of the world population across both genders and all ages and ethnic groups, and its prevalence is now maintained or even accelerated in most industrialized countries [1–4]. In recent years, the prevalence of obesity has reached epidemic proportions, and, therefore, the identification of effective lifestyle tools, including nutritional ones [5], able to produce significant

weight loss and to maintain it over time is mandatory, in order to limit its progression from the uncomplicated stage to that characterized by cardiovascular and metabolic complications [6–8], as well as oncologic diseases [9]. In this context, cardiovascular disease (CVD) risk and unhealthy lifestyle habits [10] are often underdiagnosed and undertreated, therefore highly contributing to atherosclerotic CVD (ASCVD) prevalence [11]. The current treatment options for obesity include balanced hypocaloric diets, exercise, lifestyle modifications, drugs, use of endoscopic devices (e.g., intragastric balloon) and bariatric surgery [12–15]. The therapeutic benefit of all currently available anti-obesity interventions is often limited by their subjective efficacy, variable tolerability, safety profiles and poor compliance, with the latter being a strongly limiting variable, especially when long-term treatments are needed [4,16]. Many dietary regimens that operate through various mechanisms have been proposed to reduce appetite or for weight control [17,18] and the leading non-pharmacological approach is the use of diets, particularly low-calorie and very low-calorie ketogenic diets (VLCKD) [19–21]. VLCKD has been endorsed by the European Food Safety Agency (EFSA) for reduction of body weight in subjects with obesity, according to a specific Scientific Opinion (https://www.efsa.europa.eu/it/efsajournal/pub/2271, accessed 2 April 2021), and a specific consensus statement discussing the appropriate use of VLCKD has been recently published by a scientific panel of the Italian Society of Endocrinology [22]. Indeed, in studies conducted in hospital settings, the VLCKD approach has been shown to lead to a rapid initial weight loss, which results in better long-term weight loss maintenance [23] although in some cases an adequate weight reduction at the beginning of the diet program is followed by a shotdown of weight decrease. This problem may depend upon different factors, including individual metabolic rate and patient compliance. The VLCKD approach generally includes an initial phase with a complete replacement of regular meals with food or formulations that provide 400–800 kCal/day. This type of diet may be better defined as a "therapeutical approach" since it is commonly followed under medical supervision in patients with BMI > 30 kg/m^2 or in subjects needing a rapid weight loss in preparation to other medical procedures [21,24] and is usually associated with the use of specific food supplements. Since, to our best knowledge, no information on VLCKD studies conducted in a real-world setting are available, the present multi-centre study, conducted in a real-world setting, was aimed at assessing the efficacy, according to anthropometric and cardiometabolic changes, and safety of a specific multiphasic VLCKD program in women with overweight or obesity.

2. Materials and Methods

2.1. Study Design and Population

The study was designed as a multi-center, prospective, uncontrolled trial in a real-life setting and included Caucasian outpatient women with overweight or obesity and some features of the metabolic syndrome, including increased waist circumference (WC) and pharmacologically controlled arterial hypertension [25]; 11/33 subjects were on pharmacological therapy for arterial hypertension (Table S1). All patients were consecutively admitted to one of the 5 participating clinical centers in the Milan area (Italy) in the period 2016–2018. Each clinical center is specialized in the medical management of obesity, with a specific expertise in VLCKD program, and includes expert physicians; 2 centres also included a trained dietician. The inclusion criteria were: female sex upper-range overweight or grade 1 or 2 obesity (body mass index (BMI) range: 27–37 kg/m^2), age between 25 and 65 years, negative for pregnancy test, and having signed an informed consent. The main exclusion criteria were: current or previous smoking, pregnancy and nursing, history of diabetes mellitus, renal disease or severe renal impairment (plasma creatinine >1.5 mg/dL), severe liver disease, HIV infection, nervous system and cardiovascular diseases (including uncontrolled arterial hypertension), blood diseases, cancer or any progressive severe disease, osteoporosis, eating disorders or any psychiatric disease, uncontrolled thyroid diseases, menopause hormonal replacement therapy, pharmacological treatments known to interfere with the study treatment, history of bariatric surgery, and patients who were

enrolled in another research study in the last 12 months. At the screening visit, all patients underwent fasting blood sampling and a full clinical examination, to evaluate height (in standing position and without shoes and corrected to the closer 0.5 cm), body weight, WC and hip (HC) circumferences (in standing position, measured with a flexible tape), heart rate (HR) and arterial blood pressure. These parameters were also recorded at all subsequent visits. A total of 44 eligible patients (age 49.5 ± 7.2 yrs, and BMI 30.9 ± 2.7 kg/m^2 (mean ± SD)) were enrolled in the study and started a VLCKD dietary program (Pentadiet program, Figure 1) with a total intervention duration of 24 weeks. Eleven patients were on chronic therapy known not to interfere with VLCKD treatment (Table S1). The concomitant medications of the study subjects at baseline are reported in Table S1. The indicated treatments were carried on until the end of the VLCKD program, under appropriate monitoring for possible adverse effects. The study was conducted in accordance with the guidelines of the declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/, accessed 2 April 2021), and the study protocol was approved by the Institutional Ethics Committee (approval N°441/2011). Patients were informed about all aspects related to the study, possible benefits and risks were explained at the beginning of the study and subjects were informed about the possibility to leave the study at any time without penalty. Written informed consent was obtained from each subject before starting the VLCKD program.

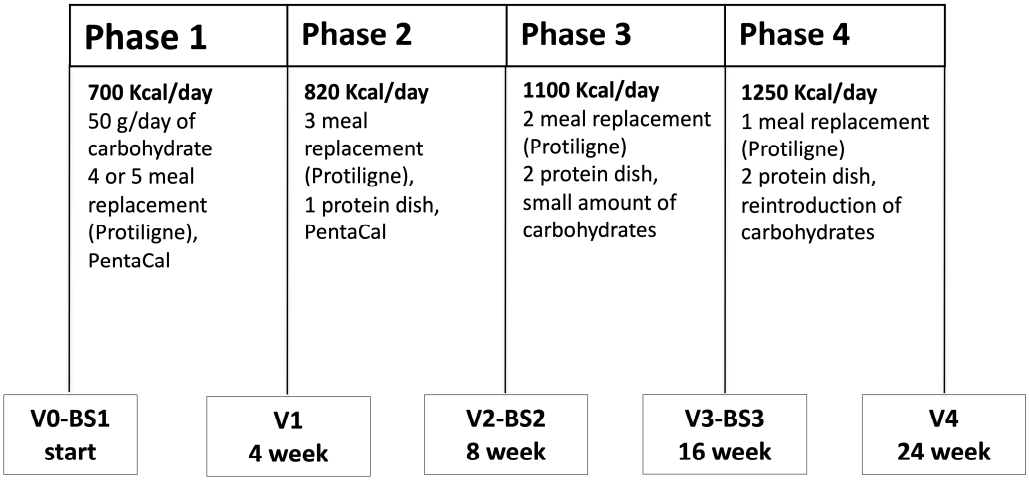


Figure 1. Outline of the VLCKD program. The program included 4 separate phases, with a total duration of 24 weeks.

2.2. Clinical Procedures

The overall duration of the study was 24 weeks, divided into 4 sequential phases: two "active phases" (phases 1 and 2) and two "stabilization phases" (phases 3 and 4) (Figure 1). Each phase had a standard duration, and the daily plan included 3 main meals (breakfast, lunch, dinner) and 1 snack in the afternoon in all phases. All low-carbohydrate foods (Protiligne) and a food supplement (PentaCal) used in the VLCKD program were provided by New Penta srl (Milan, Italy). The average daily food intake, including pre-prepared meals (Protiligne, Table S2B), varied according to each phase. As reported in Table S2, the energy and macronutrient content of meal replacement portions were within the indicated range, and varied according to each specific type (i.e., soups, cakes, meat plates, etc.). Thus, during each phase of the program, the daily target of energy and macronutrients was reached combining different meal replacement portions and the allowed foods. The daily intake of protein, carbohydrate, linoleic acid, γ-linoleic acid and micronutrients during all the phases of the VLCKD program was above the minimum content recommended by EFSA, according to a specific Scientific Opinion (https://www.efsa.europa.eu/it/efsajournal/pub/2271, accessed 2 April 2021). Patients were instructed to drink not less than 1.5–2 L of water daily and to avoid ingestion of any sweets, sugarfree chewing gums and soft drinks, herbal tea with fruit, and preserved vegetables. The program included the use of a vitamin and

mineral supplement (PentaCal, Table S2A) during phases 1 and 2. At the end of the study, a compliance survey was submitted to all patients.

The efficacy of VLCKD was assessed by evaluating anthropometric measures (height, weight, BMI, WC and HC), SBP/DBP, HR and glucose metabolism markers, whereas liver and kidney function biomarkers were assessed as safety parameters.

2.3. Blood and Urinary Biochemistry

Before starting the VLCKD program and at the end of phases 2 and 4, urine and fasting blood samples from an antecubital vein were collected at 8:00–10:00 a.m. after an overnight fast. The following haematological and biochemical parameters, used as efficacy and safety end-points, were evaluated using standard automated clinical procedures (Cobas system, Roche, Italy): complete blood count, electrolytes (chloride, potassium, calcium, magnesium, sodium), fasting plasma glucose (FPG) and insulin, HbA1c, plasma protein concentration, lipids (total cholesterol (TC), HDL cholesterol (HDL-C) and triglycerides (TG)), uric acid, blood urea nitrogen, creatinine, alanine transferase (AST), aspartate transaminase (AST), γ-glutamyl transpeptidase (γ-GT), high-sensitivity C-reactive protein (hs-CRP) and TSH reflex. Urinary ketones were evaluated using Ketostix strips (Bayer, Germany). All biochemical analyses were conducted in 3 certified clinical laboratories in the Milan area. All samples from each participating subject were collected and analyzed in the same laboratory. LDL cholesterol (LDL-C) was calculated according to the Friedewald formula [26]. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as follows: HOMA-IR = (fasting glucose (mmol/L) × insulin (mU(mL))/22.5) [27]. The triglyceride-glucose (TyG) index was calculated as follows: ln (TG × FPG/2). Creatinine clearance was calculated according to the Cockroft-Gault formula [28].

2.4. Statistical Analysis

Sample size calculation. A sample size of at least 26 subjects in the study group achieves 90% power to detect a reduction of 10% in body weight vs. population of obese women in the same range of BMI (from 27 to 37 kg/m^2; mean body weight = 85 kg; standard deviation = 13 kg), with a type I error rate of 5%. The cardiovascular risk score was calculated according to the Framingham Risk Score using lipid values (FRS lipids) and using BMI (FRS BMI) [29] and the EAS/ESC SCORE for low-risk countries (like Italy) [30]. A per protocol analysis was performed. Quantitative variables are presented as mean values ± standard deviation, SD), while qualitative variables are presented as frequencies. Comparisons between continuous variables across visits were performed by using the non-parametric Friedman test for k mutually related samples. All reported *p*-values are based on two-sided tests and compared to a significance level of 5%. All statistical analyses were performed using IBM SPSS Statistics software package for Windows, Version 25.0. Armonk, NY, USA: IBM Corp.

3. Results

3.1. Study Population

The study included women with upper-range overweight or grade 1–2 obesity and was conducted in a real-life setting. Among the 44 eligible patients, 11 were excluded before the start of the VLCKD program, due to personal reasons or duties, such as lack of motivation in undergoing the dietary plan or family problems (Figure 2). Therefore, 33 subjects were allocated to the VLCKD program, and, since 3 participants dropped-out during phase 1 (n = 2) or phase 2 (n = 1) by directly declaring to exit from the VLCKD program, due to lack of interest/motivation, 30 subjects completed the study (Figure 2) and their baseline data are reported in Table 1. The study subjects had a BMI of 30.9 ± 2.7 kg/m^2, with a relevant abdominal adiposity (WC: 96.0 ± 9.4 cm), mild dyslipidemia (LDL-C: 144.0 ± 33.6 mg/dL; non HDL-cholesterol (non-HDL-C): 164.9 ± 35.7 mg/dL) and some degree of insulin resistance, as shown by a moderately elevated HOMA-IR (3.17 ± 2.67).

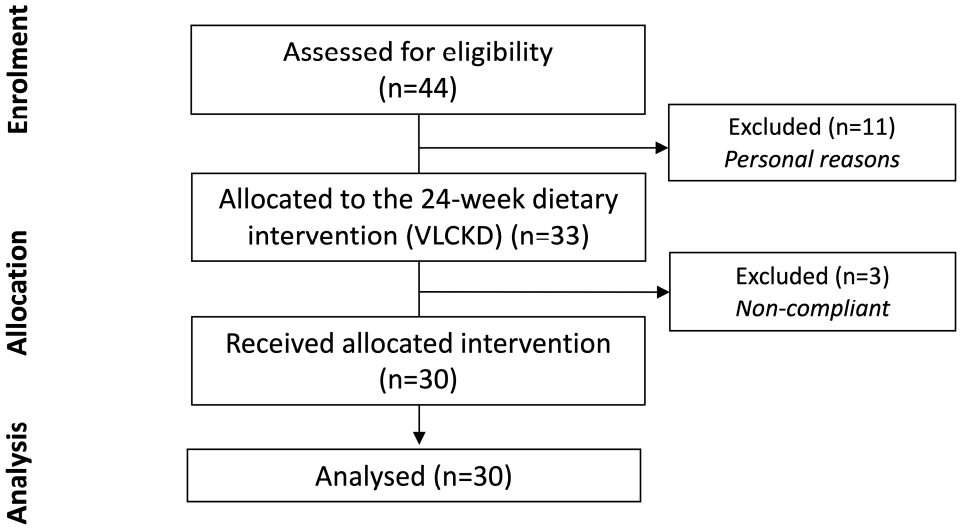


Figure 2. CONSORT statement flow diagram.

Table 1. Baseline data (n = 30).

	MEAN ± SD	MINIMUM	MAXIMUM
Age (years)	49.5 ± 7.2	27	60
Weight (kg)	81.8 ± 10.9	63.0	104.6
Height (m)	1.62 ± 0.07	1.48	1.78
BMI (kg/m^2)	30.9 ± 2.7	26.96	36.06
Waist circumference (cm)	96.0 ± 9.4	80.0	114.0
Hip circumference (cm)	113.1 ± 7.7	100.0	130.0
Waist-to-hip ratio	0.85 ± 0.08	0.72	1.04
SBP (mmHg)	127.2 ± 10.2	110	160
DBP (mmHg)	81.5 ± 8.9	60	100
Heart rate (bpm)	69.4 ± 6.3	52	80
FPG (mg/dL)	95.1 ± 15.6	73	155
HbA1c (mmol/mol)	36.98 ± 5.19	30.05	58.40
Insulin (mU/L)	12.65 ± 7.31	3.00	39.60
HOMA-IR	3.17 ± 2.67	0.64	15.16
Total cholesterol (mg/dL)	223.0 ± 37.7	159	339
HDL-cholesterol (mg/dL)	58.0 ± 12.9	37.3	82.7
Non HDL-cholesterol (mg/mL)	164.9 ± 35.7	101.3	289.3
Triglycerides (mg/dL)	104.7 ± 41.4	44	208
LDL-cholesterol (mg/dL) (*)	144.0 ± 33.6	80.1	248.3
Uric acid (mg/dL)	4.6 ± 1.0	3.1	6.6
AST (mg/dL)	18.5 ± 4.6	12	32
ALT (mg/dL)	20.5 ± 12.2	8	63
γ-GT (mg/dL)	21.0 ± 8.6	10	46
Creatinine (mg/dL)	0.74 ± 0.13	0.44	0.98
Creatinine clearance (mL/min)	122.40 ± 33.09	73.65	221.49
BUN (mg/dL)	33.39 ± 8.62	22.40	51.00
TSH (mUI/L)	2.38 ± 0.80	1.01	3.70

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA IR, homeostatic model assessment for insulin resistance; AST, aspartate transaminase; ALT, alanine transaminase; γ-GT, gamma-glutamyl transferase; BUN: blood urea nitrogen; TSH, thyroid-stimulating hormone. (*) calculated by the Friedewald formula.

3.2. Analysis of the Ketogenetic Effect of VLCKD

The determination of urinary ketones, an indirect index of carbohydrate restriction and adherence to the proposed dietary plan based on a VLCKD approach, was performed in order to evaluate the actual presence of ketogenesis produced by dietary carbohydrate restriction during the first 2 phases of the protocol. As expected, urinary ketones were not detectable at baseline. The occurrence of dietary-induced ketogenesis, detected by the

presence of urinary ketones, was observed in 78% of the patients after phase 1 and in 50% of the patients after phase 2.

3.3. Effect of VLCKD on Anthropometric Parameters

Over the entire VLCKD program, which lasted 24 weeks, all anthropometric parameters were progressively improved, with a total significant decrease of 14.6% in body weight and BMI (Figure 3A), 12.4% in WC (Figure 3B) and 10.0% in HC, resulting in a lower (−2.7%) Waist-to-Hip ratio (WHR) (Figure 3C). It should be highlighted that the reduction of BMI and WC in a single-phase, although significant after each of them compared to the start value, was greater during phases 1–2 (BMI: −6.2% and −4.9%, WC: −4.7% and −4.6%, respectively) (Figure 3A,B), although some contribution to total weight loss was observed in all subsequent phases, leading to a cumulative 11.5 kg weight loss, on average. At the end of the VLCKD protocol, 33.3% of the participants reached a normal weight and the obesity prevalence was reduced from 70% to 16.7%. As a consequence, the overweight group rose from 30 to 50% (Figure 4).

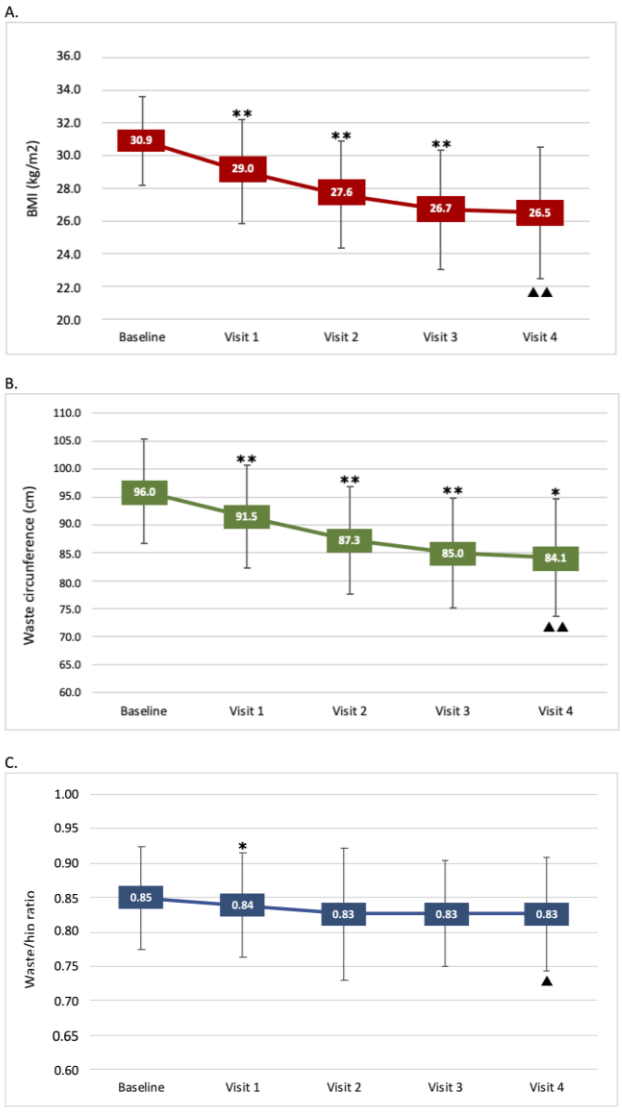


Figure 3. Effect of the VLCKD program on BMI, waist circumference and waist/hip ratio. (**A**) BMI changes during the 24-week program; (**B**) waist circumference during the 24-week program; (**C**) waist/hip ratio during the 24-week program. Data are mean ± SD. (*) $p < 0.05$ and (**) $p < 0.001$: p-value across consecutive visits. (▲) $p < 0.05$ and (▲▲) $p < 0.001$: p-value for trend.

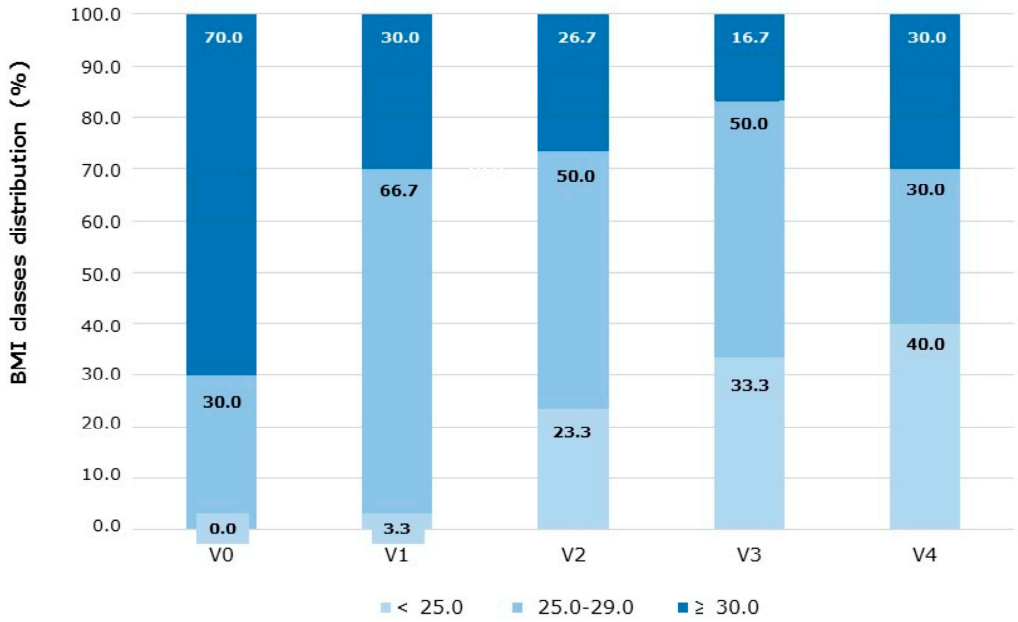


Figure 4. Effect of the VLCKD program on the BMI classes distribution. The relative % distribution of patients in the normal weight (<25.0 kg/m^2), overweight (<25.0–29.9 kg/m^2) and obese (>30 kg/m^2) BMI classes, over the 24-week VLCKD program, is reported. V, visit.

3.4. Effect of VLCKD on Glucometabolic and Cardiovascular Parameters

At baseline, patients enrolled in the study displayed a moderate rate of insulin resistance (HOMA-IR: 3.17 ± 2.67) (Table 1. The VLCKD program showed a specific effect on this parameter, as it was significantly reduced to 1.73 ± 1.23 (−38.0%; $p = 0.003$) at the end of phase 2, due to reduction of both plasma insulin (−35.0%; $p < 0.001$) and FPG (−8.7%; $p = 0.002$), in association with reduced HbA1c (−5.6%; $p = 0.008$), and then remained unchanged after phase 3 (Table 2). The TyG index was also significantly improved ($p < 0.001$) (Table 2). No changes in uric acid levels were observed (Table 3). SBP decreased after phase 1 (−3.5 mmHg; −2.5%; $p = 0.006$) and then remained unchanged until the end of the program. As reported above, the study subjects showed moderate baseline hypercholesterolemia (TC 223.0 ± 37.7) mg/dL). TC, TG and LDL-C were significantly reduced by the VLCKD program after phase 3, along with a significant increase of HDL-C ($p = 0.027$), resulting in reduced non-HDL-C (Table 3). The individual change of LDL-C level showed some variability since 6/30 patients displayed no changes and 6/30 had moderately increased concentrations (maximum 158 mg/dL in one case). Moreover, hsCRP (always below 0.1 mg/L; not shown) and uric acid (Table 3) concentrations did not significantly change during the intervention. At baseline, the study subjects were almost entirely at very low/low CVD risk, according to FRS lipids, FRS BMI and EAS/ESC SCORE algorithms. Interestingly, however, the BMI and lipid improvements driven by VLCKD resulted in a mean absolute reduction of these scores: FRS lipids (from 1.99 ± 1.57 to 1.53 ± 1.20), FRS BMI (from 6.23 ± 4.13 to 5.05 ± 3.12) and EAS/ESC SCORE (from 0.42 ± 0.34 to 0.36 ± 0.30), due to the specific reduction in the few with higher CVD risk.

Table 2. Effect of VLCKD on glucometabolic parameters.

		Mean ± SD	Absolute Change (% Change)	*p*-Value *
FPG (mg/dL)	Baseline Visit 2 Visit 3	95.1 ± 15.6 85.9 ± 12.1 85.8 ± 11.9	−9.3 (−9.8)	0.001
HbA1c (mmol/mol)	Baseline Visit 2 Visit 3	36.98 ± 5.19 34.75 ± 2.82 34.51 ± 3.14	−2.47 (−6.0)	0.001
Insulin (μU/mL)	Baseline Visit 2 Visit 3	12.65 ± 7.31 7.73 ± 4.92 7.93 ± 6.10	−4.72 (−37.3)	0.001
HOMA-IR	Baseline Visit 2 Visit 3	3.17 ± 2.67 1.73 ± 1.23 1.78 ± 1.82	−1.39 (−43.8)	0.001
TyG index	Baseline Visit 2 Visit 3	8.43 ± 0.45 8.05 ± 0.38 8.02 ± 0.49	−0.41 (−4.9)	0.001

FPG, fasting plasma glucose; HbA1c: glycosylated hemoglobin; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; TyG index, triglyceride-glucose index; * Friedman test for k mutually related samples.

Table 3. Effect of VLCKD on cardiovascular, lipid and safety parameters.

		Mean ± SD	Absolute Change (% Change)	*p*-Value *
SBP (mmHg)	Baseline Visit 1 Visit 2 Visit 3 Visit 4	127.2 ± 10.2 123.3 ± 9.8 123.2 ± 9.6 121.4 ± 8.4 123.7 ± 9.6	−3.5 (−2.8)	0.006
DBP (mmHg)	Baseline Visit 1 Visit 2 Visit 3 Visit 4	81.5 ± 8.9 80.1 ± 8.2 80.0 ± 9.3 78.6 ± 9.0 78.0 ± 8.6	−3.5 (−4.3)	0.211
HR (bpm)	Baseline Visit 1 Visit 2 Visit 3 Visit 4	69.4 ± 6.3 72.0 ± 6.7 69.7 ± 5.0 70.4 ± 6.8 69.1 ± 12.9	−0.3 (−0.4)	0.021
TC (mg/dL)	Baseline Visit 2 Visit 3	223.0 ± 37.7 194.8 ± 30.7 209.7 ± 28.4	−13.2 (−5.9)	0.000
HDL-C (mg/dL)	Baseline Visit 2 Visit 3	58.0 ± 12.9 52.7 ± 12.7 61.7 ± 13.0	3.3 (5.7)	0.000
TG (mg/dL)	Baseline Visit 2 Visit 3	104.7 ± 41.4 78.4 ± 29.1 77.6 ± 31.1	−27.1 (−25.9)	0.000
LDL-C (mg/dL) (°)	Baseline Visit 2 Visit 3	144.0 ± 33.6 126.4 ± 23.4 132.8 ± 23.7	−11.2 (−7.8)	0.000

Table 3. *Cont.*

		Mean ± SD	Absolute Change (% Change)	*p*-Value *
non HDL-C (mg/dL)	Baseline Visit 2 Visit 3	164.9 ± 35.7 142.1 ± 23.4 148.4 ± 24.4	−16.5 (−10.1)	0.000
TG/HDL-C	Baseline Visit 2 Visit 3	1.97 ± 1.14 1.62 ± 1.05 1.35 ± 0.73	−0.6 (−30.5)	0.001
Uric acid (mg/dL)	Baseline Visit 2 Visit 3	4.6 ± 1.0 4.5 ± 1.1 4.3 ± 1.1	−0.3 (−6.5)	0.093
AST (UI/L)	Baseline Visit 2 Visit 3	18.5 ± 4.6 19.5 ± 6.0 18.2 ± 5.3	−0.3 (−1.6)	0.246
ALT (UI/L)	Baseline Visit 2 Visit 3	20.5 ± 12.2 21.4 ± 13.5 19.0 ± 9.2	−1.5 (−7.3)	0.899
γ-GT (UI/L)	Baseline Visit 2 Visit 3	21.0 ± 8.6 16.0 ± 8.3 15.9 ± 9.1	−5.1 (−24.3)	0.000
Creatinine (mg/dL)	Baseline Visit 2 Visit 3	0.74 ± 0.13 0.73 ± 0.13 0.65 ± 0.11	−0.09 (−12.2)	0.004
CC (mL/min)	Baseline Visit 2 Visit 3	122.39 ± 33.09 110.32 ± 26.15 117.99 ± 25.59	−4.40 (−3.6)	0.026
BUN (mg/dL)	Baseline Visit 2 Visit 3	33.39 ± 8.62 35.35 ± 6.22 35.85 ± 8.94	2.46 (7.4)	0.092
TSH (mUI/L)	Baseline Visit 2 Visit 3	2.40 ± 0.77 2.21 ± 0.88 2.31 ± 0.86	−0.09 (−3.8)	0.629

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; HDL-C, HDL-cholesterol; TG, triglycerides; LDL-C, LDL-cholesterol; non-HDL-C, non-HDL-cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; γ-GT, gamma-glutamyl transferase; CC, creatinine clearance; BUN, blood urea nitrogen; TSH, thyroid-stimulating hormone; (°) calculated by the Friedewald formula; * Friedman test for k mutually related samples.

3.5. Effect of VLCKD on Markers of Liver, Kidney and Thyroid Function

At baseline, the markers of liver, kidney and thyroid function were within the reference range and remained within it over the entire duration of the VLCKD program (Table 3). A significant but moderate decrease was observed for γ-GT, creatinine and creatinine clearance (Table 3).

4. Discussion

This study aimed at evaluating the efficacy and the safety of a multiphasic VLCKD program, conducted in a multi-center real-world setting, in women with overweight or obesity. The main objective was to assess the actual health benefits of such approach in the context of the day-by-day management of these clinical conditions. The proposed multiphasic VLCKD program turned out to be safe, according to liver, kidney and thyroid biomarkers. Moreover, in the patients who completed the program, a set of important improvements related to cardiovascular function and cardiometabolic disease risk has been accomplished.

The efficacy data obtained show that the VLCKD program resulted in a significant reduction (−14.6%) of body weight and BMI, which is also greater than the 10% threshold proposed by the obesity guidelines [15]. The average absolute reduction of BMI (−4.4 kg/m^2) is similar to that obtained in hospital-based studies with a ketogenic phase up to 4 weeks (−4.2 kg/m^2) or at least 4 weeks (6.2 kg/m^2) [31]. Notably, the mean BMI value at the end of the protocol (26.5 kg/m^2) is just above the upper end (25 kg/m^2) of the normal range, with a reduction of subjects in the obese range from 70 to 16.7% at visit 3, but some weight regain at visit 4, leading to a final 30% obese subjects. On the other side, the percentage of subjects in the normal BMI range stably increased from 0% at baseline to 40% at the end of the VLCKD program. These findings may suggest that the health professional input is relevant not only in the initial phase of the VLCKD program but also in the last phase and the subsequent follow-up over the months and the years, in order to promote the longest time free of disease. Follow-up visits are important since, according to the obesity guidelines [15], once achieved, the body weight reduction of at least −10% or more should be maintained at least for 5 years to obtain an optimal benefit. Unfortunately, data from follow-up visits, after completion of the 6-month VLCKD program, could not be collected in this study, highlighting the relevant lack of long-term follow-up control visits in the real-world context. Possible reasons are lack of motivation, reduced synergy with the physician or the team and additional costs. In any case, this may clearly result in a long-term reduced benefit of the initial weight loss, since only one recommendation of the guidelines (weight reduction by at least −10%, but not 5 years maintenance) is fulfilled.

Interestingly, an additional important advantage of this VLCKD protocol was the marked decrease of WC, which was reduced by 11.9 cm to an average of 84.1 cm, which is even below the cut-off proposed by the harmonized criteria for metabolic syndrome [25] and in line with previous meta-analysis data [31]. Needless to say, this was a major benefit [8,32], which is reflected by the improvements of a several cardiometabolic biomarkers. In our study, we observed a reduction of SBP, TC, TG, LDL-C and a small but significant increase of HDL-C. The impact of VLCKD on LDL-C is still controversial in some instances, since it has been reported either unchanged [31] or reduced, such as, on average, in our study and in other recent studies conducted in men [33], or increased in a subset of patients (1 out of 4 patients) undergoing VLCKD [34], probably due to the impact of some gene variants [22]. These observations suggest that several factors, such as sex (our study included only women), the presence of selected gene variants, etc., may influence the individual LDL-C response to VLCKD and, indeed, also in our study we found some patients with no LDL-C changes and a few with a moderate increase of this marker. These findings then highlight the importance to evaluate LDL-C levels before and during/after a VLCKD program, making sure, when appropriate, to implement a specific diagnostic and therapeutic evaluation to assess ASCVD risk [35].

The overall reduction of CVD risk scores appears to be an important achievement of the VLCKD treatment evaluated in this study. Although the selected study cohort was already at low CVD risk at baseline, due to the female sex, no smoking, and the low-risk area (Italy) of their origin, the VLCKD program resulted in a further reduction (due to LDL-C and SBP reduction) of the SCORE CVD risk and of the FRS BMI and FRS lipids. Therefore, the VLCKD-driven improvement of several variables, either included or not in these risk algorithms, plays a role in reducing the global CVD risk.

A relevant reduction of insulin resistance, according to HOMA-IR reduction from 3.17 to 1.78 on average, represented another benefit, in line with other hospital-based studies [36]. Interestingly, subjects with HOMA-IR values above the threshold of 2, which indicates the presence of insulin resistance, were 66.7% at baseline but only 30% at the end of the protocol, suggesting that some participants did not fully improve their insulin resistance status.

These results obtained in a real-world setting thus appear comparable with those obtained in hospital-based studies and are relevant not only for body weight reduction per se but also of advantage in the overall reduction of primary CV and metabolic risk.

VLCKD may be a challenging approach for patients, especially in the first 2 phases, and requires a series of social and psychological features that may not be available to all subjects candidate to such treatment. This is reflected by a rather relevant rate of drop-out or non-compliance associated with VLCKD. Overall, 11/44 subjects either did not start our protocol and additional 3/33 (9%) dropped out within the first week of treatment, due to family reasons or lack of motivation to implement such a specific dietplan. Such drop-out rate is similar to that (7.5%) previously reported [31], suggesting that, since a VLCKD is obviously conducted as outpatients, the quality of the health personnel in our 5 clinical facilities was not substantially different from that present in research hospitals. It is important to emphasize that the maximum reduction of body weight/BMI and of WC as well as cardiometabolic improvements were achieved after completion of the entire VLCKD. Thus, it is important to avoid, especially in the real-world setting, the earlier interruption of such program after phases 1, 2 and 3, which sometimes happens due to excessively fast expectations by patients or quicker access to subsequent plastic surgery. Interestingly, some strategies to improve adherence to VLCKD in the real-world setting have been recently published [37,38]

This study has some limitations. A control group undergoing standard of care treatment (i.e., a low-calorie balanced diet) was not included, which does not allow one to compare this approach to the VLCKD one, when referring, for example, to CVD risk reduction. In this regard, a study reporting the comparison between VLCKD and standard low-calorie diet in the treatment of obesity in a hospital setting [39] showed that, over a 12-month timeframe, the VLCKD intervention was associated with much greater improvement of anthropometric parameters.

Moreover, no body composition assessment or indirect calorimetry could be conducted and no blinding was possible, nor was the compilation of a food diary was achievable. In addition, only three blood samplings were performed, along with the five visits, without the possibility to collect and store additional serum samples for additional experimental determinations (i.e., adipokines and pro-inflammatory cytokines). This precluded the opportunity for a more detailed cardiometabolic study, for example, evaluating the leptin: adiponectin ratio, which is markedly reduced by loss of adipose mass and has been shown to predict carotid intima-media thickness in males [40] or of circulating ghrelin levels [19,41]. Importantly, men and non-Caucasian subjects could not be included in this study since both are not referring in a relevant way to clinical practice for VLCKD in Italy.

The findings of this study on a multi-center VLCKD program conducted in a real-world setting in a cohort of women with overweight or obesity indicate that it is safe and effective since it results in a major improvement of cardiometabolic parameters, thus leading to benefits that span well beyond the mere body weight/abdominal adiposity reduction, as they lead to a decreased primary CVD and metabolic risk. Our data cannot however be directly extended to women with severe obesity (BMI > 37 kg/m^2) and relevant organ complication or failure, or to the male sex, which should be the focus of specific studies. Future developments in the practical application of VLCKD, especially in real-world clinics, may include the evaluation of genomic determinants of responsiveness to VLCKD and their clinical implementation following rigorous frameworks for gene variant interpretation [34].

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/nu13061804/s1, Table S1: Concomitant medications; Table S2A: Composition of the PentaCal supplement; Table S2B: Composition of the Protiligne meal replacement (range of content per portion).

Author Contributions: Conceptualization, P.M.; methodology, L.V., M.R.; software, E.T.; validation, P.M., E.T. and A.L.C.; formal analysis, M.C., E.T.; investigation, L.V., A.S. and C.M.; resources, P.M., A.L.C.; data curation, P.M., M.C.; writing—original draft preparation, P.M., E.T.; writing, review and editing, P.M., A.L.C.; project administration, P.M.; funding acquisition, P.M. All authors have read and agreed to the published version of the manuscript.

Funding: The study was supported by a non-conditioning grant by New Penta srl (Milan, Italy) to P.M. The funding sponsors had no role in the design of the study; in collection, analyses, or interpretation of data; in the manuscript writing; or in the decision to publish the results. The work of A.L.C., P.M. and M.C. at MultiMedica was supported by Ministry of Health—Ricerca Corrente—IRCCS MultiMedica).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (Italy) (approval N°441/2011).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

Acknowledgments: The Authors gratefully acknowledge the expert support of Valter Rota and Mauro Giulietti and the clinical collaboration of Simona Ferrero, Raffaella Elena Monti, Simona Nichetti and Valeria Rizzi.

Conflicts of Interest: P.M., E.T., L.V., M.R., C.M., M.C., and A.S. have no conflict of interests. A.L.C. has received honoraria, lecture fees, or research grants from: Akcea, Amgen, Astrazeneca, Eli Lilly, Genzyme, Kowa, Mediolanum, Menarini, Merck, Pfizer, Recordati, Sanofi, Sigma Tau, Amryt, and Sandoz.

References

1. Casanueva, F.F.; Moreno, B.; Rodríguez-Azeredo, R.; Massien, C.; Conthe, P.; Formiguera, X.; Barrios, V.; Balkau, B. Relationship of abdominal obesity with cardiovascular disease, diabetes and hyperlipidaemia in Spain. *Clin. Endocrinol.* **2010**, *73*, 35–40. [CrossRef]
2. Flegal, K.M.; Carroll, M.D.; Kit, B.K.; Ogden, C.L. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA* **2012**, *307*, 491–497. [CrossRef]
3. Afshin, A.; Forouzanfar, M.H.; Reitsma, M.B.; Sur, P.; Estep, K.; Lee, A.; Marczak, L.; Mokdad, A.H.; Moradi-Lakeh, M.; Naghavi, M.; et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N. Engl. J. Med.* **2017**, *377*, 13–27. [CrossRef]
4. Blüher, M. Obesity: Global epidemiology and pathogenesis. *Nat. Rev. Endocrinol.* **2019**, *15*, 288–298. [CrossRef]
5. Magni, P.; Bier, D.M.; Pecorelli, S.; Agostoni, C.; Astrup, A.; Brighenti, F.; Cook, R.; Folco, E.; Fontana, L.; Gibson, R.A.; et al. Perspective: Improving Nutritional Guidelines for Sustainable Health Policies: Current Status and Perspectives. *Adv. Nutr.* **2017**, *8*, 532–545. [CrossRef] [PubMed]
6. Yumuk, V.; Tsigos, C.; Fried, M.; Schindler, K.; Busetto, L.; Micic, D.; Toplak, H. European Guidelines for Obesity Management in Adults. *Obes. Facts* **2015**, *8*. [CrossRef]
7. Riaz, H.; Khan, M.S.; Siddiqi, T.J.; Usman, M.S.; Shah, N.; Goyal, A.; Khan, S.S.; Mookadam, F.; Krasuski, R.A.; Ahmed, H. Association between Obesity and Cardiovascular Outcomes: A Systematic Review and Meta-analysis of Mendelian Randomization Studies. *JAMA Netw. Open* **2018**, *1*, e183788. [CrossRef] [PubMed]
8. Neeland, I.J.; Ross, R.; Després, J.P.; Matsuzawa, Y.; Yamashita, S.; Shai, I.; Seidell, J.; Magni, P.; Santos, R.D.; Arsenault, B.; et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: A position statement. *Lancet Diabetes Endocrinol.* **2019**, *7*. [CrossRef]
9. Yumuk, P.F.; Dane, F.; Yumuk, V.D.; Yazici, D.; Ege, B.; Bekiroglu, N.; Toprak, A.; Iyikesici, S.; Basaran, G.; Turhal, N.S. Impact of body mass index on cancer development. *J. BUON* **2008**, *13*, 55–59. [PubMed]
10. De Backer, G.G. Prevention of cardiovascular disease: Much more is needed. *Eur. J. Prev. Cardiol.* **2018**, *25*, 1083–1086. [CrossRef]
11. Joseph, P.; Leong, D.; McKee, M.; Anand, S.S.; Schwalm, J.D.; Teo, K.; Mente, A.; Yusuf, S. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. *Circ. Res.* **2017**, *121*, 677–694. [CrossRef] [PubMed]
12. Kraak, V.I.; Swinburn, B.; Lawrence, M.; Harrison, P. An accountability framework to promote healthy food environments. *Public Health Nutr.* **2014**, *17*, 2467–2483. [CrossRef]
13. Donini, L.M.; Cuzzolaro, M.; Gnessi, L.; Lubrano, C.; Migliaccio, S.; Aversa, A.; Pinto, A.; Lenzi, A. Obesity treatment: Results after 4 years of a Nutritional and Psycho-Physical Rehabilitation Program in an outpatient setting. *Eat. Weight. Disord.* **2014**, *19*, 249–260. [CrossRef] [PubMed]
14. Sacks, F.M.; Bray, G.A.; Carey, V.J.; Smith, S.R.; Ryan, D.H.; Anton, S.D.; McManus, K.; Champagne, C.M.; Bishop, L.M.; Laranjo, N.; et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N. Engl. J. Med.* **2009**, *360*, 859–873. [CrossRef]
15. Bray, G.A.; Heisel, W.E.; Afshin, A.; Jensen, M.D.; Dietz, W.H.; Long, M.; Kushner, R.F.; Daniels, S.R.; Wadden, T.A.; Tsai, A.G.; et al. The Science of Obesity Management: An Endocrine Society Scientific Statement. *Endocr. Rev.* **2018**, *39*, 79–132. [CrossRef]
16. Gadde, K.M.; Martin, C.K.; Berthoud, H.R.; Heymsfield, S.B. Obesity: Pathophysiology and Management. *J. Am. Coll. Cardiol.* **2018**, *71*, 69–84. [CrossRef]

17. Paddon-Jones, D.; Westman, E.; Mattes, R.D.; Wolfe, R.R.; Astrup, A.; Westerterp-Plantenga, M. Protein, weight management, and satiety. *Am. J. Clin. Nutr.* **2008**, *87*, 1558S–1561S. [CrossRef]
18. Spadafranca, A.; Rinelli, S.; Riva, A.; Morazzoni, P.; Magni, P.; Bertoli, S.; Battezzati, A. Phaseolus vulgaris extract affects glycometabolic and appetite control in healthy human subjects. *Br. J. Nutr.* **2013**, *109*. [CrossRef]
19. Crujeiras, A.B.; Goyenechea, E.; Abete, I.; Lage, M.; Carreira, M.C.; Martínez, J.A.; Casanueva, F.F. Weight regain after a diet-induced loss is predicted by higher baseline leptin and lower ghrelin plasma levels. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 5037–5044. [CrossRef] [PubMed]
20. Hemmingsson, E.; Johansson, K.; Eriksson, J.; Sundström, J.; Neovius, M.; Marcus, C. Weight loss and dropout during a commercial weight-loss program including a very-low-calorie diet, a low-calorie diet, or restricted normal food: Observational cohort study. *Am. J. Clin. Nutr.* **2012**, *96*, 953–961. [CrossRef] [PubMed]
21. Basciani, S.; Costantini, D.; Contini, S.; Persichetti, A.; Watanabe, M.; Mariani, S.; Lubrano, C.; Spera, G.; Lenzi, A.; Gnessi, L. Safety and efficacy of a multiphase dietetic protocol with meal replacements including a step with very low calorie diet. *Endocrine* **2015**, *48*, 863–870. [CrossRef]
22. Caprio, M.; Infante, M.; Moriconi, E.; Armani, A.; Fabbri, A.; Mantovani, G.; Mariani, S.; Lubrano, C.; Poggiogalle, E.; Migliaccio, S.; et al. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: Systematic review and consensus statement from the Italian Society of Endocrinology (SIE). *J. Endocrinol. Investig.* **2019**, *42*, 1365–1386. [CrossRef]
23. Rolland, C.; Johnston, K.L.; Lula, S.; Macdonald, I.; Broom, J. Long-term weight loss maintenance and management following a VLCD: A 3-year outcome. *Int. J. Clin. Pract.* **2014**, *68*, 379–387. [CrossRef]
24. Moriconi, E.; Camajani, E.; Fabbri, A.; Lenzi, A.; Caprio, M. Very-Low-Calorie Ketogenic Diet as a Safe and Valuable Tool for Long-Term Glycemic Management in Patients with Obesity and Type 2 Diabetes. *Nutrients* **2021**, *13*, 758. [CrossRef] [PubMed]
25. Alberti, K.G.; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Cleeman, J.I.; Donato, K.A.; Fruchart, J.C.; James, W.P.; Loria, C.M.; Smith, S.C.; et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* **2009**, *120*, 1640–1645. [CrossRef]
26. Friedewald, W.T.; Levy, R.I.; Fredrickson, D.S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin. Chem.* **1972**, *18*, 499–502. [CrossRef]
27. Matthews, D.R.; Hosker, J.P.; Rudenski, A.S.; Naylor, B.A.; Treacher, D.F.; Turner, R.C. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* **1985**, *28*, 412–419. [CrossRef] [PubMed]
28. Cockcroft, D.W.; Gault, M.H. Prediction of creatinine clearance from serum creatinine. *Nephron* **1976**, *16*, 31–41. [CrossRef] [PubMed]
29. Andersson, C.; Johnson, A.D.; Benjamin, E.J.; Levy, D.; Vasan, R.S. 70-year Legacy of the Framingham Heart Study. *Nat. Rev. Cardiol.* **2019**, *16*. [CrossRef] [PubMed]
30. HeartScore. Access HeartScore—Full Version. Available online: https://www.heartscore.org/en_GB/access (accessed on 2 April 2021).
31. Castellana, M.; Conte, E.; Cignarelli, A.; Perrini, S.; Giustina, A.; Giovanella, L.; Giorgino, F.; Trimboli, P. Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis. *Rev. Endocr. Metab. Disord.* **2020**, *21*, 5–16. [CrossRef] [PubMed]
32. Ross, R.; Neeland, I.J.; Yamashita, S.; Shai, I.; Seidell, J.; Magni, P.; Santos, R.D.; Arsenault, B.; Cuevas, A.; Hu, F.B.; et al. Waist circumference as a vital sign in clinical practice: A Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat. Rev. Endocrinol.* **2020**, *16*. [CrossRef]
33. Mongioì, L.M.; Cimino, L.; Condorelli, R.A.; Magagnini, M.C.; Barbagallo, F.; Cannarella, R.; La Vignera, S.; Calogero, A.E. Effectiveness of a Very Low Calorie Ketogenic Diet on Testicular Function in Overweight/Obese Men. *Nutrients* **2020**, *12*, 2967. [CrossRef] [PubMed]
34. Aronica, L.; Volek, J.; Poff, A.; D'agostino, D.P. Genetic variants for personalised management of very low carbohydrate ketogenic diets. *BMJ Nutr. Prev. Health* **2020**, *3*, 363–373. [CrossRef] [PubMed]
35. Ference, B.A.; Graham, I.; Tokgozoglu, L.; Catapano, A.L. Impact of Lipids on Cardiovascular Health: JACC Health Promotion Series. *J. Am. Coll. Cardiol.* **2018**, *72*, 1141–1156. [CrossRef] [PubMed]
36. Watanabe, M.; Risi, R.; Camajani, E.; Contini, S.; Persichetti, A.; Tuccinardi, D.; Ernesti, I.; Mariani, S.; Lubrano, C.; Genco, A.; et al. Baseline HOMA IR and Circulating FGF21 Levels Predict NAFLD Improvement in Patients Undergoing a Low Carbohydrate Dietary Intervention for Weight Loss: A Prospective Observational Pilot Study. *Nutrients* **2020**, *12*, 2141. [CrossRef] [PubMed]
37. Gibson, A.A.; Sainsbury, A. Strategies to Improve Adherence to Dietary Weight Loss Interventions in Research and Real-World Settings. *Behav. Sci.* **2017**, *7*, 44. [CrossRef]
38. Muscogiuri, G.; Barrea, L.; Laudisio, D.; Pugliese, G.; Salzano, C.; Savastano, S.; Colao, A. The management of very low-calorie ketogenic diet in obesity outpatient clinic: A practical guide. *J. Transl. Med.* **2019**, *17*, 356. [CrossRef] [PubMed]
39. Moreno, B.; Bellido, D.; Sajoux, I.; Goday, A.; Saavedra, D.; Crujeiras, A.B.; Casanueva, F.F. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. *Endocrine* **2014**, *47*, 793–805. [CrossRef]

40. Norata, G.D.; Raselli, S.; Grigore, L.; Garlaschelli, K.; Dozio, E.; Magni, P.; Catapano, A.L. Leptin:adiponectin ratio is an independent predictor of intima media thickness of the common carotid artery. *Stroke* **2007**, *38*. [CrossRef] [PubMed]
41. Bertoli, S.; Magni, P.; Krogh, V.; Ruscica, M.; Dozio, E.; Testolin, G.; Battezzati, A. Is ghrelin a signal of decreased fat-free mass in elderly subjects? *Eur. J. Endocrinol.* **2006**, *155*, 321–330. [CrossRef] [PubMed]

nutrients

MDPI

Review

Alternative Dietary Patterns for Americans: Low-Carbohydrate Diets

Jeff S. Volek [1,*], Stephen D. Phinney [2], Ronald M. Krauss [3], Richard J. Johnson [4], Laura R. Saslow [5], Barbara Gower [6], William S. Yancy, Jr. [7], Janet C. King [8], Frederick M. Hecht [9], Nina Teicholz [10], Bruce R. Bistrian [11] and Osama Hamdy [12]

1 Department of Human Sciences, Ohio State University, Columbus, OH 43017, USA
2 Virta Health, San Francisco, CA 94015, USA; steve@virtahealth.com
3 Departments of Pediatrics and Medicine, University of California, San Francisco, CA 94143, USA; ronald.krauss@ucsf.edu
4 Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA; richard.johnson@cuanschutz.edu
5 Department of Behavior & Biological Sciences, University of Michigan, Ann Arbor, MI 48109, USA; saslowl@umich.edu
6 Department of Nutrition Sciences, University of Alabama, Birmingham, AL 35233, USA; bgower@uab.edu
7 Department of Medicine, Lifestyle and Weight Management Center, Duke University, Durham, NC 27705, USA; will.yancy@duke.edu
8 Department of Nutritional Sciences & Toxicology, University of California, Berkley, CA 94720, USA; janet.king@ucsf.edu
9 Osher Center for Integrative Medicine, University of California San Francisco, San Francisco, CA 94115, USA; rick.hecht@ucsf.edu
10 The Nutrition Coalition, New York, NY 10011, USA; teicholz@gmail.com
11 Beth Israel Deaconess Medical Center, Boston, MA 02215, USA; bbistria@bidmc.harvard.edu
12 Joslin Diabetes Center, Harvard Medical School, Boston, MA 02215, USA; osama.hamdy@joslin.harvard.edu
* Correspondence: volek.1@osu.edu; Tel.: +614-688-1701

Abstract: The decades-long dietary experiment embodied in the Dietary Guidelines for Americans (DGA) focused on limiting fat, especially saturated fat, and higher carbohydrate intake has coincided with rapidly escalating epidemics of obesity and type 2 diabetes (T2D) that are contributing to the progression of cardiovascular disease (CVD) and other diet-related chronic diseases. Moreover, the lack of flexibility in the DGA as it pertains to low carbohydrate approaches does not align with the contemporary trend toward precision nutrition. We argue that personalizing the level of dietary carbohydrate should be a high priority based on evidence that Americans have a wide spectrum of metabolic variability in their tolerance to high carbohydrate loads. Obesity, metabolic syndrome, and T2D are conditions strongly associated with insulin resistance, a condition exacerbated by increased dietary carbohydrate and improved by restricting carbohydrate. Low-carbohydrate diets are grounded across the time-span of human evolution, have well-established biochemical principles, and are now supported by multiple clinical trials in humans that demonstrate consistent improvements in multiple established risk factors associated with insulin resistance and cardiovascular disease. The American Diabetes Association (ADA) recently recognized a low carbohydrate eating pattern as an effective approach for patients with diabetes. Despite this evidence base, low-carbohydrate diets are not reflected in the DGA. As the DGA Dietary Patterns have not been demonstrated to be universally effective in addressing the needs of many Americans and recognizing the lack of widely available treatments for obesity, metabolic syndrome, and T2D that are safe, effective, and sustainable, the argument for an alternative, low-carbohydrate Dietary Pattern is all the more compelling.

Keywords: low-carbohydrate; diets; high-fat; insulin resistance; obesity; type-2 diabetes; dietary guidelines; eating patterns

Citation: Volek, J.S.; Phinney, S.D.; Krauss, R.M.; Johnson, R.J.; Saslow, L.R.; Gower, B.; Yancy, W.S., Jr.; King, J.C.; Hecht, F.M.; Teicholz, N.; et al. Alternative Dietary Patterns for Americans: Low-Carbohydrate Diets. *Nutrients* **2021**, *13*, 3299. https://doi.org/10.3390/nu13103299

Academic Editor: Maria Luz Fernandez

Received: 16 July 2021
Accepted: 9 September 2021
Published: 22 September 2021

1. Introduction: The Current 2020 Dietary Guidelines Need Greater Flexibility

The current 2020-2025 Dietary Guidelines for Americans (DGA) recommends "Dietary Patterns" that provide little flexibility in the distribution of fat, protein, and carbohydrate. Relying on the "Acceptable Macronutrient Distribution Ranges (AMDR)," as defined by the National Academies, the 2020 DGA allows dietary fat to range from 20% to 35% of calories, and carbohydrate, from 45% to 65% [1]. Even more narrow ranges, modeled by the expert advisory committee for the DGA, show the government's recommended Dietary Patterns to be 29–32% fat and 51–54% carbohydrate, as a percent of total energy [2]. It is unclear which standard will drive the federal government's food and nutrition programs, but either can be considered relatively low in fat and high in carbohydrates, compared to the average American diet before the implementation of the DGA in 1980 [3]. In addition, the quality of carbohydrate consumed today is poor, with higher intakes of high-glycemic index carbohydrates including processed grains and simple sugars (e.g., high fructose corn syrup). These are narrow recommendations relative to the much broader range of carbohydrate consumed throughout human evolution [4], and the past or current DGA macronutrient recommendations clearly do not encompass a low-carbohydrate eating pattern.

Despite the AMDRs, carbohydrate is not an essential dietary macronutrient as there is no minimum requirement that prevents deficiency symptoms [5]. Over half of Americans have a diet-related chronic disease with some degree of insulin resistance involving carbohydrate intolerance [6,7], and thus many could benefit from limiting carbohydrate intake. Because accurate quantification of nutrient intake in most human studies is lacking, we do not emphasize comparisons among different low-carbohydrate diets in this review. Our central point is that an alternative eating pattern, characterized by lower carbohydrate and higher fat intake than is recommended by the 2020 Dietary Guidelines, is supported by a substantial body of evidence.

2. Low-Carbohydrate Diets Defined

There are no formal or universally accepted definitions for low-carbohydrate diets, although as the name implies, the key feature is a reduction in carbohydrate in the diet. Since variations in caloric intake significantly influence the percent of calories derived from carbohydrate at any given carbohydrate intake, it is preferred to define low-carbohydrate diets by their absolute content in grams. Currently, the U.S. Dietary Guidelines advise [8], and Americans typically consume, more than half of total calories derived from carbohydrate. Based on average caloric consumption data, this corresponds to a daily carbohydrate intake of more than 300 grams for men per day and 200 grams for women [9]. The National Academy of Sciences recommends a daily allowance (RDA) for carbohydrate of 130 grams. This carbohydrate requirement is presumably based on the minimum amount required to provide the brain with an adequate supply of glucose, although this rationale does not have a physiological basis, given that humans can make glucose from non-carbohydrate sources and that the brain can use alternative fuels like ketones. Nevertheless, these numbers provide context for determining a reasonable place to start in terms of defining low-carbohydrate diets. In alignment with others [10], we suggest that a definition of a low-carbohydrate diet is one consisting of fewer than 130 grams per day. This level of carbohydrate is a general threshold for purposes of broadly defining diets and does not necessarily reflect the wide variation in response to carbohydrate at the individual level. Because low-carbohydrate diets generally consist of no more than 130 grams per day (520 kcals) and moderate protein, the majority of other calories are derived from dietary fat. Thus, low-carbohydrate diets are often referred to as low-carbohydrate and high-fat (LCHF).

Ketogenic diets (KD) are a subset of low-carbohydrate diets that usually consist of less than 50 grams carbohydrate per day with adequate but not excessive protein, and varying amounts of fat depending on the intended body weight goals. Energy content of KD can fluctuate from very low-calorie (e.g., semi-starvation, <800 kcal/day) to mildly hypocaloric to eucaloric diets [11]. Ketogenic diets aim to increase the production of ketones, in order

to achieve a state of 'nutritional ketosis.' In nutritional ketosis, fatty acids and ketones rather than glucose become the body's primary sources of fuel. In the keto-adapted state, the liver typically consumes 50–75 grams of fat to produce and secrete 100–150 grams of ketones per day. In effect, fat-derived metabolites replace carbohydrates as a fuel source. Typical mixed diets (non low-carbohydrate diets) are associated with a low level of blood ketones, typically less than 0.2 mM [12,13]. By contrast, nutritional ketosis starts at a blood level of beta-hydroxybutyrate (the predominant circulating 'ketone') of 0.5 mM and extends up to 5 mM [12,13]. Carbohydrate, and to a lesser extent protein, both inhibit liver production of ketones. The amount of carbohydrate that can be consumed while still promoting nutritional ketosis varies from person to person, but a general range is 20–50 grams per day, assuming protein is not consumed in excess. Thus, ketogenic diets are very low in carbohydrate and moderate/adequate in protein, translating into a carbohydrate level less than 50 grams per day and a protein level between 1.2 to 2.0 grams per kilogram of adjusted body weight.

As defined by carbohydrate content, low-carbohydrate eating patterns could encompass approaches that vary widely in both total calories and protein and fat, which affects the percentage of macronutrients. Thus, it is preferred to define low-carbohydrate diets based on absolute amount of carbohydrate.

3. Unintended Consequences of the DGA: The Obesity and Type 2 Diabetes Epidemic

Since the first DGA was released 40 years ago, there has been a consistent emphasis on limiting fat, especially saturated fat, and replacement of much of those calories with carbohydrate or polyunsaturated fat. Consequently, and over time, there has been an increase in the absolute intake of carbohydrate, resulting in a dietary pattern temporally associated with the marked rise in obesity, insulin resistance and type 2 diabetes (T2D) [3] as well as an increase in total mortality across multiple countries [14]. Today, more than two-thirds of American adults are overweight or obese [6], one-half have either prediabetes or T2D [7], and the numbers continue to rise. The economic burden of diabetes exceeds $300 billion per year [15]. Despite billions of dollars in investments by the private and public sectors, traditional drug and lifestyle treatments have had limited success in curtailing the obesity and diabetes epidemics.

Indeed, excessive intake of carbohydrate was acknowledged and foreseen by previous Dietary Guidelines Advisory Committees (DGAC). The 2000 committee expressed concern that the government's low-fat advice "could engender an overconsumption of total calories in the form of carbohydrates, resulting in the adverse metabolic consequences of high-carbohydrate diets," adding, "Further, the possibility that overconsumption of carbohydrates may contribute to obesity cannot be ignored." [16]. In 2015, the DGA Report explained that dietary advice should not emphasize reducing total fat, because low-fat/high carbohydrate "diets are generally associated with dyslipidemia (hypertriglyceridemia and low HDL-C concentrations" [17], which are indicators of increased risk for cardiovascular disease [18,19]. For this reason, the 2015 DGAC Vice Chair noted that " . . . there is no conventional message to recommend low-fat diets" [20]. However, despite removing the "low-fat" language from the 2015 and 2020 DGA, the current advice to consume between 20% and 35% of calories as fat is almost exactly the traditional low-fat diet, as commonly defined in the scientific literature [21].

One conclusion from this 4-decade long national experiment driven by the DGA is that the one-size-fits-all public health approach that encouraged people to eat less fat resulted in many Americans replacing fat calories with a greater amount of carbohydrate [3]. According to government data, since 1965, Americans have decreased fat intake by 25% and increased carbohydrates by 30%, expressed as percent of total energy [3]. Coupled with the fact that many Americans are insulin resistant, it is not surprising that only a small subset of the population has maintained metabolic health in the context of the current, de-facto low-fat dietary guidelines [22].

4. The Role of Carbohydrate in the Obesity and T2D Epidemics

Since fat is the most calorically dense macronutrient and excess body fat is the hallmark of obesity, low-fat and low-calorie diets have been the cornerstones of recommendations to manage both the obesity and T2D epidemics. By contrast, an alternative hypothesis is that the epidemics of obesity and T2D are driven by a systemic metabolic distortion of fuel partitioning as a result of overconsumption of sugars and starches, the two major categories of carbohydrate providing calories in the human diet.

Metabolically, when dietary carbohydrate is replaced by fat, blood glucose and insulin do not increase as much after meals, facilitating a person's metabolism to rely to a greater degree on fat for fuel. By contrast, carbohydrate intake is the most potent stimulant of the secretion of insulin, a lipogenic and anti-lipolytic hormone that promotes fat storage and strongly inhibits a person's ability to mobilize and oxidize body fat. More specifically, insulin inhibits adipose tissue lipolysis and fatty acid oxidation – with effects that are both potent and immediate [23]. Over time, high carbohydrate consumption above a person's tolerance overwhelms the body's compensatory capacity to respond to persistent over-signaling from insulin, and, this, coupled with insulin's role in the development of excess adiposity, can lead to a condition called insulin resistance. This further potentiates hyperinsulinemia, which is strongly linked to metabolic syndrome pathogenesis and a higher risk for cardiovascular disease [24].

In addition to the effects of chronic hyperinsulinemia on fat production and metabolic syndrome, the intake of added sugars containing fructose has also been shown to induce features of metabolic syndrome [25]. Fructose appears to be relatively powerful in its effects in this regard, likely related to its effect on energy levels in the liver and brain [26]. Experimental studies also suggest that a high glycemic response to carbohydrates may promote fat production by stimulation of insulin, and also by production of fructose via the polyol pathway, which then stimulates fat synthesis and accumulation [27].

These observations point to a role of high-carbohydrate intake, especially fructose, in the development of obesity, metabolic syndrome, and T2D. In support of this view, a burgeoning body of scientific evidence demonstrates that metabolic improvements are intimately connected with carbohydrate restriction [28,29]. Embracing this perspective that excessive carbohydrate intake is a fundamental driver of our obesity and T2D epidemics would represent a break from the DGA to date, yet it would allow for greater therapeutic flexibility, as people could personalize carbohydrate restriction each according to one's metabolic needs.

5. Obesity and T2D Are Conditions Strongly Associated with Insulin Resistance

Clinically, insulin resistance (IR) refers to a state in which a given concentration of insulin is associated with a suboptimal response [30]. Conditions highly associated with IR (e.g., metabolic syndrome, pre-diabetes, T2D) are identified by some combination of hyperglycemia and hyperinsulinemia. The molecular details are complex and diverse, but we know that most features can be triggered by the over-consumption of carbohydrate beyond the person's capacity to use it for energy, and reversed by carbohydrate restriction [28,29], even before significant weight loss [31,32]. In this model, IR is correlated with, but not caused by, obesity.

Insulin resistance is the primary feature underlying T2D that exists across a continuum in the general population. Insulin action in cells is disrupted to varying extents, which can cause a wide spectrum of signs and symptoms such as increased weight/adiposity, high blood pressure, high blood glucose, excessive circulating insulin, chronic inflammation, and dyslipidemia. A primary feature of IR is an impaired ability of muscle cells to take up circulating glucose, which manifests as persistently high blood glucose. The ability of insulin to suppress hepatic glucose production may also be impaired, further contributing to high blood glucose. Since the majority of dietary carbohydrate appears in the blood as glucose, it is apparent that individuals with IR have a fundamental problem metabolizing dietary carbohydrate. In response to an inadequate ability to clear glucose from the blood,

a person with IR will divert a greater proportion of dietary carbohydrate to the liver, where much of it is converted to fat (i.e., *de novo* lipogenesis), as opposed to being oxidized for energy in skeletal muscle [33]. This greater conversion of dietary carbohydrate into fat, much of it entering the circulation as saturated fat [34], is an early metabolic abnormality that contributes to atherogenic dyslipidemia (i.e., high triglycerides, low HDL-C, and a predominance of small LDL particles), an atherogenic pattern that increases cardiovascular risk [18,19,35].

As a general phenomenon, increasing carbohydrate intake is a driver that moves people toward an IR phenotype, whereas decreasing carbohydrate intake promotes metabolic health (Figure 1). In other words, the IR and insulin sensitive phenotypes are the opposite ends of a continuum whose expression is primarily driven by an increased or decreased carbohydrate intake, respectively. The thresholds of carbohydrate intake that move a person up or down this continuum of metabolic health may vary by genetic factors and may be modulated by age, lifestyle (e.g., exercise, carbohydrate quality, stress, sleep quantity/quality, etc.), and potentially gender, although there are few rigorous studies examining gender differences. Such a model fits with the growing body of evidence supporting low-carbohydrate diets as an effective tool to manage multiple metabolic impairments attributed to IR [28,29,31,32]. In fact, a very low-carbohydrate eating plan was the only successful therapy for T2D before insulin and other therapies became available [36]. Viewed through this lens, a large percentage of Americans may be metabolically positioned to benefit from a low-carbohydrate diet. Although individuals with IR may be expected to exhibit greater metabolic improvement, people across the insulin sensitivity spectrum respond favorably to a low-carbohydrate eating pattern [37–40].

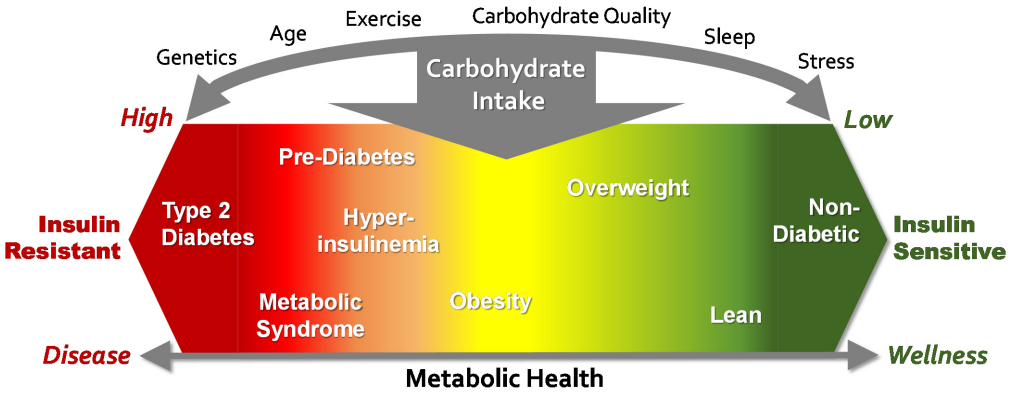


Figure 1. Expression of an insulin resistant or sensitive phenotype is a continuum that is strongly influenced by carbohydrate intake, with modulation based on genetic predisposition, age, and lifestyle choices.

Determining if a person is IR or carbohydrate intolerant and a good candidate for a low-carbohydrate or KD could be based on a number of observations and clinical tests. These measures can also be used to track progress over time. Standard clinical indicators of IR may include fasting glucose and insulin to calculate HOMA-IR, a glucose tolerance test including measures of insulin, or a diagnosis of prediabetes or type 2 diabetes based on fasting glucose or HbA1c. Other signs/symptoms of consuming carbohydrate at levels above an individual's tolerance include weight gain (especially in the mid-section), dyslipidemia (high triglycerides, low HDL-C), poor success with low-fat diets, wide fluctuations in blood glucose after carbohydrate intake, and low energy levels during the day.

6. Scientific Support for a Low-Carbohydrate Diet Option in the DGA

Low-carbohydrate diets have a long record of safe use. From a historical perspective, aboriginal hunting, fishing, and herding cultures survived for millennia with little available dietary carbohydrate [41–43]. A KD has been successfully used for 100 years in the treatment of epilepsy and diabetes [36,44–46], but this historical record of safe and

therapeutic use has been overshadowed during the last half century by the introduction of pharmacologic management of these conditions as well as concerns regarding the intake of saturated fat at high levels. Quality long-term studies addressing safety and efficacy of very low-carbohydrate diets are lacking. However, aboriginal cultures such as the Inuit, Maasai, and Native Americans who had limited access to dietary carbohydrate maintained good health [41–43]. Two Arctic explorers who lived among the pre-contact Intuit in the Arctic were sequestered in a metabolic ward and then closely monitored as outpatients for a total of 12 months each [42]. Throughout this period, they ate a meticulously analyzed diet (15% protein, 80% fat, and <5% carbohydrate) patterned after that of the Inuit, and both maintained their health and function for the duration of the study.

The metabolic and hormonal responses to a low-carbohydrate diet are associated with less oxidative stress and inflammatory responses after meals [12,47] as well as improvements in the features of IR and the metabolic syndrome [28,29,31,32]. These beneficial effects tend to increase in tandem with increased carbohydrate restriction. Evidence suggests that a KD may have unique therapeutic effects, owing in part to the increased endogenous production and availability of ketones which serve as both an alternative fuel and signaling molecule with wide-ranging health-promoting effects [48,49]. An increasing number of studies are now examining the basic science of ketones and their potential application across many indications (e.g., cancer, heart disease, neurological diseases, etc.). Ketones affect gene expression and pathways regulating inflammation, oxidative stress, immune function, membrane health, cell signaling, and antioxidant status [48–50].

Many different types of low-carbohydrate diets have been studied varying in total calories, the quantity and quality of carbohydrate, protein, and fat prescribed, as well as the level of education/support provided and adherence rates. For purposes of reviewing the published literature, the studies reviewed for this article share the common theme of aspiring to be carbohydrate restricted, generally targeting <130 grams of carbohydrate per day. Included among these studies are those intended to represent KD, which for most people require restricting carbohydrate to 30–50 g/day and, which may or may not have been verified by an objective measure of nutritional ketosis. As reviewed below, despite variability across studies in the formulation and implementation of diet interventions, a clear theme emerges — compared to low-fat diets, low-carbohydrate eating patterns result in equal or superior weight loss as well as the improvement of multiple established risk factors associated with IR and CVD [28,29,51]. Moreover, there may be unique, additional outcomes associated with KD including the superior benefits attributed to the increased availability of ketones that act both as a preferred fuel and a beneficial signaling molecule [48–50].

6.1. Obesity

While there is a body of literature examining the use of very low-calorie or semi-starvation KD (<800 kcal/day) in the medical treatment of obesity [11,52,53], the majority of more recent studies have involved mild caloric restriction. Several systematic reviews and meta-analyses have concluded that low-carbohydrate diets are at least as effective as low-fat diets for weight loss, and often more so [51,54–58]. Individuals who are insulin sensitive tend to respond well to either low-fat or low-carbohydrate diets, but those with insulin resistance tend to lose significantly more weight on the latter [59,60]. It is generally agreed that the primary driver of weight loss during a KD is greater satiety, resulting in a spontaneous reduction in calories [13,38,61–63]. Caloric restriction may be more sustainable on a low-carbohydrate diet because the lower insulin level and enhanced use of body fat for energy (including fatty acids and their derivatives, ketones) ensures increased mobilization of fat out of the fat tissues [23]. This results not only in weight loss but also more stable and efficient fuel delivery throughout the body, especially to the brain and the heart, and reduction in the wide excursions in blood glucose [64]. By contrast, low-fat diets usually require intentional caloric restriction as part of the dietary plan.

There is some initial water loss including reduced extra-vascular volume associated with the KD that contributes to rapid weight loss [65]. This loss of water is an expected positive outcome due primarily to the natural excretion of sodium (natriuresis) and fluid (diuresis) that occurs when insulin is reduced [66], which likely contributes to the blood pressure lowering effect of this eating pattern. Additional water is lost from metabolism of both intracellular glycogen (~3 grams of water is stored with each gram of glycogen) and fat, which can account for 2–3 kg weight loss during the first few weeks of a KD [65,67].

Whether weight loss is derived from fat-free mass or fat mass is important, as these have differing relationships to health [68]. Studies lasting beyond a few weeks that have measured body composition show a similar or greater loss of body fat in subjects on a low-carbohydrate diet compared to those on a low-fat diet [69–72]. Ketogenic diets also result in decreased visceral fat [38], which is highly associated with IR and metabolic impairment. In trials of very low-carbohydrate diets in adults with T2D, lean mass is preserved, and abdominal fat mass is reduced [73,74].

In the context of very low-calorie semi-starvation KD, a few studies have reported less protein sparing attributed to the KD [75,76], which could translate into a greater loss of lean mass over time. However, these studies [75,76] did not provide adequate protein and/or mineral replacement (sodium and potassium) [77]. Failure to compensate for the natriuretic effect of low-carbohydrate diets can lead to a general stress response (e.g., increased aldosterone, cortisol, catecholamine secretion), which may result in mineral imbalances (i.e., negative potassium balance) that adversely affect maintenance of lean tissue. A positive nitrogen balance on a KD, whether fed at a very low-calorie [78,79] or eucaloric [80] energy level, is achieved by ensuring adequate protein (i.e., ~1.2–2.0 g/kg ideal body weight) and minerals (see Section 7).

This success of very low-carbohydrate eating patterns for achieving weight loss and favorable body composition stands in contrast to several large trials, funded by the National Institutes of Health, which demonstrated that weight loss on a low-fat diet is limited [81]. For perhaps this reason, the 2020 DGAC decided to exclude all studies on weight loss [82], despite widespread acknowledgment that weight reduction among overweight and particularly among obese individuals is crucial for both primary and secondary prevention of chronic disease [83]. Furthermore, the DGA itself has long held, as one of its three primary goals, the objective of helping Americans "reach and maintain a healthy weight," [84] and the 2010 Dietary Guidelines stated, "[p]rimary prevention of obesity and related risk factors is the single most powerful public health approach to reversing America's obesity epidemic over the long term." [85].

Many long-term studies have shown no differences between low-carbohydrate and low-fat diet interventions after 1–2 years [86–90]. While it is tempting to conclude from these studies that the type of calories does not matter, these studies were associated with poor long-term dietary adherence and high attrition rates. Low-carbohydrate diet participants were allowed to increase their carbohydrate consumption as the trials progressed, making it likely that this reintroduction of carbohydrate blunted the benefits of carbohydrate restriction and led to weight regain. Despite similar weight loss among the comparison diets, the low-carbohydrate diets nevertheless consistently resulted in greater improvements in cardiometabolic risk markers [51,57].

6.2. Metabolic Syndrome

Metabolic syndrome is diagnosed when a person has at least three of the following physiologic signs: high triglycerides, low HDL-cholesterol, high fasting plasma glucose, high blood pressure, and high waist circumference [91]. Metabolic syndrome indicates a predisposition to T2D and cardiovascular disease. The condition has increased in parallel with higher carbohydrate intake over the last four decades, such that more than one in three American adults are now affected [92] and just one in eight Americans are metabolically healthy, where "healthy" is defined as having all five of these cardiometabolic risk markers in a normal range [22].

Dietary carbohydrate is a direct source of elevated blood glucose, which is the primary driver of insulin secretion. Therefore, low-carbohydrate diets naturally lead to fewer fluctuations in blood glucose and more stable insulin levels as evidenced in studies of individuals with T2D [74,93]. Consistent with the idea that a relative intolerance to carbohydrate is a common underlying feature of metabolic syndrome, clinical trials have shown that reductions in dietary carbohydrate, even without significant weight loss [31,32], result in improvements in the vast majority of cardiovascular and metabolic risk factors [28,29,51,56,57].

For example, outpatients with metabolic syndrome randomized to a 12-week KD lost more weight, total fat and abdominal fat compared to a matched group consuming a traditional low-fat, energy-restricted diet [12,13]. Patients consuming the KD also showed decreased serum triglycerides, increased HDL-C, decreased inflammatory markers and improved fatty acid composition profiles including lower circulating levels of saturated fat [12,13]. These experimental results point to the KD as a uniquely effective solution for addressing metabolic syndrome, with clear advantages over pharmaceutical approaches involving multiple drugs, often with significant cost and potentially harmful side effects [28,29].

6.3. Type 2 Diabetes (T2D)

A low-carbohydrate diet may provide exceptional benefits for T2D, which is essentially a disease of abnormal carbohydrate intolerance that affects more than 30 million Americans [7]. Even more alarming is the fact that 3-times that many people, or approximately 88 million U.S. adults, have prediabetes [7], that if left unchecked, can progress to T2D. Ketogenic diets were the treatment of choice for diabetes prior to the discovery of insulin in the early 1920s [36]. Insulin has been lifesaving for patients with type 1 diabetes. However, the use of insulin came at a high cost of weight gain as a side effect in patients with T2D, yet by the 1980s, this treatment, along with a low-fat, high-carbohydrate diet, had become the standard of care. Recently, the American Diabetes Association (ADA) has updated its nutrition recommendations to allow for more flexibility. Starting with their 2019 standards of care for patients with diabetes, the ADA stated that "Low-carbohydrate eating patterns, especially very low-carbohydrate (VLC) eating patterns, have been shown to reduce A1C and the need for antihyperglycemic medications. These eating patterns are among the most studied eating patterns for type 2 diabetes." [94,95]

Low-carbohydrate and KDs have therefore re-emerged as a scientifically validated dietary pattern for individuals with T2D. In fact, there is good evidence supporting the use of low-carbohydrate diets as the first-line approach to treating T2D and as the most effective co-therapy with insulin in type 1 diabetes, partly because carbohydrate restriction decreases the requirement for insulin, and therefore the multiple adverse effects of insulin [10].

Individuals with prediabetes and T2D have greater intraday glycemic variability [96], which may exacerbate oxidative stress and vascular endothelial damage [97]. In people with T2D, glycemic variability has been tied to a higher risk of renal disease, macrovascular events, ulceration/gangrene, cardiovascular disease, and mortality [98]. Given the primary effect of carbohydrate on insulin secretion, it is not surprising that very low-carbohydrate diets are related to lower glycemic variability in people with type 1 diabetes [99,100] and T2D [64,74,93,101], which at a basic level enables many of the positive responses observed in clinical trials.

Several well-controlled studies have evaluated the response of groups with T2D to low-carbohydrate and KDs over short- and long-term periods. After just 2-weeks of a low-carbohydrate diet in an inpatient setting, ten obese individuals with T2D demonstrated dramatic reductions in blood glucose and insulin levels, along with improved insulin sensitivity, and dyslipidemia [31]. Similar results have been reported over longer periods in outpatients [63,102–106]. For example, 363 pre-diabetic and diabetic subjects were offered either a standard low-fat/low-calorie diet or a KD for 6 months [106]. Weight loss and blood lipid changes were significantly better in the group receiving the KD.

An even longer study on 262 adults with T2D who received telemedicine counseling on a KD by a health coach and physician-guided medication management team demonstrated that over half of the participants reversed their T2D after 1 year [104], where T2D reversal was defined as having a HbA1c below 6.5% while taking no diabetes medication or only metformin. Subjects also successfully reduced body weight, by an average of 12%, improved most of their cardiovascular risk factors, and 94% of subjects eliminated or reduced use of insulin medication [104,107]. The majority of participants in this trial have remained engaged in the program with patient retention of 83% at 1-year and 74% at 2-years [61]. In a similar longitudinal study using this telemedicine approach over 2-years, 96 patients with pre-diabetes experienced a 52% reversal of their pre-diabetes diagnoses [63].

Improvements in diabetes outcomes with KD are also associated with decreased healthcare costs. A large survey of adults following a low-carbohydrate eating pattern reported reductions in the need for medications related to glycemic control, hypertension, pain, depression, anxiety, and sleep, with 25% reporting lower medication costs [108]. In a retrospective examination of 67 insulin-dependent adults with T2D at one year, 40% were able to discontinue their long-acting insulin, and 88% were able to reduce their short-acting insulin These reductions were calculated to save more than $6,500 a year in insulin per patient [109]. In a 9000-patient primary care practice in the United Kingdom that prescribes the KD, the cost for glycemic-control medications was the lowest cost-per-patient among the other 19 medical practices in the area [110]. After 1-year in adults with T2D, glycemic control medications were reduced more in the very low-carbohydrate diet group compared to the moderate-carbohydrate or the usual care group [104,106].

These multiple trials from diverse groups have revealed that contrary to the conventional wisdom, T2D may not, in fact, be a chronic progressive disease. A T2D diagnosis can safely be reversed in many people using a very low-carbohydrate eating pattern, often while discontinuing insulin and other glucose-lowering medications. These findings were confirmed in a recent meta-analysis [111].

6.4. Cardiovascular Disease (CVD)

A substantial body of published work over the past 20 years has documented that low-carbohydrate diets induce favorable changes in cholesterol and other CVD risk markers, especially the cluster of abnormal risk factors associated with the IR phenotype, including high triglycerides, low HDL-cholesterol, increased small, dense LDL particles, high blood sugar, hyperinsulinemia, hypertension, and chronic inflammation [12,13,28,29,56,57,112].

For example, in a randomized, parallel trial comparing the effects of a low-carbohydrate diet to a low-fat diet in obese adults, the low-carbohydrate diet after 1-year resulted in greater weight and fat loss, a larger increase in HDL-cholesterol, and greater decreases in triglycerides and C-reactive protein as well as other markers of inflammation and endothelial dysfunction [113,114]. In another trial comparing a calorie-unrestricted low-carbohydrate diet to a reduced-calorie, low-fat diet in obese individuals with metabolic syndrome, the low-carbohydrate KD diet after 3-months resulted in a significant reduction in fasting and postprandial triglycerides, increased HDL-cholesterol, decreased small LDL particles, decreased glucose and insulin, improved vascular functioning as assessed by flow-mediated dilation of the brachial artery, decreased circulating saturated fatty acids, and lower concentrations of several pro-inflammatory meditators [12,64,115]. After 1-year, a group of participants with T2D following a KD showed a small increase in LDL-cholesterol (LDL-C), but robust improvement in the vast majority of CVD risk markers including decreases in triglycerides, small LDL particles, blood pressure, antihypertensive medications, C-reactive protein, white blood cell count, and the 10-year atherosclerotic cardiovascular risk score [107].

These examples are further supported by results from a meta-analysis concluding that low-carbohydrate diets significantly lowered the predicted risk of developing atherosclerotic CVD [57]. Although decreased body mass often accompanies low-carbohydrate diets,

the broad-spectrum effects of low-carbohydrate diets on these CVD risk factors, including significant improvement in insulin sensitivity [31], are mostly independent of weight loss [31,32,40,115–117].

Chronic exposure to high levels of circulating insulin is a significant risk factor for CVD [118]. In non-diabetic adults, higher fasting and postprandial blood glucose and insulin are associated with substantially higher risk for CVD [119,120]. Reducing dietary carbohydrate, which is the primary driver of both blood glucose and insulin secretion, directly targets these problems. According to a meta-analysis that studied the relationship between insulin and CVD mortality in people without diabetes, those with the highest degree of IR compared to the lowest had a higher risk of CVD mortality [121]. Given the clear advantage of a low-carbohydrate diet in lowering circulating insulin throughout the day, these findings underscore the diet's potential for reducing risk of CVD.

It is notable that LDL-C increases on average in response to a low-carbohydrate diet, although the effect is quite variable [122]. While the LDL-C concentration may either increase or decrease in different individuals depending on mostly unknown factors, a low-carbohydrate diet consistently shifts the LDL sub-fraction pattern to a less atherogenic profile, characterized by fewer small LDL particles [12,32,39,40,107,117,123,124]. This favorable shift happens even in the setting of high LDL-C concentrations as demonstrated in highly insulin sensitive elite athletes [37]. The isolated increase in LDL-C observed in some individuals consuming a low-carbohydrate diet needs to be understood in the broader context of improvements in multiple other well-established CVD risk factors. Furthermore, LDL-C, when lowered by a low-fat diet, has not been shown to have the same beneficial effect as lowering LDL-C with medications [125,126].

In the context of low-carbohydrate/high-fat diets, saturated fat is typically consumed in higher amounts, yet multiple studies have reported that circulating levels of saturated fatty acids stay the same or even decrease [12,13,32,124,127–129]. The primary reason for this phenomenon is that increased dietary saturated fat does not accumulate in the body even when intake is as much as 3-fold higher, due to the fact that metabolic adaptation to low-carbohydrate diets dramatically increases oxidation of these fatty acids [13,130] while at the same time decreasing hepatic production of saturated fatty acids from carbohydrate (i.e., *de novo* lipogenesis) [33,131].

Lower levels of circulating saturated fatty acids have relevance to CVD risk, because longitudinal studies consistently show that people with higher levels of circulating saturated fatty acids are at increased risk for developing metabolic syndrome [132], diabetes [133–135], heart failure [136], and mortality [137]. The observations that excessive circulating saturated fatty acids are a significant risk factor are consistent with in vitro and animal studies linking saturated fat to pro-inflammatory effects [138]. Saturated fat from dairy products, however, has no impact on metabolic or cardiovascular parameters in patients with T2D. In a recent randomized clinical trial, high-fat dairy food has similar impact on A1C, lipid profile, body weight and blood pressure in patients with T2D in comparison to low-fat dairy when total caloric consumption per day is equated [139].

High-carbohydrate, low-fat diets have been shown to be more likely to increase not only circulating saturated fatty acids but also the monounsaturated fatty acid palmitoleic acid (cis-16:1n7), which is also a product of *de novo* lipogenesis [34]. There is a remarkable stepwise uniformity in the response of circulating palmitoleic acid in response to varying carbohydrate intakes [13,32,124]. Likewise, palmitoleic acid consistently decreases when carbohydrates are restricted, especially on a KD [13,32,124]. Palmitoleic acid is therefore a useful proxy for the metabolic pathway that converts carbohydrate to fat. High palmitoleic acid in the blood or in tissue membranes is strongly linked to a host of metabolic derangements including obesity and metabolic syndrome [132,140], T2D [135,141,142], heart failure [136,143], and CVD mortality [137,144].

More than a billion people internationally have hypertension, and uncontrolled or untreated high blood pressure, which is the strongest risk factor for CVD and stroke [145]. Consistent with other markers of metabolic syndrome, a low-carbohydrate diet consis-

tently decreases blood pressure in individuals with hypertension [58,104], which is likely mediated in part by lower circulating insulin levels and the associated natriuretic/diuretic effect described previously [66].

6.5. Low-Carbohydrate Diets and Mortality Outcomes

Concerns have been raised about the apparent association between low-carbohydrate diets and increased mortality. A search of Pubmed.gov yielded 14 such papers. Studies were excluded if there was no clear definition for "low-carbohydrate" [146–148] or if the paper did not isolate the link between a low-carbohydrate diet and health outcomes but instead reported on a score that combined intake measures of carbohydrate, fat and protein [149,150]. One systematic review was also identified, but that paper also did not report on the isolated link between a "low-carbohydrate" diet and health outcomes [151]. The remaining papers based their findings on cohorts from Japan [152], Sweden [153], the United Kingdom [154], and the United States [155–160]. In these 9 papers, "low-carbohydrate," as a percent of total energy, is defined as follows (listed in order of the citations in the previous sentence): 53% (Japan), 40% (Sweden), 40.9% (United Kingdom). 37%, 39%, 47.3%, 40%, 37.2%, and 43.2% (United States). None of these numbers falls within the current definition of a low-carbohydrate diet, which allows for carbohydrates at 30% of energy or less. Thus, these studies cannot be characterized as representing a true low-carbohydrate diet, and their conclusions cannot be viewed as relevant to the low-carbohydrate scientific literature. Interestingly, in the largest study published to date which included 135,335 individuals across 18 countries, higher carbohydrate intake was associated with an increased risk of total mortality, although this study too was not designed to test low-carbohydrate diets [14].

6.6. Qualitative Research

Qualitative and survey research has shown that adults consuming a low-carbohydrate eating pattern have positive health outcomes such as less hunger, greater energy, and improved health, but that lack of support from family and physicians can be a barrier to adherence [161,162]. Qualitative surveys of healthcare providers reveals that many practitioners have found low-carbohydrate diets to be helpful for their patients and as a consequence, have changed the way they view and practice healthcare [163].

In summary, an increasing body of scientific evidence indicate that low-carbohydrate diets are uniquely effective for combating IR, a root cause of obesity, metabolic syndrome, prediabetes, and T2D that affects well over 100 million Americans [6,7].

7. Principles of Very Low-Carbohydrate (Ketogenic) Diets

There are many different types of low-carbohydrate eating patterns that can vary in the quantity and quality of macronutrients. In general, a greater degree of IR and carbohydrate intolerance requires a greater level of carbohydrate restriction to manage this condition effectively, but the quality as well as the quantity of carbohydrate are both important considerations. Effective management of IR and its multiple manifestations may be improved by substituting lower quality carbohydrates with higher quality ones. For example, limiting simple and added sugars, especially fructose, as well as high-glycemic, overly processed, nutrient-depleted carbohydrate sources in favor of lower glycemic, nutrient-rich, whole foods (e.g., non-starchy vegetables, legumes) is likely to yield benefits on IR. The glycemic index is a method of determining the quality of carbohydrate-containing foods based on the 2-hr postprandial blood glucose response. High-glycemic foods raise blood glucose to a greater extent than low glycemic index food. The many variations and nuances of diets containing different amounts and sources of carbohydrate-containing foods are complex and beyond the scope of this review. However, since educational content specific to low-carbohydrate diets is absent from nearly all training of healthcare professionals, including dietitians, we provide a general overview of important considerations in designing the

most carbohydrate-restricted subset of low-carbohydrate eating patterns (i.e., a KD) aimed at achieving nutritional ketosis.

The formulation of safe, effective, palatable, and sustainable KD entails relatively simple adjustments in conventional diets, focused primarily on replacing sugar- and carbohydrate-dense foods with un-processed, low-carbohydrate/high-fat foods. Proper formulation of a KD entails restriction of carbohydrate and intake of adequate—but not high—protein and sufficient minerals to offset the natriuretic effect of ketosis and lower insulin levels. Counting calories is usually not necessary. Several studies demonstrate that obese individuals in nutritional ketosis instructed to eat to satiety, with no specific caloric prescription, spontaneously eat less and achieve sustainable weight loss [13,38,61–63].

8. Macronutrients

8.1. Carbohydrate

Carbohydrate, and to a far lesser extent, protein are the two primary dietary factors stimulating blood glucose and insulin responses while inhibiting blood ketones. The amount of time and level of carbohydrate restriction that are needed to normalize blood sugar and achieve nutritional ketosis vary widely from person to person. Nutritional ketosis usually requires less than 50 grams per day of carbohydrate but may range from 30 to >70 g/day across individuals [38]. Generally, the more overweight or IR the person at the start of the diet, the greater degree of carbohydrate restriction is needed to normalize blood glucose and insulin. The time needed for the body to achieve full metabolic adaptation to a KD takes at least several weeks if not months [130].

A wide range of nutrient-rich whole foods can be incorporated into KD, including non-starchy vegetables, meats (beef, chicken, pork, fish, shellfish, lamb), nuts and seeds, fruit oils (olive, avocado, coconut), cheeses, butter, cream, whole eggs, and small amounts of fruits (berries, olives, avocado, tomatoes, lemons/limes). Depending on the individual and the degree of carbohydrate restriction, the approximate daily carbohydrate allotment in terms of food sources generally breaks down as follows on a KD:

- 5–10 g from protein-based foods. Eggs, cheese, and shellfish will carry a few residual grams of carbohydrate from natural sources and added marinades and spices.
- 10–15 g from non-starchy vegetables.
- 5–10 g from nuts/seeds. Most nuts contain 5–6 g carb per ounce.
- 5–10 g from fruits such as berries, olives, tomatoes, avocados.
- 5–10 g from miscellaneous sources such as low-carb desserts, high-fat dressings or drinks with very small amounts of sugar.

8.2. Protein

Consuming too much protein will prevent a person from achieving nutritional ketosis, while consuming too little protein will adversely affect meal acceptability/satiety and potentially lead to loss of muscle mass and function. Target protein intakes are typically between 1.2 and 1.5 g/kg body weight. There is little evidence to support protein intakes higher than 2.0 g/kg, and such high levels of protein will make it harder to achieve nutritional ketosis. In the context of a weight maintenance KD, this level of protein is approximately 15–20% of the individuals' daily energy expenditure, which is similar to the current average protein intake in the standard American diet.

In people with excess adiposity, using actual body weight is likely to result in protein being over-prescribed. In these cases, use of ideal body weight (IBW) or adjusted body weight is warranted [164,165], although correction formulas are also limited in accuracy due to individual variations in physical activity, muscle mass, health status, and other factors influencing protein metabolism and requirements. The World Health Organization recommends a healthy body mass index (BMI) of 18.5 – 25 g/km^2, which can be used to determine an IBW range for any given height. Adjusted body weight = IBW + [(current weight – IBW) $\times$ 0.25].

Those who engage in moderate or vigorous activity may benefit from a slight increase in protein consumption, but the recommended range noted above is more than adequate to meet the needs of most active individuals with goals of muscle gain. Individuals with T2D typically lose 8% of their lean muscle mass every decade from age 40 and 15% per decade from age 70 [166]. Thus, ensuring adequate protein intake is important to offset this loss of muscle. Resistance training may be considered as a form of activity that helps preserve and build lean tissue, even in older adults [167].

Based upon published cardio-metabolic health responses to a well-formulated KD, there is no objective evidence in favor of avoiding animal protein consumed in moderation. However, individuals who choose a lacto-ovo vegetarian or even a vegan low-carbohydrate diet can do so successfully. If eggs and dairy proteins are restricted, attention to quality protein sources to achieve adequate essential amino acid intakes is warranted. And, as is true for any vegetarian diet that excludes eggs and fish, dietary supplements may be necessary to cover vitamin B12 and long-chain omega-3 fatty acid requirements.

8.3. Fat

Determining the appropriate amount of fat to eat on a KD is best achieved by encouraging people to eat to satiety. Emphasis should be placed on foods high in monounsaturated and saturated fatty acids while limiting sources rich in omega-6 polyunsaturated fatty acids (e.g., seed oils such as soybean, peanut, safflower, sunflower, corn). The primary functions of dietary fat in the context of a KD is to serve as fuel, add flavor and pleasure to meals, and to promote satiety. While omega-6 polyunsaturated fats are essential, the amount needed to meet this requirement is very small. Empirically, concentrated sources of polyunsaturated fats are not well tolerated at the high levels of fat consumed on KD due to gastro-intestinal symptoms. By contrast, monounsaturated and saturated fats are optimal fuels and should comprise most of the fat consumed. As noted previously, while KD that are higher in saturated fat can lead to increased circulating LDL-C, there is a net benefit on CVD risk factors in at-risk individuals (e.g., T2D) [28,29,51,56,57]. A minority of individuals, however, experience a marked increase in LDL-C, and it remains unknown whether this poses any long-term risk or if these individuals should limit foods with high saturated fatty acid content (e.g, fatty meats, full fat dairy products). These "hyper-responders" usually experience other clinical benefits attributed to the KD (e.g., weight loss and improvement in markers associated with IR). Finally, maintaining a good source of the long-chain omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, is also important. This can be achieved by consuming fatty fish (salmon, tuna, sardines, etc.) twice per week.

9. Micronutrients

A well-formulated low-carbohydrate/KD is not associated with micronutrient deficiencies [168]. When composed of unprocessed, natural foods, this diet contains adequate essential vitamins and minerals achieved through the consumption of a wide variety of whole foods prepared using appropriate methods to preserve nutrients. Certain medical conditions or avoidance of specific foods on a KD may necessitate supplementation. Below is a discussion of some of the most relevant nutrients that may require special attention.

9.1. Sodium and Potassium

Ensuring adequate sodium intake is particularly important because lower insulin and nutritional ketosis trigger increased excretion of sodium along with fluids. This natriuretic effect leads to the loss of both sodium and fluid, which, if not replaced, can have side effects. For many people who achieve nutritional ketosis, losing extra fluids results in perceived benefits such as rapid weight loss, reduced/eliminated need for diuretic medication, lessening of edema, and improved blood pressure. However, once the excess fluid has been cleared, this natriuretic effect of nutritional ketosis persists, causing continued losses of sodium and reduced blood plasma volume. Consequences can include dizziness, orthostatic hypotension, fainting, fatigue, constipation, and headaches. Other potential

consequences are adrenal stress, characterized by increased aldosterone, cortisol, and epinephrine. Aldosterone acts on the kidneys to increase sodium reabsorption to restore sodium balance, but in so doing accelerates the loss of potassium. Thus, sodium restriction on a KD can lead to potassium wasting by the kidneys. Negative potassium balance manifests as muscle twitches, cramps, irregular heartbeats, neuromuscular dysfunction, and loss of muscle mass.

Countering these potential side effects simply requires consuming adequate sodium and potassium. An additional 1–2 grams of sodium is generally needed beyond the normal consumption of about 3 g/day, for a total of 4–5 g/day for non-hypertensive individuals [169]. Recent research also indicates that an optimal target for potassium intake for adults is 4 grams per day [169]. The best sources of potassium are vegetables and homemade broths. Other good sources are avocados, nuts/seeds, canned salmon, and unprocessed meats. Intra-cellular potassium is released during cooking, so it is important not to discard nutrient-rich drippings when preparing meats, and to steam rather than boil vegetables. Thus, adequate sodium and potassium intake, which can be achieved though the selection of appropriate food sources and cooking methods, along with careful monitoring of symptoms, is critical to avoid potential side effects and optimize a person's ability to enjoy and continue with a ketogenic eating plan.

While ensuring adequate sodium intake is important, there is also increasing evidence that high salt intake may increase the risk for obesity, hypertension, and metabolic syndrome [170]. The mechanism appears to be that rising serum osmolality triggers the production of fructose [170,171]. These negative effects of high sodium intake can be reversed by hydration [171,172]. A recommendation of six to eight glasses of water a day, in addition to other fluid intake, is recommended.

9.2. Calcium

The recommended dietary allowance for calcium in adults is 1000–1200 mg/day. The primary and best source of calcium is dairy foods. Since many dairy foods like milk and yogurt contain several grams of carbohydrate, the best source of calcium on the KD is cheese, especially hard cheeses, such as parmesan, cheddar, gouda, and provolone, which contain virtually no carbohydrate. Green vegetables like broccoli, spinach, and kale also have calcium but less so than cheese and in a less bioavailable form. Other sources of calcium on a ketogenic diet include sour cream, tofu, sardines with bones, nuts/seeds, and home-made broths made from chicken or beef, including the bones. A calcium supplement is generally not needed on this diet if foods with calcium are consumed, but a supplement may be considered for people at risk for osteoporosis.

9.3. Magnesium

Magnesium is an essential mineral. Because it is often lost during food processing, marginal deficiency of this nutrient is not uncommon in the general population. Diuretic medications and heavy use of alcohol also deplete magnesium. Magnesium has a key role in muscle and nerve transmission. Since most magnesium is contained within cells, serum tests for magnesium are of little value. Deficiency can result in muscle twitching and spasms or cramps, as well as persistently low blood potassium levels. Good sources of magnesium include dark green vegetables, nuts/seeds, non-processed meats, and homemade broths. It is important to capture the drippings from meat to retain magnesium. Magnesium depletion is common in individuals with T2D, in part due to increased urinary excretion [173]. Because magnesium depletion impairs glucose control [174], it is often necessary to provide supplemental oral magnesium in combination with KD in order to optimize T2D reversal.

9.4. Vitamin D

It is increasingly apparent that many people are marginally deficient in vitamin D based on serum levels of 25-hydroxyvitamin D [175]. This may reflect less sun exposure

and use of sunscreens, which limit the natural vitamin D synthesis that occurs with sun exposure. Vitamin D fortified milk is not recommended in appreciable amounts on KD due to its 50 grams per liter of sugar content. Food sources of vitamin D include fatty fish such as salmon, egg yolks, and cheese. For people who do not get regular sun exposure, a vitamin D supplement or use of a multivitamin that includes vitamin D (~1000 IU) may be necessary to bring serum levels into an acceptable range.

9.5. Fiber

The beneficial effects of fiber are attributed mainly to its ability to slow absorption of glucose, promote satiety, and contribute to the bacterial production of short-chain fatty acids, principally butyrate. Butyrate is a preferred energy source of intestinal cells and is associated with well-documented effects on gut health. However, the need for ample fiber on a KD is less clear, since the diet inherently decreases postprandial glucose and insulin while promoting satiety. Low fiber intake would likely result in decreased bacterially produced butyrate, but KD accelerate endogenous production of beta-hydroxybutyrate in the liver, estimated to be in the range of 100–150 grams per day during nutritional ketosis [176]. Ketones are short-chain fatty acids that can function like butyrate as a preferred energy source and a signaling molecule to promote gut health [177]. From this perspective, nutritional ketosis may promote gut health. It should be noted that KD are not devoid of fiber. Inclusion of non-starchy vegetables and 1–2 ounces of nuts/seeds results in ~15–20 grams of fiber per day, which appears to be sufficient. Controlled studies of fiber in the context of a KD have not yet been conducted.

10. Summary

Many Americans have varying degrees of IR as evidenced by the high prevalence of obesity, metabolic syndrome, prediabetes, and T2D, which have all been demonstrated in a large body of scientific literature to be highly responsive to a low-carbohydrate eating pattern. A broad range of markers linked with the IR phenotype and associated with an increased risk of CVD are also improved by a low-carbohydrate approach. The 2020 DGAC stated that its review process did not find any studies of KD and only one study of low-carbohydrate diets. It appears that unrealistic inclusion criteria for the literature search resulted in the dismissal of a large and credible body of published research. Furthermore, while the stated purpose of the 2020 DGA is to provide dietary advice for "healthy" Americans, the high proportion of Americans with IR makes the case for redefining the target population of the guidelines to include this majority of Americas who would likely benefit from the inclusion of a low-carbohydrate dietary option.

Author Contributions: J.S.V. wrote the original draft of the manuscript and takes responsibility for the final design and content. All other authors (S.D.P., R.M.K., R.J.J., L.R.S., B.G., W.S.Y.J., J.C.K., F.M.H., N.T., B.R.B., O.H.) contributed specific sections and participated in manuscript revisions. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No original data were generated for this manuscript.

Conflicts of Interest: JSV receives royalties for low-carbohydrate nutrition books, is co-founder and has equity in Virta Health Corp, and is a scientific advisor to Simply Good Foods; SDP receives royalties for low-carbohydrate nutrition books and is co-founder and has equity in Virta Health Corp; RMK is on the scientific advisory boards of Virta Health Corp, Seraphina Therapeutics, and Day Two, and has licensed patents for lipoprotein particle analysis; RJJ has received honoraria from Horizon Pharma and Danone, has stocks with XORTX Therapeutics, and has equity with Colorado Partners LLC (CRP); LRS is a consultant with Sentinel Management; WSY is a consultant for Guideline Central and dietdoctor.com; NT receives book royalties and honoraria for speeches via the Harry Walker Agency.

Abbreviations

Acceptable Macronutrient Distribution Ranges (AMDR), American Diabetes Association (ADA), cardiovascular disease (CVD), Dietary Guidelines for Americans (DGA), Dietary Guidelines Advisory Committees (DGAC), high-density lipoprotein cholesterol (HDL-C), ideal body weight (IBW), insulin resistance (IR), ketogenic diet (KD), low-density lipoprotein cholesterol (LDL-C), type 2 diabetes (T2D), very low-carbohydrate (VLC).

References

1. Dietary Guidelines Advisory Committee. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*; U.S. Department of Agriculture, Agricultural Research Service: Washington, DC, USA, 2020; p. 25.
2. Dietary Guidelines Advisory Committee. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*; U.S. Department of Agriculture, Agricultural Research Service: Washington, DC, USA, 2020; pp. 54; 64; 70.
3. Cohen, E.; Cragg, M.; de Fonseka, J.; Hite, A.; Rosenberg, M.; Zhou, B. Statistical review of US macronutrient consumption data, 1965–2011: Americans have been following dietary guidelines, coincident with the rise in obesity. *Nutrition* **2015**, *31*, 727–732. [CrossRef] [PubMed]
4. Ströhle, A.; Hahn, A. Diets of modern hunter-gatherers vary substantially in their carbohydrate content depending on ecoenvironments: Results from an ethnographic analysis. *Nutr. Res.* **2011**, *31*, 429–435. [CrossRef] [PubMed]
5. Tondt, J.; Yancy, W.S.; Westman, E.C. Application of nutrient essentiality criteria to dietary carbohydrates. *Nutr. Res. Rev.* **2020**, *33*, 260–270. [CrossRef] [PubMed]
6. Hales, C.M.; Fryar, C.D.; Carroll, M.D.; Freedman, D.S.; Ogden, C.L. Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007–2008 to 2015–2016. *JAMA* **2018**, *319*, 1723–1725. [CrossRef]
7. Menke, A.; Casagrande, S.; Geiss, L.; Cowie, C.C. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA* **2015**, *314*, 1021–1029. [CrossRef]
8. 2020 Dietary Guidelines Advisory Committee and Food Pattern Modeling Team. *Added Sugars: Food Pattern Modeling: Ages 2 Years and Older*; 2020 Dietary Guidelines Advisory Committee Project; U.S. Department of Agriculture: Washington, DC, USA, 2020; Tables 5.1, 5.10 and 5.11. Available online: https://www.dietaryguidelines.gov/sites/default/files/2020-07/FoodPatternModeling_Report_2YearsandOlder.pdf (accessed on 25 February 2020).
9. Shan, Z.; Rehm, C.D.; Rogers, G.; Ruan, M.; Wang, D.D.; Hu, F.B.; Mozaffarian, D.; Zhang, F.F.; Bhupathiraju, S.N. Trends in dietary carbohydrate, protein, and fat intake and diet quality among US adults, 1999–2016. *JAMA* **2019**, *322*, 1178–1187. [CrossRef] [PubMed]
10. Feinman, R.D.; Pogozelski, W.K.; Astrup, A.; Bernstein, R.K.; Fine, E.J.; Westman, E.C.; Accurso, A.; Frassetto, L.; Gower, B.A.; McFarlane, S.I. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. *Nutrition* **2015**, *31*, 1–13. [CrossRef]
11. Bistrian, B.R. Two Types of Very Low–Carbohydrate Diets. *Pediatrics* **2018**, *142*, e20181536A. [CrossRef]
12. Forsythe, C.E.; Phinney, S.D.; Fernandez, M.L.; Quann, E.E.; Wood, R.J.; Bibus, D.M.; Kraemer, W.J.; Feinman, R.D.; Volek, J.S. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. *Lipids* **2008**, *43*, 65–77. [CrossRef]
13. Volek, J.S.; Phinney, S.D.; Forsythe, C.E.; Quann, E.E.; Wood, R.J.; Puglisi, M.J.; Kraemer, W.J.; Bibus, D.M.; Fernandez, M.L.; Feinman, R.D. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. *Lipids* **2009**, *44*, 297–309. [CrossRef]
14. Dehghan, M.; Mente, A.; Zhang, X.; Swaminathan, S.; Li, W.; Mohan, V.; Iqbal, R.; Kumar, R.; Wentzel-Viljoen, E.; Rosengren, A.; et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective cohort study. *Lancet* **2017**, *390*, 2050–2062. [CrossRef]
15. The Cost of Diabetes. ADA. 2020. Available online: www.diabetes.org/resources/statistics/cost-diabetes (accessed on 26 February 2020).
16. Dietary Guidelines Advisory Committee. *Scientific Report of the 2000 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*; U.S. Department of Agriculture, Agricultural Research Service: Washington, DC, USA, 2000; p. 36.
17. Dietary Guidelines Advisory Committee. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*; U.S. Department of Agriculture, Agricultural Research Service: Washington, DC, USA, 2015; Part D, Ch 6; p. 13, lines 460–461.
18. Sarwar, N.; Danesh, J.; Eiriksdottir, G.; Sigurdsson, G.; Wareham, N.; Bingham, S.; Boekholdt, S.M.; Khaw, K.-T.; Gudnason, V. Triglycerides and the risk of coronary heart disease: 10 158 incident cases among 262 525 participants in 29 Western prospective studies. *Circulation* **2007**, *115*, 450–458. [CrossRef]
19. Zhang, B.; Menzin, J.; Friedman, M.; Korn, J.R.; Burge, R.T. Predicted coronary risk for adults with coronary heart disease and low HDL-C: An analysis from the US National Health and Nutrition Examination Survey. *Curr. Med. Res. Opin.* **2008**, *24*, 2711–2717. [CrossRef]

20. Lichtenstein, A. Proceedings of the Public Meeting of the Dietary Guidelines Advisory Committee, Washington, DC, USA, 15 September 2015. minute 4:35:10 (no longer publicly available).
21. Ludwig, D.S.; Willett, W.C.; Volek, J.S.; Neuhouser, M.L. Dietary fat: From foe to friend? *Science* **2018**, *362*, 764–770. [CrossRef]
22. Araújo, J.; Cai, J.; Stevens, J. Prevalence of optimal metabolic health in American adults: National Health and Nutrition Examination Survey 2009–2016. *Metab. Syndr. Relat. Disord.* **2019**, *17*, 46–52. [CrossRef] [PubMed]
23. Coppack, S.W.; Jensen, M.D.; Miles, J.M. In vivo regulation of lipolysis in humans. *J. Lipid Res.* **1994**, *35*, 177–193. [CrossRef]
24. Kelly, C.T.; Mansoor, J.; Dohm, G.L.; Chapman, W.H., III; Pender, J.R., IV; Pories, W.J. Hyperinsulinemic syndrome: The metabolic syndrome is broader than you think. *Surgery* **2014**, *156*, 405–411. [CrossRef] [PubMed]
25. Malik, V.S.; Hu, F.B. Fructose and cardiometabolic health: What the evidence from sugar-sweetened beverages tells us. *J. Am. Coll. Cardiol.* **2015**, *66*, 1615–1624. [CrossRef]
26. Johnson, R.; Stenvinkel, P.; Andrews, P.; Sánchez-Lozada, L.; Nakagawa, T.; Gaucher, E.; Andres-Hernando, A.; Rodriguez-Iturbe, B.; Jimenez, C.R.; Garcia, G. Fructose metabolism as a common evolutionary pathway of survival associated with climate change, food shortage and droughts. *J. Intern. Med.* **2020**, *287*, 252–262. [CrossRef]
27. Lanaspa, M.A.; Ishimoto, T.; Li, N.; Cicerchi, C.; Orlicky, D.J.; Ruzycki, P.; Rivard, C.; Inaba, S.; Roncal-Jimenez, C.A.; Bales, E.S.; et al. Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. *Nat. Commun.* **2013**, *4*, 2434. [CrossRef]
28. Volek, J.S.; Feinman, R.D. Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction. *Nutr. Metab.* **2005**, *2*, 1–17. [CrossRef]
29. Volek, J.S.; Fernandez, M.L.; Feinman, R.D.; Phinney, S.D. Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome. *Prog. Lipid Res.* **2008**, *47*, 307–318. [CrossRef]
30. Moller, D.E.; Flier, J.S. Insulin resistance—mechanisms, syndromes, and implications. *N. Engl. J. Med.* **1991**, *325*, 938–948. [PubMed]
31. Boden, G.; Sargrad, K.; Homko, C.; Mozzoli, M.; Stein, T.P. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann. Intern. Med.* **2005**, *142*, 403–411. [CrossRef]
32. Hyde, P.N.; Sapper, T.N.; Crabtree, C.D.; LaFountain, R.A.; Bowling, M.L.; Buga, A.; Fell, B.; McSwiney, F.T.; Dickerson, R.M.; Miller, V.J.; et al. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. *JCI Insight* **2019**, *4*, e128308. [CrossRef] [PubMed]
33. Petersen, K.F.; Dufour, S.; Savage, D.B.; Bilz, S.; Solomon, G.; Yonemitsu, S.; Cline, G.W.; Befroy, D.; Zemany, L.; Kahn, B.B.; et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 12587–12594. [CrossRef] [PubMed]
34. Aarsland, A.; Wolfe, R.R. Hepatic secretion of VLDL fatty acids during stimulated lipogenesis in men. *J. Lipid Res.* **1998**, *39*, 1280–1286. [CrossRef]
35. Krauss, R.M. All low-density lipoprotein particles are not created equal. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 959–961. [CrossRef] [PubMed]
36. Westman, E.C.; Yancy, W.S., Jr.; Humphreys, M. Dietary treatment of diabetes mellitus in the pre-insulin era (1914-1922). *Perspect. Biol. Med.* **2006**, *49*, 77–83. [CrossRef]
37. Creighton, B.C.; Hyde, P.N.; Maresh, C.M.; Kraemer, W.J.; Phinney, S.D.; Volek, J.S. Paradox of hypercholesterolaemia in highly trained, keto-adapted athletes. *BMJ Open Sport Exerc. Med.* **2018**, *4*, e000429. [CrossRef] [PubMed]
38. LaFountain, R.A.; Miller, V.J.; Barnhart, E.C.; Hyde, P.N.; Crabtree, C.D.; McSwiney, F.T.; Beeler, M.K.; Buga, A.; Sapper, T.N.; Short, J.A.; et al. Extended Ketogenic Diet and Physical Training Intervention in Military Personnel. *Mil. Med.* **2019**, *184*, e538–e547. [CrossRef]
39. Sharman, M.J.; Gómez, A.L.; Kraemer, W.J.; Volek, J.S. Very low-carbohydrate and low-fat diets affect fasting lipids and postprandial lipemia differently in overweight men. *J. Nutr.* **2004**, *134*, 880–885. [CrossRef] [PubMed]
40. Volek, J.S.; Sharman, M.J.; Gomez, A.L.; Scheett, T.P.; Kraemer, W.J. An isoenergetic very low carbohydrate diet improves serum HDL cholesterol and triacylglycerol concentrations, the total cholesterol to HDL cholesterol ratio and postprandial lipemic responses compared with a low fat diet in normal weight, normolipidemic women. *J. Nutr.* **2003**, *133*, 2756–2761. [PubMed]
41. Catlin, G. *Letters and Notes on the Manners, Customs, and Conditions of the North American Indians*; Willis P. Hazard: Whitefish MT, USA, 1844; Volume 1 & 2.
42. McClellan, W.S.; Du Bois, E.F. Clinical calorimetry XLV. Prolonged meat diets with a study of kidney function and ketosis. *J. Biol. Chem.* **1930**, *87*, 651–668. [CrossRef]
43. Orr, J.B.; Gilks, J.L. *Studies of Nutrition. The Physique and Health of Two African Tribes*; His Majesty's Stationery Office: London, UK, 1931.
44. Kossoff, E.H.; Zupec-Kania, B.A.; Amark, P.E.; Ballaban-Gil, K.R.; Christina Bergqvist, A.G.; Blackford, R.; Buchhalter, J.R.; Caraballo, R.H.; Helen Cross, J.; Dahlin, M.G.; et al. Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group. *Epilepsia* **2009**, *50*, 304–317. [CrossRef]
45. Stafstrom, C.E.; Rho, J.M. *Epilepsy and the Ketogenic Diet*; Springer Science & Business Media: Berlin, Germany, 2004.
46. Wilder, R.M. The effects of ketonemia on the course of epilepsy. *Mayo Clin. Proc.* **1921**, *2*, 307–308.

47. Ludwig, D.S. The glycemic index: Physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* **2002**, *287*, 2414–2423. [CrossRef]
48. Newman, J.C.; Verdin, E. beta-Hydroxybutyrate: A Signaling Metabolite. *Annu. Rev. Nutr.* **2017**, *37*, 51–76. [CrossRef] [PubMed]
49. Stubbs, B.J.; Koutnik, A.P.; Goldberg, E.L.; Upadhyay, V.; Turnbaugh, P.J.; Verdin, E.; Newman, J.C. Investigating ketone bodies as immunometabolic countermeasures against respiratory viral infections. *Med* **2020**, *1*, 43–65. [CrossRef]
50. Yurista, S.R.; Chong, C.R.; Badimon, J.J.; Kelly, D.P.; de Boer, R.A.; Westenbrink, B.D. Therapeutic Potential of Ketone Bodies for Patients With Cardiovascular Disease: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2021**, *77*, 1660–1669. [CrossRef]
51. Hamdy, O.; Tasabehji, M.W.; Elseaidy, T.; Tomah, S.; Ashrafzadeh, S.; Mottalib, A. Fat Versus Carbohydrate-Based Energy-Restricted Diets for Weight Loss in Patients With Type 2 Diabetes. *Curr. Diab. Rep.* **2018**, *18*, 128. [CrossRef]
52. Palgi, A.; Read, J.L.; Greenberg, I.; Hoefer, M.A.; Bistrian, B.R.; Blackburn, G.L. Multidisciplinary treatment of obesity with a protein-sparing modified fast: Results in 668 outpatients. *Am. J. Public Health* **1985**, *75*, 1190–1194. [CrossRef] [PubMed]
53. Vertes, V. Very low calorie diets–history, safety and recent developments. *Postgrad. Med.* **1984**, *60*, 56–58.
54. Ajala, O.; English, P.; Pinkney, J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am. J. Clin. Nutr.* **2013**, *97*, 505–516. [CrossRef] [PubMed]
55. Bueno, N.B.; de Melo, I.S.; de Oliveira, S.L.; da Rocha Ataide, T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: A meta-analysis of randomised controlled trials. *Br. J. Nutr.* **2013**, *110*, 1178–1187. [CrossRef] [PubMed]
56. Hu, T.; Mills, K.T.; Yao, L.; Demanelis, K.; Eloustaz, M.; Yancy, W.S., Jr.; Kelly, T.N.; He, J.; Bazzano, L.A. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: A meta-analysis of randomized controlled clinical trials. *Am. J. Epidemiol.* **2012**, *176* (Suppl. 7), S44–S54. [CrossRef]
57. Sackner-Bernstein, J.; Kanter, D.; Kaul, S. Dietary Intervention for Overweight and Obese Adults: Comparison of Low-Carbohydrate and Low-Fat Diets. A Meta-Analysis. *PLoS One* **2015**, *10*, e0139817. [CrossRef]
58. Santos, F.L.; Esteves, S.S.; da Costa Pereira, A.; Yancy, W.S., Jr.; Nunes, J.P. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. *Obes. Rev.* **2012**, *13*, 1048–1066. [CrossRef]
59. Hjorth, M.F.; Zohar, Y.; Hill, J.O.; Astrup, A. Personalized Dietary Management of Overweight and Obesity Based on Measures of Insulin and Glucose. *Annu. Rev. Nutr.* **2018**, *38*, 245–272. [CrossRef]
60. McClain, A.D.; Otten, J.J.; Hekler, E.B.; Gardner, C.D. Adherence to a low-fat vs. low-carbohydrate diet differs by insulin resistance status. *Diabetes Obes. Metab.* **2013**, *15*, 87–90. [CrossRef] [PubMed]
61. Athinarayanan, S.J.; Adams, R.N.; Hallberg, S.J.; McKenzie, A.L.; Bhanpuri, N.H.; Campbell, W.W.; Volek, J.S.; Phinney, S.D.; McCarter, J.P. Long-Term Effects of a Novel Continuous Remote Care Intervention Including Nutritional Ketosis for the Management of Type 2 Diabetes: A 2-Year Non-randomized Clinical Trial. *Front. Endocrinol. (Lausanne)* **2019**, *10*, 348. [CrossRef] [PubMed]
62. Gibson, A.A.; Seimon, R.V.; Lee, C.M.; Ayre, J.; Franklin, J.; Markovic, T.; Caterson, I.; Sainsbury, A. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obes. Rev.* **2015**, *16*, 64–76. [CrossRef]
63. McKenzie, A.L.; Athinarayanan, S.J.; McCue, J.J.; Adams, R.N.; Keyes, M.; McCarter, J.P.; Volek, J.S.; Phinney, S.D.; Hallberg, S.J. Type 2 Diabetes Prevention Focused on Normalization of Glycemia: A Two-Year Pilot Study. *Nutrients* **2021**, *13*, 749. [CrossRef]
64. Myette-Côté, É.; Durrer, C.; Neudorf, H.; Bammert, T.D.; Botezelli, J.D.; Johnson, J.D.; DeSouza, C.A.; Little, J.P. The effect of a short-term low-carbohydrate, high-fat diet with or without postmeal walks on glycemic control and inflammation in type 2 diabetes: A randomized trial. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2018**, *315*, R1210–R1219. [CrossRef]
65. Yang, M.U.; Van Itallie, T.B. Composition of weight lost during short-term weight reduction. Metabolic responses of obese subjects to starvation and low-calorie ketogenic and nonketogenic diets. *J. Clin. Invest.* **1976**, *58*, 722–730. [CrossRef]
66. DeFronzo, R.A. The effect of insulin on renal sodium metabolism. A review with clinical implications. *Diabetologia* **1981**, *21*, 165–171. [CrossRef]
67. Phinney, S.D.; Horton, E.S.; Sims, E.A.; Hanson, J.S.; Danforth, E., Jr.; LaGrange, B.M. Capacity for moderate exercise in obese subjects after adaptation to a hypocaloric, ketogenic diet. *J. Clin. Invest.* **1980**, *66*, 1152–1161. [CrossRef]
68. Brown, J.C.; Harhay, M.O.; Harhay, M.N. Appendicular lean mass and mortality among prefrail and frail older adults. *J. Nutr. Health Aging* **2017**, *21*, 342–345. [CrossRef]
69. Coleman, J.L.; Carrigan, C.T.; Margolis, L.M. Body composition changes in physically active individuals consuming ketogenic diets: A systematic review. *J. Int. Soc. Sports Nutr.* **2021**, *18*, 41. [CrossRef] [PubMed]
70. Di Rosa, C.; Lattanzi, G.; Taylor, S.F.; Manfrini, S.; Khazrai, Y.M. Very low calorie ketogenic diets in overweight and obesity treatment: Effects on anthropometric parameters, body composition, satiety, lipid profile and microbiota. *Obes. Res. Clin. Pract.* **2020**, *14*, 491–503. [CrossRef]
71. Hashimoto, Y.; Fukuda, T.; Oyabu, C.; Tanaka, M.; Asano, M.; Yamazaki, M.; Fukui, M. Impact of low-carbohydrate diet on body composition: Meta-analysis of randomized controlled studies. *Obes. Rev.* **2016**, *17*, 499–509. [CrossRef]
72. Krieger, J.W.; Sitren, H.S.; Daniels, M.J.; Langkamp-Henken, B. Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: A meta-regression 1. *Am. J. Clin. Nutr.* **2006**, *83*, 260–274. [CrossRef]
73. Romano, L.; Marchetti, M.; Gualtieri, P.; Di Renzo, L.; Belcastro, M.; De Santis, G.L.; Perrone, M.A.; De Lorenzo, A. Effects of a Personalized VLCKD on Body Composition and Resting Energy Expenditure in the Reversal of Diabetes to Prevent Complications. *Nutrients* **2019**, *11*, 1526. [CrossRef]

74. Tay, J.; Luscombe-Marsh, N.D.; Thompson, C.H.; Noakes, M.; Buckley, J.D.; Wittert, G.A.; Yancy, W.S., Jr.; Brinkworth, G.D. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: A randomized trial. *Am. J. Clin. Nutr.* **2015**, *102*, 780–790. [CrossRef]
75. DeHaven, J.; Sherwin, R.; Hendler, R.; Felig, P. Nitrogen and sodium balance and sympathetic-nervous-system activity in obese subjects treated with a low-calorie protein or mixed diet. *N. Engl. J. Med.* **1980**, *302*, 477–482. [CrossRef]
76. Vazquez, J.A.; Adibi, S.A. Protein sparing during treatment of obesity: Ketogenic versus nonketogenic very low calorie diet. *Metabolism* **1992**, *41*, 406–414. [CrossRef]
77. Phinney, S.D. Low-calorie protein versus mixed diet. *N. Engl. J. Med.* **1980**, *303*, 158. [PubMed]
78. Hoffer, L.J.; Bistrian, B.R.; Young, V.; Blackburn, G.; Matthews, D. Metabolic effects of very low calorie weight reduction diets. *J. Clin. Investig.* **1984**, *73*, 750–758. [CrossRef] [PubMed]
79. Phinney, S.D.; LaGrange, B.M.; O'Connell, M.; Danforth, E., Jr. Effects of aerobic exercise on energy expenditure and nitrogen balance during very low calorie dieting. *Metabolism* **1988**, *37*, 758–765. [CrossRef]
80. Phinney, S.D.; Bistrian, B.R.; Wolfe, R.; Blackburn, G. The human metabolic response to chronic ketosis without caloric restriction: Physical and biochemical adaptation. *Metabolism* **1983**, *32*, 757–768. [CrossRef]
81. Howard, B.V.; Manson, J.E.; Stefanick, M.L.; Beresford, S.A.; Frank, G.; Jones, B.; Rodabough, R.J.; Snetselaar, L.; Thomson, C.; Tinker, L.; et al. Low-fat dietary pattern and weight change over 7 years: The Women's Health Initiative Dietary Modification Trial. *JAMA* **2006**, *295*, 39–49. [CrossRef] [PubMed]
82. The 2020 Dietary Guidelines Advisory Committee. Afternoon Session. Minute 29:16. In Proceedings of the 2020 Dietary Guidelines Advisory Committee Public Meeting, Online, 12 March 2020.
83. Minute 29:16. In Proceedings of the Public meeting of the Dietary Guidelines Advisory Committee, Little Elm, TX, USA, 23 March 2020.
84. USDA. What is a Healthy Diet? Available online: https://ask.usda.gov/s/article/What-is-a-healthy-diet (accessed on 26 February 2020).
85. US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans*, 7th ed.; US Government Printing Office: Washington, DC, USA, 2010.
86. Brinkworth, G.D.; Noakes, M.; Buckley, J.D.; Keogh, J.B.; Clifton, P.M. Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. *Am. J. Clin. Nutr.* **2009**, *90*, 23–32. [CrossRef] [PubMed]
87. Dansinger, M.L.; Gleason, J.A.; Griffith, J.L.; Selker, H.P.; Schaefer, E.J. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: A randomized trial. *JAMA* **2005**, *293*, 43–53. [CrossRef] [PubMed]
88. Foster, G.D.; Wyatt, H.R.; Hill, J.O.; Makris, A.P.; Rosenbaum, D.L.; Brill, C.; Stein, R.I.; Mohammed, B.S.; Miller, B.; Rader, D.J.; et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: A randomized trial. *Ann. Intern. Med.* **2010**, *153*, 147–157. [CrossRef]
89. Gardner, C.D.; Trepanowski, J.F.; Del Gobbo, L.C.; Hauser, M.E.; Rigdon, J.; Ioannidis, J.P.A.; Desai, M.; King, A.C. Effect of Low-Fat vs Low-Carbohydrate Diet on 12-Month Weight Loss in Overweight Adults and the Association With Genotype Pattern or Insulin Secretion: The DIETFITS Randomized Clinical Trial. *JAMA* **2018**, *319*, 667–679. [CrossRef]
90. Stern, L.; Iqbal, N.; Seshadri, P.; Chicano, K.L.; Daily, D.A.; McGrory, J.; Williams, M.; Gracely, E.J.; Samaha, F.F. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: One-year follow-up of a randomized trial. *Ann. Intern. Med.* **2004**, *140*, 778–785. [CrossRef]
91. Grundy, S.M.; Brewer Jr, H.B.; Cleeman, J.I.; Smith Jr, S.C.; Lenfant, C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* **2004**, *109*, 433–438. [CrossRef]
92. Moore, J.X.; Chaudhary, N.; Akinyemiju, T. Peer reviewed: Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. *Prev. Chronic Dis.* **2017**, *14*, E24. [CrossRef]
93. Tay, J.; Thompson, C.H.; Luscombe-Marsh, N.D.; Wycherley, T.P.; Noakes, M.; Buckley, J.D.; Wittert, G.A.; Yancy, W.S., Jr.; Brinkworth, G.D. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. *Diabetes Obes. Metab.* **2018**, *20*, 858–871. [CrossRef]
94. Davies, M.J.; D'Alessio, D.A.; Fradkin, J.; Kernan, W.N.; Mathieu, C.; Mingrone, G.; Rossing, P.; Tsapas, A.; Wexler, D.J.; Buse, J.B. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **2018**, *41*, 2669–2701. [CrossRef] [PubMed]
95. Evert, A.B.; Dennison, M.; Gardner, C.D.; Garvey, W.T.; Lau, K.H.K.; MacLeod, J.; Mitri, J.; Pereira, R.F.; Rawlings, K.; Robinson, S.; et al. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. *Diabetes Care* **2019**, *42*, 731–754. [CrossRef]
96. Wang, C.; Lv, L.; Yang, Y.; Chen, D.; Liu, G.; Chen, L.; Song, Y.; He, L.; Li, X.; Tian, H.; et al. Glucose fluctuations in subjects with normal glucose tolerance, impaired glucose regulation and newly diagnosed type 2 diabetes mellitus. *Clin. Endocrinol. (Oxf)* **2012**, *76*, 810–815. [CrossRef] [PubMed]
97. Saisho, Y. Glycemic variability and oxidative stress: A link between diabetes and cardiovascular disease? *Int. J. Mol. Sci.* **2014**, *15*, 18381–18406. [CrossRef] [PubMed]

98. Gorst, C.; Kwok, C.S.; Aslam, S.; Buchan, I.; Kontopantelis, E.; Myint, P.K.; Heatlie, G.; Loke, Y.; Rutter, M.K.; Mamas, M.A. Long-term Glycemic Variability and Risk of Adverse Outcomes: A Systematic Review and Meta-analysis. *Diabetes Care* **2015**, *38*, 2354–2369. [CrossRef]
99. Ahola, A.J.; Harjutsalo, V.; Forsblom, C.; Saraheimo, M.; Groop, P.H. Associations of dietary macronutrient and fibre intake with glycaemia in individuals with Type 1 diabetes. *Diabet Med.* **2019**, *36*, 1391–1398. [CrossRef]
100. Ranjan, A.; Schmidt, S.; Damm-Frydenberg, C.; Holst, J.J.; Madsbad, S.; Norgaard, K. Short-term effects of a low carbohydrate diet on glycaemic variables and cardiovascular risk markers in patients with type 1 diabetes: A randomized open-label crossover trial. *Diabetes Obes. Metab.* **2017**, *19*, 1479–1484. [CrossRef]
101. Chang, C.R.; Francois, M.E.; Little, J.P. Restricting carbohydrates at breakfast is sufficient to reduce 24-hour exposure to postprandial hyperglycemia and improve glycemic variability. *Am. J. Clin. Nutr.* **2019**, *109*, 1302–1309. [CrossRef]
102. Bistrian, B.R.; Blackburn, G.L.; Flatt, J.P.; Sizer, J.; Scrimshaw, N.S.; Sherman, M. Nitrogen metabolism and insulin requirements in obese diabetic adults on a protein-sparing modified fast. *Diabetes* **1976**, *25*, 494–504. [CrossRef]
103. Dashti, H.M.; Al-Zaid, N.S.; Mathew, T.C.; Al-Mousawi, M.; Talib, H.; Asfar, S.K.; Behbahani, A.I. Long term effects of ketogenic diet in obese subjects with high cholesterol level. *Mol. Cell Biochem.* **2006**, *286*, 1–9. [CrossRef]
104. Hallberg, S.J.; McKenzie, A.L.; Williams, P.T.; Bhanpuri, N.H.; Peters, A.L.; Campbell, W.W.; Hazbun, T.L.; Volk, B.M.; McCarter, J.P.; Phinney, S.D. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: An open-label, non-randomized, controlled study. *Diabetes Ther.* **2018**, *9*, 583–612. [CrossRef] [PubMed]
105. Hussain, T.A.; Mathew, T.C.; Dashti, A.A.; Asfar, S.; Al-Zaid, N.; Dashti, H.M. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition* **2012**, *28*, 1016–1021. [CrossRef]
106. Saslow, L.R.; Daubenmier, J.J.; Moskowitz, J.T.; Kim, S.; Murphy, E.J.; Phinney, S.D.; Ploutz-Snyder, R.; Goldman, V.; Cox, R.M.; Mason, A.E. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. *Nutr. Diabetes* **2017**, *7*, 1–6. [CrossRef] [PubMed]
107. Bhanpuri, N.H.; Hallberg, S.J.; Williams, P.T.; McKenzie, A.L.; Ballard, K.D.; Campbell, W.W.; McCarter, J.P.; Phinney, S.D.; Volek, J.S. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: An open label, non-randomized, controlled study. *Cardiovasc. Diabetol.* **2018**, *17*, 1–16. [CrossRef] [PubMed]
108. Cucuzzella, M.T.; Tondt, J.; Dockter, N.E.; Saslow, L.; Wood, T.R. A low-carbohydrate survey: Evidence for sustainable metabolic syndrome reversal. *J. Insul. Resist.* **2017**, *2*, 25. [CrossRef]
109. Gann, D.; Gann, E. Type 2 Diabetic Patients on Insulin Can Reduce or Eliminate Insulin with Lifestyle Change and Carbohydrate Restriction. *Curr. Res. Diabetes Obes. J.* **2015**, *1*, 1–5. [CrossRef]
110. Unwin, D.; Livesey, G.; Haslam, D. It is the glycaemic response to, not the carbohydrate content of food that matters in diabetes and obesity: The glycaemic index revisited. *J. Insul. Resist.* **2016**, *1*, 1–9. [CrossRef]
111. Goldenberg, J.Z.; Day, A.; Brinkworth, G.D.; Sato, J.; Yamada, S.; Jönsson, T.; Beardsley, J.; Johnson, J.A.; Thabane, L.; Johnston, B.C. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: Systematic review and meta-analysis of published and unpublished randomized trial data. *BMJ* **2021**, *372*, m4743.
112. Hamdy, O.; Mottalib, A.; Morsi, A.; El-Sayed, N.; Goebel-Fabbri, A.; Arathuzik, G.; Shahar, J.; Kirpitch, A.; Zrebiec, J. Long-term effect of intensive lifestyle intervention on cardiovascular risk factors in patients with diabetes in real-world clinical practice: A 5-year longitudinal study. *BMJ Open Diabetes Res. Care* **2017**, *5*, e000259. [CrossRef]
113. Bazzano, L.A.; Hu, T.; Reynolds, K.; Yao, L.; Bunol, C.; Liu, Y.; Chen, C.S.; Klag, M.J.; Whelton, P.K.; He, J. Effects of low-carbohydrate and low-fat diets: A randomized trial. *Ann. Intern. Med.* **2014**, *161*, 309–318. [CrossRef]
114. Hu, T.; Yao, L.; Reynolds, K.; Whelton, P.K.; Niu, T.; Li, S.; He, J.; Bazzano, L.A. The Effects of a Low-Carbohydrate Diet vs. a Low-Fat Diet on Novel Cardiovascular Risk Factors: A Randomized Controlled Trial. *Nutrients* **2015**, *7*, 7978–7994. [CrossRef]
115. Volek, J.S.; Ballard, K.D.; Silvestre, R.; Judelson, D.A.; Quann, E.E.; Forsythe, C.E.; Fernandez, M.L.; Kraemer, W.J. Effects of dietary carbohydrate restriction versus low-fat diet on flow-mediated dilation. *Metabolism* **2009**, *58*, 1769–1777. [CrossRef]
116. Feinman, R.D.; Volek, J.S. Low carbohydrate diets improve atherogenic dyslipidemia even in the absence of weight loss. *Nutr. Metab. (Lond)* **2006**, *3*, 24. [CrossRef]
117. Sharman, M.J.; Kraemer, W.J.; Love, D.M.; Avery, N.G.; Gomez, A.L.; Scheett, T.P.; Volek, J.S. A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. *J. Nutr.* **2002**, *132*, 1879–1885. [CrossRef] [PubMed]
118. Wang, X.; Yu, C.; Zhang, B.; Wang, Y. The injurious effects of hyperinsulinism on blood vessels. *Cell Biochem. Biophys.* **2014**, *69*, 213–218. [CrossRef] [PubMed]
119. Bhat, S.L.; Abbasi, F.A.; Blasey, C.; Reaven, G.M.; Kim, S.H. Beyond fasting plasma glucose: The association between coronary heart disease risk and postprandial glucose, postprandial insulin and insulin resistance in healthy, nondiabetic adults. *Metabolism* **2013**, *62*, 1223–1226. [CrossRef]
120. Gast, K.B.; Tjeerdema, N.; Stijnen, T.; Smit, J.W.; Dekkers, O.M. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: Meta-analysis. *PLoS One* **2012**, *7*, e52036. [CrossRef] [PubMed]
121. Zhang, X.; Li, J.; Zheng, S.; Luo, Q.; Zhou, C.; Wang, C. Fasting insulin, insulin resistance, and risk of cardiovascular or all-cause mortality in non-diabetic adults: A meta-analysis. *Biosci. Rep.* **2017**, *37*, BSR20170947. [CrossRef] [PubMed]
122. Volek, J.S.; Sharman, M.J.; Forsythe, C.E. Modification of lipoproteins by very low-carbohydrate diets. *J. Nutr.* **2005**, *135*, 1339–1342. [CrossRef] [PubMed]

123. Samaha, F.F.; Foster, G.D.; Makris, A.P. Low-carbohydrate diets, obesity, and metabolic risk factors for cardiovascular disease. *Curr. Atheroscler. Rep.* **2007**, *9*, 441–447. [CrossRef]
124. Volk, B.M.; Kunces, L.J.; Freidenreich, D.J.; Kupchak, B.R.; Saenz, C.; Artistizabal, J.C.; Fernandez, M.L.; Bruno, R.S.; Maresh, C.M.; Kraemer, W.J.; et al. Effects of step-wise increases in dietary carbohydrate on circulating saturated Fatty acids and palmitoleic Acid in adults with metabolic syndrome. *PLoS ONE* **2014**, *9*, e113605. [CrossRef] [PubMed]
125. Astrup, A.; Magkos, F.; Bier, D.M.; Brenna, J.T.; de Oliveira Otto, M.C.; Hill, J.O.; King, J.C.; Mente, A.; Ordovas, J.M.; Volek, J.S.; et al. Saturated Fats and Health: A Reassessment and Proposal for Food-Based Recommendations: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2020**, *76*, 844–857. [CrossRef]
126. Diamond, D.M.; O'Neill, B.J.; Volek, J.S. Low carbohydrate diet: Are concerns with saturated fat, lipids, and cardiovascular disease risk justified? *Curr. Opin. Endocrinol. Diabetes Obes.* **2020**, *27*, 291–300. [CrossRef] [PubMed]
127. Forsythe, C.E.; Phinney, S.D.; Feinman, R.D.; Volk, B.M.; Freidenreich, D.; Quann, E.; Ballard, K.; Puglisi, M.J.; Maresh, C.M.; Kraemer, W.J.; et al. Limited effect of dietary saturated fat on plasma saturated fat in the context of a low carbohydrate diet. *Lipids* **2010**, *45*, 947–962. [CrossRef]
128. King, I.B.; Lemaitre, R.N.; Kestin, M. Effect of a low-fat diet on fatty acid composition in red cells, plasma phospholipids, and cholesterol esters: Investigation of a biomarker of total fat intake. *Am. J. Clin. Nutr.* **2006**, *83*, 227–236. [CrossRef] [PubMed]
129. Raatz, S.K.; Bibus, D.; Thomas, W.; Kris-Etherton, P. Total fat intake modifies plasma fatty acid composition in humans. *J. Nutr.* **2001**, *131*, 231–234. [CrossRef]
130. Phinney, S.D.; Bistrian, B.R.; Evans, W.; Gervino, E.; Blackburn, G. The human metabolic response to chronic ketosis without caloric restriction: Preservation of submaximal exercise capability with reduced carbohydrate oxidation. *Metabolism* **1983**, *32*, 769–776. [CrossRef]
131. Klein, S.; Wolfe, R.R. Carbohydrate restriction regulates the adaptive response to fasting. *Am. J. Physiol.* **1992**, *262*, E631–E636. [CrossRef]
132. Warensjö, E.; Risérus, U.; Vessby, B. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men. *Diabetologia* **2005**, *48*, 1999–2005. [CrossRef]
133. Forouhi, N.G.; Koulman, A.; Sharp, S.J.; Imamura, F.; Kröger, J.; Schulze, M.B.; Crowe, F.L.; Huerta, J.M.; Guevara, M.; Beulens, J.W. Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: The EPIC-InterAct case-cohort study. *Lancet Diabetes Endocrinol.* **2014**, *2*, 810–818. [CrossRef]
134. Patel, P.S.; Sharp, S.J.; Jansen, E.; Luben, R.N.; Khaw, K.-T.; Wareham, N.J.; Forouhi, N.G. Fatty acids measured in plasma and erythrocyte-membrane phospholipids and derived by food-frequency questionnaire and the risk of new-onset type 2 diabetes: A pilot study in the European Prospective Investigation into Cancer and Nutrition (EPIC)–Norfolk cohort. *Am. J. Clin. Nutr.* **2010**, *92*, 1214–1222.
135. Wang, L.; Folsom, A.R.; Zheng, Z.-J.; Pankow, J.S.; Eckfeldt, J. Investigators AS. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: The Atherosclerosis Risk in Communities (ARIC) Study. *Am. J. Clin. Nutr.* **2003**, *78*, 91–98.
136. Yamagishi, K.; Nettleton, J.A.; Folsom, A.R.; Investigators, A.S. Plasma fatty acid composition and incident heart failure in middle-aged adults: The Atherosclerosis Risk in Communities (ARIC) Study. *Am. Heart J.* **2008**, *156*, 965–974. [CrossRef] [PubMed]
137. Warensjö, E.; Sundström, J.; Vessby, B.; Cederholm, T.; Risérus, U. Markers of dietary fat quality and fatty acid desaturation as predictors of total and cardiovascular mortality: A population-based prospective study. *Am. J. Clin. Nutr.* **2008**, *88*, 203–209. [CrossRef]
138. Fritsche, K.L. The science of fatty acids and inflammation. *Adv. Nutr.* **2015**, *6*, 293S–301S. [CrossRef]
139. Mitri, J.; Tomah, S.; Mottalib, A.; Salsberg, V.; Ashrafzadeh, S.; Pober, D.M.; Eldib, A.H.; Tasabehji, M.W.; Hamdy, O. Effect of dairy consumption and its fat content on glycemic control and cardiovascular disease risk factors in patients with type 2 diabetes: A randomized controlled study. *Am. J. Clin. Nutr.* **2020**, *112*, 293–302. [CrossRef]
140. Paillard, F.; Catheline, D.; Le Duff, F.; Bouriel, M.; Deugnier, Y.; Pouchard, M.; Daubert, J.-C.; Legrand, P. Plasma palmitoleic acid, a product of stearoyl-coA desaturase activity, is an independent marker of triglyceridemia and abdominal adiposity. *Nutr. Metab. Cardiovasc. Dis.* **2008**, *18*, 436–440. [CrossRef] [PubMed]
141. Mahendran, Y.; Agren, J.; Uusitupa, M.; Cederberg, H.; Vangipurapu, J.; Stancakova, A.; Schwab, U.; Kuusisto, J.; Laakso, M. Association of erythrocyte membrane fatty acids with changes in glycemia and risk of type 2 diabetes. *Am. J. Clin. Nutr.* **2014**, *99*, 79–85. [CrossRef]
142. Vessby, B.; Aro, A.; Skarfors, E.; Berglund, L.; Salminen, I.; Lithell, H. The risk to develop NIDDM is related to the fatty acid composition of the serum cholesterol esters. *Diabetes* **1994**, *43*, 1353–1357. [CrossRef]
143. Djoussé, L.; Weir, N.L.; Hanson, N.Q.; Tsai, M.Y.; Gaziano, J.M. Plasma phospholipid concentration of cis-palmitoleic acid and risk of heart failure. *Circ. Heart Fail.* **2012**, *5*, 703–709. [CrossRef] [PubMed]
144. Djoussé, L.; Matthan, N.R.; Lichtenstein, A.H.; Gaziano, J.M. Red blood cell membrane concentration of cis-palmitoleic and cis-vaccenic acids and risk of coronary heart disease. *Am. J. Cardiol.* **2012**, *110*, 539–544. [CrossRef]
145. Fisher, N.D.; Curfman, G. Hypertension—a public health challenge of global proportions. *JAMA* **2018**, *320*, 1757–1759. [CrossRef] [PubMed]
146. Lagiou, P.; Sandin, S.; Lof, M.; Trichopoulos, D.; Adami, H.O.; Weiderpass, E. Low carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: Prospective cohort study. *BMJ* **2012**, *344*, e4026. [CrossRef]

147. Nilsson, L.M.; Winkvist, A.; Eliasson, M.; Jansson, J.H.; Hallmans, G.; Johansson, I.; Lindahl, B.; Lenner, P.; Van Guelpen, B. Low-carbohydrate, high-protein score and mortality in a northern Swedish population-based cohort. *Eur. J. Clin. Nutr.* **2012**, *66*, 694–700. [CrossRef] [PubMed]
148. Trichopoulou, A.; Psaltopoulou, T.; Orfanos, P.; Hsieh, C.; Trichopoulos, D. Low-carbohydrate–high-protein diet and long-term survival in a general population cohort. *Eur. J. Clin. Nutr.* **2007**, *61*, 575–581. [CrossRef]
149. Akter, S.; Mizoue, T.; Nanri, A.; Goto, A.; Noda, M.; Sawada, N.; Yamaji, T.; Iwasaki, M.; Inoue, M.; Tsugane, S. Low carbohydrate diet and all cause and cause-specific mortality. *Clin. Nutr.* **2021**, *40*, 2016–2024. [CrossRef]
150. Halton, T.L.; Willett, W.C.; Liu, S.; Manson, J.E.; Albert, C.M.; Rexrode, K.; Hu, F.B. Low-carbohydrate-diet score and the risk of coronary heart disease in women. *N. Engl. J. Med.* **2006**, *355*, 1991–2002. [CrossRef]
151. Noto, H.; Goto, A.; Tsujimoto, T.; Noda, M. Low-carbohydrate diets and all-cause mortality: A systematic review and meta-analysis of observational studies. *PLoS ONE* **2013**, *8*, e55030. [CrossRef]
152. Nakamura, Y.; Okuda, N.; Okamura, T.; Kadota, A.; Miyagawa, N.; Hayakawa, T.; Kita, Y.; Fujiyoshi, A.; Nagai, M.; Takashima, N.; et al. Low-carbohydrate diets and cardiovascular and total mortality in Japanese: A 29-year follow-up of NIPPON DATA80. *Br. J. Nutr.* **2014**, *112*, 916–924. [CrossRef] [PubMed]
153. Sjögren, P.; Becker, W.; Warensjö, E.; Olsson, E.; Byberg, L.; Gustafsson, I.-B.; Karlström, B.; Cederholm, T. Mediterranean and carbohydrate-restricted diets and mortality among elderly men: A cohort study in Sweden. *Am. J. Clin. Nutr.* **2010**, *92*, 967–974. [CrossRef]
154. Ho, F.K.; Gray, S.R.; Welsh, P.; Petermann-Rocha, F.; Foster, H.; Waddell, H.; Anderson, J.; Lyall, D.; Sattar, N.; Gill, J.M.R.; et al. Associations of fat and carbohydrate intake with cardiovascular disease and mortality: Prospective cohort study of UK Biobank participants. *BMJ* **2020**, *368*, m688. [CrossRef]
155. Fung, T.T.; van Dam, R.M.; Hankinson, S.E.; Stampfer, M.; Willett, W.C.; Hu, F.B. Low-carbohydrate diets and all-cause and cause-specific mortality: Two cohort studies. *Ann. Intern. Med.* **2010**, *153*, 289–298. [CrossRef]
156. Lee, C.-L.; Liu, W.-J.; Wang, J.-S. Associations of low-carbohydrate and low-fat intakes with all-cause mortality in subjects with prediabetes with and without insulin resistance. *Am. J. Clin. Nutr.* **2021**, *40*, 3601–3607. [CrossRef]
157. Li, S.; Flint, A.; Pai, J.K.; Forman, J.P.; Hu, F.B.; Willett, W.C.; Rexrode, K.M.; Mukamal, K.J.; Rimm, E.B. Low carbohydrate diet from plant or animal sources and mortality among myocardial infarction survivors. *J. Am. Heart Assoc.* **2014**, *3*, e001169. [CrossRef]
158. Mazidi, M.; Katsiki, N.; Mikhailidis, D.P.; Sattar, N.; Banach, M. Lower carbohydrate diets and all-cause and cause-specific mortality: A population-based cohort study and pooling of prospective studies. *Eur. Heart J.* **2019**, *40*, 2870–2879. [CrossRef] [PubMed]
159. Seidelmann, S.B.; Claggett, B.; Cheng, S.; Henglin, M.; Shah, A.; Steffen, L.M.; Folsom, A.R.; Rimm, E.B.; Willett, W.C.; Solomon, S.D. Dietary carbohydrate intake and mortality: A prospective cohort study and meta-analysis. *Lancet Public Health* **2018**, *3*, e419–e428. [CrossRef]
160. Shan, Z.; Guo, Y.; Hu, F.B.; Liu, L.; Qi, Q. Association of low-carbohydrate and low-fat diets with mortality among US adults. *JAMA Intern. Med.* **2020**, *180*, 513–523. [CrossRef]
161. Pujol-Busquets, G.; Smith, J.; Larmuth, K.; Fàbregues, S.; Bach-Faig, A. Exploring the Perceptions of Women from Under-Resourced South African Communities about Participating in a Low-Carbohydrate High-Fat Nutrition and Health Education Program: A Qualitative Focus Group Study. *Nutrients* **2020**, *12*, 894. [CrossRef] [PubMed]
162. Wong, K.; Raffray, M.; Roy-Fleming, A.; Blunden, S.; Brazeau, A.-S. Ketogenic diet as a normal way of eating in adults with type 1 and type 2 diabetes: A qualitative study. *Can. J. Diabetes* **2021**, *45*, 137–143.e131. [CrossRef] [PubMed]
163. Cupit, C.; Redman, E. Supporting people to implement a reduced carbohydrate diet: A qualitative study in family practice. *BMJ Nutr. Prev. Health* **2021**, *4*, 226–234. [CrossRef]
164. Hamdy, O.; Barakatun-Nisak, M.Y. Nutrition in Diabetes. *Endocrinol. Metab. Clin. N. Am.* **2016**, *45*, 799–817. [CrossRef]
165. Hamdy, O.; Horton, E.S. Protein content in diabetes nutrition plan. *Curr. Diab. Rep.* **2011**, *11*, 111–119. [CrossRef] [PubMed]
166. Park, S.W.; Goodpaster, B.H.; Lee, J.S.; Kuller, L.H.; Boudreau, R.; de Rekeneire, N.; Harris, T.B.; Kritchevsky, S.; Tylavsky, F.A.; Nevitt, M.; et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. *Diabetes Care* **2009**, *32*, 1993–1997. [CrossRef] [PubMed]
167. Fragala, M.S.; Cadore, E.L.; Dorgo, S.; Izquierdo, M.; Kraemer, W.J.; Peterson, M.D.; Ryan, E.D. Resistance Training for Older Adults: Position Statement From the National Strength and Conditioning Association. *J. Strength Cond. Res.* **2019**, *33*, 2019–2052. [CrossRef] [PubMed]
168. Zinn, C.; Rush, A.; Johnson, R. Assessing the nutrient intake of a low-carbohydrate, high-fat (LCHF) diet: A hypothetical case study design. *BMJ Open* **2018**, *8*, e018846. [CrossRef]
169. O'Donnell, M.; Mente, A.; Rangarajan, S.; McQueen, M.J.; Wang, X.; Liu, L.; Yan, H.; Lee, S.F.; Mony, P.; Devanath, A.; et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N. Engl. J. Med.* **2014**, *371*, 612–623. [CrossRef]
170. Lanaspa, M.A.; Kuwabara, M.; Andres-Hernando, A.; Li, N.; Cicerchi, C.; Jensen, T.; Orlicky, D.J.; Roncal-Jimenez, C.A.; Ishimoto, T.; Nakagawa, T.; et al. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 3138–3143. [CrossRef]

171. Andres-Hernando, A.; Jensen, T.J.; Kuwabara, M.; Orlicky, D.J.; Cicerchi, C.; Li, N.; Roncal-Jimenez, C.A.; Garcia, G.E.; Ishimoto, T.; Maclean, P.S.; et al. Vasopressin mediates fructose-induced metabolic syndrome by activating the V1b receptor. *JCI Insight* **2021**, *6*, e140848. [CrossRef]
172. Kanbay, M.; Aslan, G.; Afsar, B.; Dagel, T.; Siriopol, D.; Kuwabara, M.; Incir, S.; Camkiran, V.; Rodriguez-Iturbe, B.; Lanaspa, M.A.; et al. Acute effects of salt on blood pressure are mediated by serum osmolality. *J. Clin. Hypertens. (Greenwich)* **2018**, *20*, 1447–1454. [CrossRef]
173. Barbagallo, M.; Dominguez, L.J. Magnesium and type 2 diabetes. *World J. Diabetes* **2015**, *6*, 1152–1157. [CrossRef]
174. Rodríguez-Morán, M.; Guerrero-Romero, F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: A randomized double-blind controlled trial. *Diabetes Care* **2003**, *26*, 1147–1152. [CrossRef] [PubMed]
175. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M.; Endocrine, S. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 1911–1930. [CrossRef] [PubMed]
176. Féry, F.; Balasse, E.O. Ketone body production and disposal in diabetic ketosis: A comparison with fasting ketosis. *Diabetes* **1985**, *34*, 326–332. [CrossRef] [PubMed]
177. Sholl, J.; Mailing, L.J.; Wood, T.R. Reframing Nutritional Microbiota Studies To Reflect an Inherent Metabolic Flexibility of the Human Gut: A Narrative Review Focusing on High-Fat Diets. *mBio* **2021**, *12*, e00579-00521. [CrossRef]

nutrients

MDPI

Review

Very Low-Calorie Ketogenic Diet (VLCKD) as Pre-Operative First-Line Dietary Therapy in Patients with Obesity Who Are Candidates for Bariatric Surgery

Luigi Barrea [1,2,*,†], Ludovica Verde [2,3,†], Luigi Schiavo [4], Gerardo Sarno [5], Elisabetta Camajani [6], Antonio Iannelli [7,8,9], Massimiliano Caprio [6,10], Vincenzo Pilone [4], Annamaria Colao [2,11,12] and Giovanna Muscogiuri [2,11,12]

1 Dipartimento di Scienze Umanistiche, Università Telematica Pegaso, Centro Direzionale, Via Porzio, Isola F2, 80143 Naples, Italy
2 Centro Italiano per la cura e il Benessere del Paziente con Obesità (C.I.B.O), Unità di Endocrinologia, Diabetologia e Andrologia, Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli Federico II, Via Sergio Pansini 5, 80131 Naples, Italy
3 Department of Public Health, University of Naples Federico II, Via Sergio Pansini 5, 80131 Naples, Italy
4 Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", Complex Operative Unit of General and Emergency Surgery and Bariatric Centre of Excellence SICOB, University of Salerno, 84081 Salerno, Italy
5 San Giovanni di Dio e Ruggi D'Aragona University Hospital, Scuola Medica Salernitana, 84131 Salerno, Italy
6 Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Open University, 00166 Rome, Italy
7 Centre Hospitalier Universitaire de Nice-Digestive Surgery and Liver Transplantation Unit, Archet 2 Hospital, 151 Route Saint Antoine de Ginestière, BP 3079, CEDEX 3, 06200 Nice, France
8 Faculté de Medicine, Université Côte d'Azur, 06000 Nice, France
9 Inserm, U1065, Team 8 "Hepatic Complications of Obesity and Alcohol", 06204 Nice, France
10 Laboratory of Cardiovascular Endocrinology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele, 00166 Rome, Italy
11 Unità di Endocrinologia, Diabetologia e Andrologia, Dipartimento di Medicina Clinica e Chirurgia, Università degli Studi di Napoli Federico II, Via Sergio Pansini 5, 80131 Naples, Italy
12 Cattedra Unesco "Educazione Alla Salute e Allo Sviluppo Sostenibile", Università degli Studi di Napoli Federico II, Via Sergio Pansini 5, 80131 Naples, Italy
* Correspondence: luigi.barrea@unipegaso.it; Tel.: +39-0817463779; Fax: +39-0817463688
† These authors contributed equally to this work.

Abstract: Bariatric surgery is currently the most effective method for achieving long-term weight loss and reducing the risk of comorbidities and mortality in individuals with severe obesity. The pre-operative diet is an important factor in determining patients' suitability for surgery, as well as their post-operative outcomes and success in achieving weight loss. Therefore, the nutritional management of bariatric patients requires specialized expertise. Very low-calorie diets and intragastric balloon placement have already been studied and shown to be effective in promoting pre-operative weight loss. In addition, the very low-calorie ketogenic diet has a well-established role in the treatment of obesity and type 2 diabetes mellitus, but its potential role as a pre-operative dietary treatment prior to bariatric surgery has received less attention. Thus, this article will provide a brief overview of the current evidence on the very low-calorie ketogenic diet as a pre-operative dietary treatment in patients with obesity who are candidates for bariatric surgery.

Keywords: ketogenic diet; very low-calorie ketogenic diet; obesity; bariatric surgery; nutrition

check for updates

Citation: Barrea, L.; Verde, L.; Schiavo, L.; Sarno, G.; Camajani, E.; Iannelli, A.; Caprio, M.; Pilone, V.; Colao, A.; Muscogiuri, G. Very Low-Calorie Ketogenic Diet (VLCKD) as Pre-Operative First-Line Dietary Therapy in Patients with Obesity Who Are Candidates for Bariatric Surgery. *Nutrients* **2023**, *15*, 1907. https://doi.org/10.3390/nu15081907

Academic Editor: Hayato Tada

Received: 7 March 2023
Revised: 24 March 2023
Accepted: 13 April 2023
Published: 14 April 2023

1. Introduction

Obesity is a growing concern worldwide, with significant health and economic consequences. This chronic condition is associated with increased risk of mortality [1] and a range of health problems including hypertension, dyslipidaemia, type 2 diabetes mellitus

(T2DM), cardiovascular disease, and several types of cancers [2]. Bariatric surgery (BS) has emerged as a definitive treatment for obesity and its related complications [3,4]. In fact, BS is the most effective treatment for patients with severe obesity in terms of permanent weight loss and the reduction of comorbidity and mortality [3,4].

Among the various surgical techniques, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most commonly used [5], and they are usually performed laparoscopically [6]. However, laparoscopic surgery in patients with obesity can be challenging, as the thickness of the abdominal wall, the accumulation of visceral adipose tissue, and an enlarged liver volume can obstruct the surgical field [7] and increase the risk of complications, such as anastomotic leakage, bleeding, and infection [8]. Excess visceral fat can increase the risk of surgical complications and prolong the conversion rate and surgical time [8]. For instance, an enlarged liver and the accumulation of visceral fat can obstruct the surgical field, which is responsible for approximately 50% of conversion cases in RYGB [9]. Additionally, a large neck circumference (>44 cm) may lead to difficulties in intubation and mechanical ventilation [10]. Immediate preoperative weight loss has been reported to reduce anaesthesiological and surgical risks [11] and improve short- and long-term outcomes [12], but its role is still a subject of debate [13]. The evidence on the effects of preoperative weight loss comes mainly from retrospective studies, as there is a lack of multicentre randomized controlled trials (RCTs) on this specific topic [14]. Therefore, guidelines do not currently provide conclusive evidence for preoperative weight loss [15,16].

Several approaches to weight loss before surgery have been explored, including pharmacotherapy with glucagon-like peptide-1 receptor agonists [17] or a hypocaloric diet combined with gastric balloon insertion [18]. These methods appear to be effective in reducing the rate of surgical complications and conversions [19].

However, in clinical practice, diet is probably the most common approach. There are various diets that can be recommended to patients undergoing BS, with studies showing that there are a wide range of diets prescribed across different centres [20,21]. These diets include low-calorie (LCD), low-carbohydrate, and liquid-based diets [20,21].

The Mediterranean diet, which mainly consists of plant-based foods and uses olive oil as the primary source of added fat, has been linked to numerous health advantages, such as a decreased risk of chronic diseases [2]. However, research indicates that it may not be the most efficient method for rapid weight loss prior to BS [22]. By adopting a balanced, energy-controlled diet before the operation, similar to the Mediterranean diet, patients can improve their nutritional habits and enhance their nutritional status [23]. However, it may not be restrictive enough to help reduce body weight significantly and quickly before BS [22]. According to some authors, patients who follow a diet more strictly before surgery tend to lose more weight after surgery, for example, with an LCD [24]. For high-risk patients, a very low-calorie diet (VLCD), which involves consuming 600–800 kcal per day, may be a viable option to achieve rapid weight loss [25]. However, LCDs have certain disadvantages, which are the greater the more restrictive they are, such as the loss of lean mass; poor nutrient intake, if not well supplemented; and difficult diet adherence.

Research has shown that low-carbohydrate diets can help reduce liver fat and volume [26,27], which may be beneficial for patients undergoing BS. While personalized diets are generally more effective in promoting adherence, standardized diets may be more appropriate in preparing patients for surgery in a short period of time. In this regard, although they do not promote sustainable changes in eating habits, ketogenic diets (KDs) may be more effective as pre-operative diets for BS, while diets along the Mediterranean lines may better serve as post-operative diets for maintaining the weight loss.

KD is a term that refers to various low-carbohydrate diet protocols. These diets are characterized by a high intake of fats and proteins, resulting in a fasting-like state that promotes physiological ketosis [28]. For instance, the very low-calorie ketogenic diet (VLCKD) involves a significant reduction in carbohydrate consumption (less than 50 g per day), adequate protein intake, and high fat consumption, with an average energy intake of 800 kcal/day [28–30]. While the KD was originally used to treat epilepsy in children [31],

it has been shown to be an effective means of inducing rapid weight loss and managing obesity-related disorders in adults [32–35]. Recent research has demonstrated that the VLCKD may be a particularly attractive pre-operative dietary treatment for patients with obesity who are candidates for bariatric surgery. In fact, a recent RCT found that VLCKD resulted in better surgical outcomes than a VLCD in 178 patients undergoing laparoscopic SG [36].

Overall, KD has been shown to be an effective strategy for inducing rapid weight loss, and its use before surgery, especially when available in the short term, is particularly attractive [37]. The aim of this review was to summarize the current evidence on the VLCKD as pre-operative dietary treatment in patients with obesity candidates for BS.

2. Very Low-Calorie Ketogenic Diet

2.1. Definition of Ketogenic Diets

KDs are high-fat diets, characterized by a carbohydrate restriction (30–50 g per day) [28]. This drastic reduction in the content of exogenous carbohydrates drives the body into a state of mild physiological ketosis: a metabolic state characterised by an increase in the concentration of ketone bodies [38]. Ketone bodies are the products of hepatic ketogenesis, namely acetoacetate, acetone, and β-hydroxybutyrate (although the latter is not defined as a ketone by IUPAC nomenclature) [38]. Various KD protocols exist, differing from each other based on calories, macronutrients composition, and the achievable ketogenic ratio [28]. The term ketogenic ratio refers to the ratio between the amount of lipids (expressed in grams) in the diet protocol and the amount of protein and carbohydrates [28].

The most used KD therapies in the treatment of obesity are the low-calorie ketogenic diet (LCKD) and the VLCKD. These nutritional approaches exploit nutritional ketosis, induced not only by low carbohydrate intake but also by calorie restriction, to achieve a rapid loss of fat mass while preserving lean mass [39]. Recently, VLCKD has been shown to result in significant weight loss along with improved glycaemic control in subjects with obesity and T2DM [40–42]. The VLCKD protocol is characterized by a daily calorie diet of 700–800 kcal/day with a carbohydrate restriction of 30–50 g/day (≃13% of total energy intake), a 30–40 g/day (≃44%) increase in fats, and about 1.2–1.4 g/day proteins per kg body weight (≃43%) [29,30]. While some may mistakenly believe that VLCKD is a high-protein diet, it actually maintains a daily protein intake of around 1.2–1.5 g/kg of ideal body weight. Furthermore, VLCKD is based on high-quality protein sources from both animal and non-animal sources, such as eggs, peas, soy, and whey protein [29,30].

2.2. Mechanisms of Action and Benefits of Very Low-Calorie Ketogenic Diet before Bariatric Surgery

As reported in the Italian Society of Obesity Surgery and Metabolic Diseases (SICOB) guidelines, the pre-operative reduction of body weight is recommended in patients who are candidates for BS, especially in the presence of BMI > 40 kg/m^2 or severe visceral obesity, including the prescription of a LCD/KD in the pre-operative period [43]. Decreasing body weight significantly reduces visceral adipose tissue and fat liver [44], facilitating the performance of laparoscopic operations, reducing the performance time and the risk of conversion [9], and improving short- and long-term results, especially in patients with BMI > 40 kg/m^2 [45,46].

Several methods have been proposed to promote preoperative weight loss. In a prospective observational study, Colles et al. investigated the efficacy and acceptability of a preoperative very low energy diet (VLED) [47].

In a study involving 32 participants (19 men and 13 women) with a mean BMI of 47.3 ± 5.3 kg/m^2, a VLED was implemented for 12 weeks. The study aimed to measure changes in liver volume, visceral and subcutaneous adipose tissue, body weight, anthropometric measures, and biochemical variables. Compliance, acceptability, and side effects were also evaluated. The study found that the degree of liver volume reduction was directly related to the reduction in relative body weight and initial liver volume. Eighty percent of the reduction in liver volume occurred between weeks 0 and 2. Reductions in body

weight and visceral adipose tissue were consistent over the 12-week period. Based on these findings, the authors suggest that a pre-operative VLED should be followed for a minimum of 2 weeks to achieve reductions in liver volume and visceral adipose tissue. Ideally, a 6-week duration would be best to achieve maximal liver volume reduction and significant reductions in visceral adipose tissue and body weight without affecting compliance or acceptability [47]. Leonetti et al. enrolled 50 patients (31 females and 19 males, mean age 47.7 ± 11.2 years, mean BMI 53.5 ± 8.4 kg/m^2) who followed a VLCKD and VLCD protocol prior to BS treatment (the obese preoperative diet (OPOD) group) and were compared with 30 patients (18 females and 12 males, mean age 43.3 ± 8.7 years, mean BMI 54.8 ± 9.4 kg/m^2), who followed a standard LCD (control group) [48]. Body weight and waist circumference decreased significantly in the OPOD group, whereas no significant changes occurred in the control group. The OPOD group also recorded an improvement in fasting plasma glucose levels, even in patients with T2DM taking antidiabetic drugs. No significant changes were found in plasma creatinine, urea, uric acid, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, γ-glutamyl transferase, or alkaline phosphatase levels, confirming the liver and kidney safety of this protocol. An ultrasound evaluation was performed and an average 30% reduction in liver volume was found [48].

From the evidence in the literature, it seems clear that the use of a VLCD or VLCKD in the 15 to 30 days prior to surgery achieves satisfactory results in less time, at a lower cost, and with fewer side effects than the intragastric balloon [18,49].

According to Albanese et al., the main advantage of VLCKD is not only fast and substantial weight loss but also its positive influence on parameters strongly related to surgical outcome [36]. In fact, in a recent study of 178 patients who underwent either VLCKD or VLCD before SG, blood drainage outputs were lower and post-operative haemoglobin levels were higher in the group following VLCKD than the group following VLCD. Considering that weight loss and mean operative time were comparable between the two groups, it can be assumed that this advantage was also influenced by the greater ease of surgical manoeuvres due to hepatomegaly and visceral adipose tissue reduction. The authors surmised that patients with VLCKD achieved a better metabolic and nutritional status that influenced tissue healing and response to surgery [36]. In line with these results, a 4-week preoperative VLCKD that included micronutrient supplementation led to better blood glucose and hypertension, as well as a 19.8% decrease in the initial volume of the left hepatic lobe [50].

Another important benefit of VLCKD is the high compliance rate due to the anorexigenic effect and hunger reduction caused by ketone bodies [51]. When the body is in a state of ketosis, it uses ketone bodies as a primary source of energy instead of carbohydrates. This shift in metabolism can lead to decreased hunger and cravings, making it easier for patients to stick to the prescribed diet [51]. In addition, the physiological production of beta-hydroxybutyrate during VLCKD exerts an important anticatabolic effect on skeletal muscle, thus leading to a decrease in fat mass, preserving lean mass and muscle strength [52].

For this reason, the Italian Society of Endocrinology (SIE) Consensus Statement recommends a 2- to 6-week preoperative weight-loss program with VLCKD for patients who are candidates for BS in order to induce weight loss and a reduction in liver volume and visceral adipose tissue [40].

Therefore, VLCKD is effective in rapidly reducing weight, waist circumference, and liver volume and consequently reduces the risk of transitioning to an open procedure, as well as the risk of perioperative complications (Figure 1).

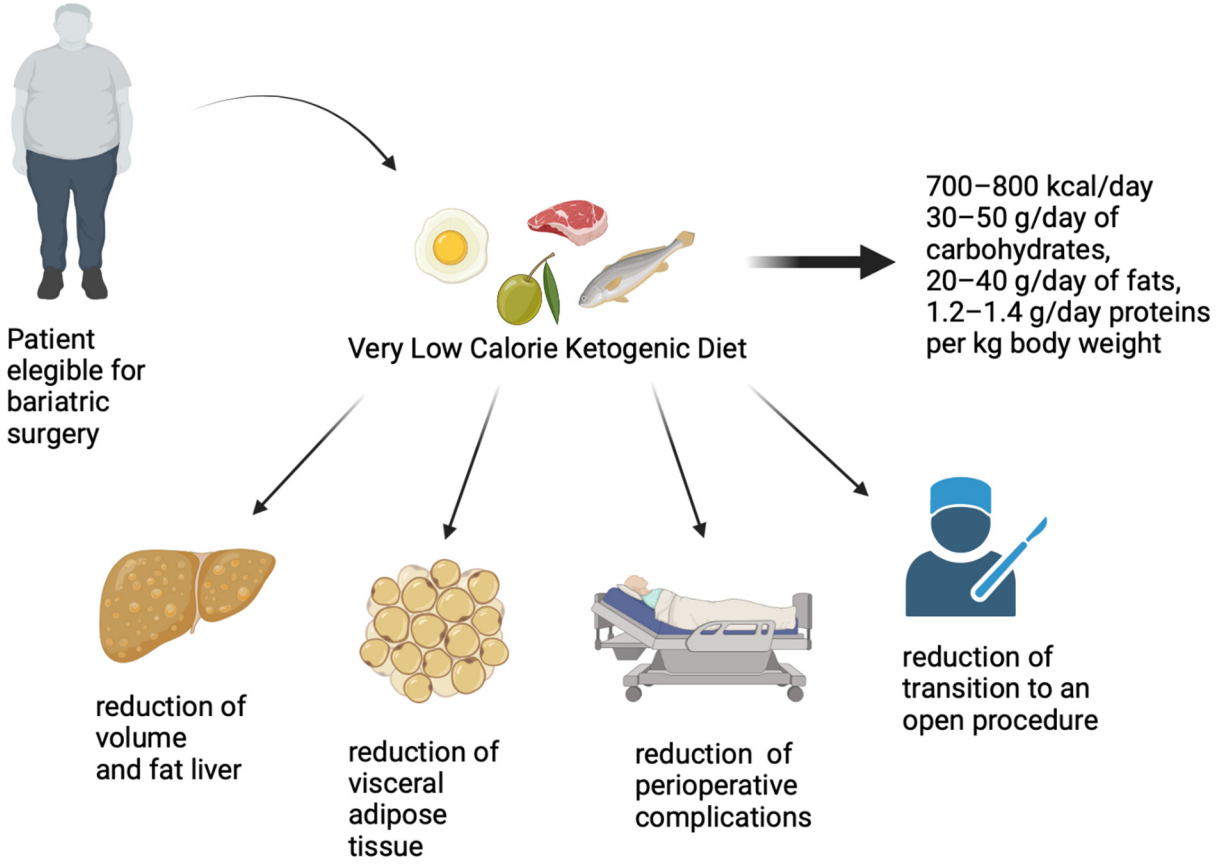


Figure 1. Pre-operative effects of very low-calorie ketogenic diet in a candidate for bariatric surgery.

2.3. Indications and Contraindications of Very Low-Calorie Ketogenic Diet in Pre-Bariatric Surgery

According to Marinari et al., losing weight before surgery can decrease liver volume and potentially make the surgery easier [53]. However, there is still debate over whether weight loss before surgery reduces the risk of complications after surgery [16,54].

As stated in the European Association for Endoscopic Surgery (EAES) clinical practice guidelines on BS (2020) endorsed by the European Association for the Study of Obesity (EASO), the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO-EC) and the European Society for the Peri-operative Care of the Obese Patient (ESPCOP), three RCTs were found regarding preoperative diet consultation versus standard care in patients undergoing BS [54]. The results showed that the group that received preoperative diet consultation had more significant weight loss after surgery (SMD 0.4, 95% CI 0.03 to 0.78 higher), but there was no significant difference in the likelihood of postoperative complications (risk ratio, RR, 0.80, 95% CI 0.22 to 2.86), although interval estimates were wide [54]. However, a study from a Swedish registry showed a decrease in complications after gastric bypass surgery [55].

Moreover, as reported by Marinari et al., it is necessary to improve the preoperative fasting blood glucose level by using diet, exercise, and medication [55]. This is because having a blood glucose level higher than 180 mg/dl has been linked to an increase in complications and mortality during the surgery [56]. Considering these assumptions, it would seem evident that a VLCKD is effective in the rapid loss of visceral adipose tissue and hepatic adipose tissue prior to BS, thus aiding the surgery.

According to the Position Statement of SIE, VLCKD should be stopped 48 h prior to elective surgery or invasive procedures and perioperative period [40]. On the other hand, there are several absolute contraindications regarding the use of VLCKD, such as type 1 diabetes mellitus, latent autoimmune diabetes in adults, β-cell failure in T2DM, the use

of sodium/glucose cotransporter 2 inhibitors, kidney failure, moderate-to-severe chronic kidney disease, liver failure, hearth failure (NYHA III-IV), and respiratory failure [29,30].

2.4. Side Effects and Transient Complications of Very Low-Calorie Ketogenic Diet

VLCKD is a dietary treatment that may have transient adverse effects in the short to medium term. One of the most frequent complications of the VLCKD nutritional program is dehydration, and for this reason, an intake of 2–2.5 L of water or other sugar-free beverages daily is recommended, especially during the active phase of ketosis (PMID: 35653127). Dehydration can lead to electrolyte disorders, such as hyponatremia, hypokalemia, and hypomagnesemia (PMID: 31665015). As reported by Barrea et al. (PMID: 35653127), these disorders can also develop due to the urinary excretion of ketone bodies and low micronutrient intake, especially during the active phase. Therefore, proper hydration and supplementation with vitamins and minerals, as reported by the European Food Safety Authority (EFSA), is essential.

Another complication that may occur in the short to medium term is increased uricemia. In a study by Bruci and colleagues, uric acid was finally shown to be significantly reduced after a 90-day VLCKD protocol, ruling out a correlation between VLCKD and hyperuricemia (PMID: 32012661). A meta-analysis conducted by Castellana et al. reported an overall neutral effect on uric acid by VLCKDs (PMID: 31705259). These controversial results could be explained by the timing and extent of weight loss, as food groups that typically increase serum uric acid levels (including red meat and anchovies) are widely consumed in KDs and could lead to this effect in the short term (PMID: 32012661). However, it is recognized that weight loss is associated with a significant reduction in urate levels (PMID: 31468681). For this reason, it seems reasonable to suggest that it is necessary to monitor uricemia throughout the course of VLCKD, and, in the case of patients with hyperglycaemia, limit foods with high urate content and administer allopurinol if necessary.

Another complication that could occur due to lower food and fibre intake is constipation, which responds well to sufficient fluid intake, the daily intake of vegetables allowed during VLCKD, and low-calorie laxatives.

2.5. Differences between Very Low-Calorie Ketogenic Diets with Meal Replacement or with Traditional Protein

According to the European Guidelines for the Management of Obesity in Adults, VLCKD includes proteins with a high biological value that are derived from milk, peas, whey, and soy [30]. This diet can be achieved by using meal replacement or natural foods [30]. Basciani et al. conducted a study comparing the effectiveness and safety of VLCKD for 45 days using whey or vegetable protein meal replacement foods with conventional animal protein in a group of patients with obesity and insulin resistance [57]. The results showed that after 45 days of VLCKD, there was a significant reduction in initial body weight in both the whey protein and plant protein groups. Although the animal protein group also showed a reduction in body weight, it was not statistically significant. The animal protein group also showed an increase in blood urea nitrogen and uric acid and a significant reduction in the estimated glomerular filtration rate compared to baseline values. The authors concluded that VLCKD based on whey or vegetable protein is a safer option than animal protein for patients with obesity [57]. Therefore, a VLCKD with whey and vegetable protein-based meal replacements is a more suitable option for these patients.

Based on scientific evidence, it is recommended to use meal replacements during the initial active ketogenic phase of a VLCKD to ensure a safe, effective, and controlled administration [57,58]. In fact, with the use of single-portioned meal replacement meals, the calibration of the diet is more accurate, and the content of calories, macronutrients, and micronutrients needed by the patient can be set more precisely and individually. Therefore, it would seem more appropriate to set up a VLCKD protocol with the use of meal replacements to determine greater safety, efficacy, and compliance prior to BS, with

preference given to freeze-dried meal replacements, which generally have a higher protein content and lower fat and carbohydrate content. This would ensure a higher degree of weight loss and a better adherence, which is critical when considering of the short duration of the protocol.

3. Bariatric Surgery

3.1. Sleeve Gastrectomy

SG was conceived as the first surgical stage of biliopancreatic diversion with duodenal switch producing a malabsorptive and restrictive bariatric procedure [59]. When Regan et al. reported the results of SG as a first-stage procedure before RYGB in patients with BMI > 60 kg/m^2 showing a mean weight loss of 37 kg and a mean BMI decrease of 13 kg/m^2 after 11 months of follow-up, SG gained increasing interest as a stand-alone bariatric procedure [60]. Today, SG represents the most performed BS worldwide and further innovations, such as the use of the laparoscopy, changes in the surgical techniques, and the use of natural transluminal orifice endoscopic surgery, have been put in place to improve its outcomes [61].

Laparoscopic SG comprises a subtotal vertical gastrectomy, creating a tubular duct along the lesser curve with pylorus preservation [62]. Being considered quicker and easier to perform as it does not include any intestinal anastomosis, compared to other more complex bariatric procedures, its wide diffusion and acceptance also depends on the favourable outcomes reported in terms of weight loss, the reduction in obesity-related comorbidities, and the low rate of postoperative complications. SG does not only work as a restrictive procedure, but it provides important hormonal changes involving GLP-1, peptide YY (PYY), and ghrelin and leptin pathways, accounting not only for the several metabolic changes but also for the sharp decrease in feelings of hunger [62]. A review of the literature by Diamantis et al. revealed the percentage of excess weight loss to be 62.3%, 53.8%, 43%, and 54.8% at 5, 6, 7, and 8 or more years of follow-up, respectively [63]. Concerning T2DM, the research by Madadi et al. involving 2480 patients who underwent SG, the remission rate was 56.29% after 1 year follow-up [64]. However, the literature concerning long-term outcomes after SG alone or compared to other procedures is poor and disparate. Han et al. conducted a meta-analysis encompassing 2917 patients from randomized prospective and retrospective studies, which highlighted no differences in mid- and long-term weight loss between SG and RYGB; moreover, no difference in long-term T2DM remission was found [65]. On the other hand, a meta-analysis from Gu et al. reported the superiority of RYGB in T2DM remission at 3 years follow-up and in the percentage of excess weight loss and remission of T2DM, hypertension, and dyslipidaemia [66]. Furthermore, another meta-analysis by Lee et al. showed the superiority of RYGB in 1 and 3 years BMI loss and 1 and 5 years dyslipidaemia remission, but no differences were found in T2DM and hypertension remission compared to SG [67]. While the latter evaluated only early (<30 days) postoperative complication rates, reporting no differences between RYGB and SG [67], the research by Han et al. highlighted higher early postoperative complications (RR: 2.14) and reoperation (RR: 1.73) risks for RYGB and no difference in terms of late (≥30 days) postoperative morbidity [65].

Although SG is a safe procedure, burdened by low postoperative morbidity and negligible mortality, postoperative gastroesophageal reflux disease (GERD) represents a common issue for patients undergoing this procedure. The physiopathology of GERD has not been completely elucidated and different causes, such as increased intragastric pressure, reduced gastric emptying, and decreased lower oesophageal sphincter pressure, have been evocated [66,67]. The study by Yeung et al., involving 10,718 patients, showed a 23% rate of de novo GERD after SG, which is associated with a 28% and 8% rate of long-term esophagitis and Barrett's oesophagus prevalence, respectively; in addition, GERD was the reason for conversion to RYGB in 4% of patients [68]. Weight regain represents another major drawback of SG. A recent meta-analysis including studies with long follow-up after

SG showed a 27.8% rate of weight recidivism and a 19.9% rate of subsequent revisional rate [69].

SG is currently surgeons' most preferred bariatric procedure due to its simplicity, the low related morbidity, and the good short- and mid-term weight loss and results regarding obesity-related comorbidities. However, its long-term reliability is uncertain, and GERD represents a major cause of discomfort and morbidity for individuals with SG.

3.2. Roux-en-Y Gastric Bypass

For many decades, RYGB represented the most frequently used bariatric procedure performed before being recently superseded by SG [70]. It consists of the creation of a small gastric pouch that is separated from the gastric remnant, the anastomosis of the gastric pouch to the distal part of a transected bowel loop (Roux-en-Y limb), and the connection of the proximal part of the transected small bowel loop (biliopancreatic limb) to the Roux limb at a previously defined distance from its anastomosis with the gastric pouch; many different methods of reproducing this anatomical construction have been described [71]. The aim of this reconstruction is to combine the restrictive effect of a tiny gastric pouch to the malabsorption occurring in the common alimentary and biliopancreatic limb length [71]. Once thought to be the most relevant mechanism to determine weight loss after RYGB, the recent literature has showed how no changes in carbohydrate and protein absorption and only low fat malabsorption after proximal RYGB with an estimated 11% contribution on total postoperative weight loss in the early period due to the malabsorptive phenomenon [72]. However, recent studies focusing on mid- and long-term weight loss after RYGB has showed encouraging results supporting its employment [73–75]. Golzarand et al. reported the percentage of excess weight loss being 62.58% after 5 years and 63.52% after 10 years in 1671 patients who underwent RYGB [73]. Similar results were outlined by O'Brien et al., with 55.4% of excess weight loss after 10 years or more from BS [74]. Concerning obesity-associated medical problems, RYGB has also been demonstrated to be effective [75]. Compared to medical treatment, RYGB has been revealed to be superior in terms of T2DM remission (OR: 76.37) and patients after RYGB showed significantly inferior serum levels of HbA1c, triglyceride, low-density lipoprotein cholesterol, and systolic blood pressure [75].

On the other hand, RYGB is characterized by some drawbacks which are still debated. Although RYGB showed better results in long-lasting T2DM remission compared to SG, T2DM relapse after 10 or more years follow-up is estimated to be 30% [76]. Furthermore, RYGB may be badly tolerated due to the occurrence of nutritional issues. Post-RYGB anaemia can reach 45–50% incidence as a consequence of iron and B12 vitamin deficiency; hypoproteinaemia has a 10–15% incidence and mineral deficiency is also frequent [77]. In the end, in contrast with the short- and mid-term results of optimal weight loss, long-term weight regain after RYGB is documented in 20–35% of patients [78].

3.3. One-Anastomosis Gastric Bypass

OAGB consists in producing a small size gastric pouch on a 36 Fr bougie with a single anastomosis with the small bowel at 150–200 cm from the Treitz ligament [79]. With this anatomical reconstruction, the restrictive and malabsorptive principia of RYGB are conserved with only one anastomosis, reducing surgical complexity and the sources of postoperative complications at the same time [79]. The IFSO published an update position statement on OAGB analysing the results of all the literature on this procedure [80]. Short-term results in terms of weight loss are encouraging. Nine RCTs with 501 patients who underwent OAGB showed a global percentage of excess weight loss of 67.85% and 87.54% excessive BMI loss after 25.33 months of mean follow-up. Concerning associated medical problems, patients who underwent OAGB showed positive T2DM, obstructive sleep apnoea syndrome (OSAS), hypertension, and dyslipidaemia remission rates [80]. Although OAGB is widely carried out, as it considered effective, easy, and quick to perform and has a low postoperative complication rate [81], some nutritional and malabsorptive issues must be

considered [82,83]. A comparative systemic review and meta-analysis by Tourky et al. showed a significantly increased percentage of excess weight loss and percentage of total body weight loss at 3-year follow-up but also highlighted an increased risk of postoperative malnutrition (OR: 3) and hypoalbuminemia (OR: 2.38) for OAGB compared to RYGB [83]. Moreover, the anatomical reconstruction of OAGB theoretically exposes the patients to an increased incidence of bile reflux, which can cause esophagitis and is a potential risk factor for oesophageal cancer; postoperative bile reflux incidence varies between studies from 7.8 to 55.5% [82]. In the end, long-term postoperative outcomes after OAGB are still not well documented in the literature with only few retrospective studies reporting a 10-year or more follow-up.

3.4. Single-Anastomosis Duodeno-Ileal Bypass

SADI consists of a gastric greater curvature resection, followed by a resection of the duodenum 3–4 cm from the pylorus, and then a duodeno-ileal anastomosis is performed, producing a 200 cm efferent limb [84].

As it has only recently been proposed and adopted, research evaluating outcomes after SADI is limited, especially when considering long-term results. A comparative systematic review and meta-analysis by Verhoeff et al. evaluated 3319 patients who underwent a malabsorptive procedure, including 1704 patients receiving SADI [85]. They reported a significantly shorter operative time and length of stay and postoperative complication rate for SADI. In addition, no differences in terms of weight loss, associated medical problems remission, and nutritional deficiencies were highlighted; however, follow-up in the included studies was too short to produce solid conclusions and, although subgroup analysis was performed, the reliability of the results of this meta-analysis was affected by the heterogeneity of the comparative group, which included patients who underwent different malabsorptive procedures [85]. Sanchez-Pernaute et al. published their 10-year follow-up case series of 123 SADI, showing 80% and 34% of excess weight loss and total body weight loss, respectively; a total of 12 of 41 diabetic patients needed insulin treatment at the end of follow-up and 12 of 123 had undergone revisional surgery due to chronic hypoproteinaemia [86].

SADI has also demonstrated encouraging results as revisional surgery after failure of previous restrictive procedures [87], but long, high-quality follow-up studies are needed to evaluate long-term efficacy of this procedure in a primary and revisional setting.

3.5. Perioperative Issues

3.5.1. Perioperative Technical Issues

Individuals undergoing BS represent a peculiar population with their own specific characteristics that make each surgical step insidious. As a matter of fact, considering the two most common bariatric procedures performed worldwide, the learning curve threshold has been shown to be set at 100–200 laparoscopic SG and up to 500 laparoscopic RYGB for the single surgeon to master these procedures [88].

3.5.2. Port Placement

Port placement is the first step of any laparoscopic surgery. Hasson's technique, conceived in 1971, consists of performing a mini-laparotomy to gain access to the peritoneal cavity and place the optic trocar under direct visualization to avoid inadvertent abdominal organ injuries [89]. This technique, which was introduced as an alternative to blind trocar placement to reduce procedure-associated complications, is often impossible to realize as a consequence of the abdominal wall thickness in bariatric patients, although a "large" mini-laparotomy is performed with the successive risk of CO_2 leakage that can compromise the surgical performance [90]. Access to the abdominal cavity is challenging not only due to abdominal wall thickness but also because individuals with obesity, especially females, have a high dense abdominal barrier and thick peritoneum [90]. Moreover, the umbilicus in this population can have variable positions and the bariatric surgeon has to

use different landmarks to avoid optic port placement in a position that can affect surgical performance [91,92].

Closed techniques, such as direct trocar insertion (DTI) and the Veress technique, are commonly used in individuals with obesity, but they are not riskless, as they consist in the blind insertion of a sharp instrument into the abdomen [93,94]. Two randomized clinical trials have been performed comparing these access techniques in individuals with obesity [93,94]. Ertugrul et al. reported two major complications in the DTI group vs. no major complications in the Veress group in 81 patients scheduled for bariatric laparoscopic surgery using a bladed trocar for the DTI technique; abdominal access was faster in the DTI group while no difference in terms of access failure rate was found [93]. Similar findings were reported by Ikechebelu et al. in 135 women with obesity undergoing diagnostic laparoscopy for infertility—the only difference resulting from the two groups was faster access time to the abdominal cavity in favour of the DTI group [94]. At present, no recommendation has been developed regarding which technique is the most safe and feasible and any bariatric surgeon should be comfortable with multiple techniques.

3.5.3. Patient-Related and Intraoperative Factors

How anatomical and intraoperative factors can affect the complexity of bariatric procedures is a debated topic, as most surgeons agree that some specific features have a relevant impact, but the current literature is very scant regarding this issue. A worldwide international survey based on 370 expert bariatric surgeons was performed by Shahabi et al., which focused on how many anatomical and intraoperative factors could make the procedure easier or more complicated [92]. Some anatomical features, such as hepatomegaly, a large sized hiatal hernia, a thick falciform ligament, and a thick omentum, were considered as moderately or highly complicating to the bariatric procedure. As a matter of fact, the aforementioned characteristics play a part in reducing the accessibility to the stomach and the bowel for resecting, stapling, and suturing and make it more difficult to achieve a correct operative position. Consequently, the higher is the patient's BMI, the harder the operation is expected to be. A total of 39.7% of the experts surveyed agreed that a BMI > 50 kg/m^2 makes the performance of operations moderately difficult and 10.8% thought that it makes the procedure very difficult; a BMI > 60 kg/m^2 makes the operation very difficult for 34.3% of experts and extremely difficult for 12.1%. These data should, however, be taken carefully, as the distribution of adipose tissue determines surgical difficulty to a greater extent than BMI and patients' phenotype, i.e., gynoid vs. android, may play a pivotal role in determining surgical difficulty. Indeed, some individuals with a BMI > 50 kg/m^2 may present with peripheral obesity (gynoid phenotype) and be easy to operate on, while on the other hand an individual with central obesity and a BMI between 35 and 40 kg/m^2, may be very challenging to operate on because the presence of most of the fat in the abdomen hinders the possibility of obtaining enough room with the pneumoperitoneum to perform the bariatric procedure with ease. Liver cirrhosis, which is not rarely associated because of progressive non-alcoholic steatohepatitis, also represents an unfavourable characteristic and 32.4% of the surgeons surveyed affirmed that it makes the operation moderately difficult, while 21.8% declared that it makes the procedure very difficult [92].

3.5.4. Anaesthesia

Individuals with obesity represent a significant challenge for anaesthesiologists, as obesity and its related medical issues deeply affect bariatric perioperative management. With the current obesity epidemic, the literature concerning the pitfalls of anaesthesia in this specific population is progressively developing.

3.5.5. Perfusion

Providing one or more venous access is the first step in preparing the patient for anaesthesia. Intravenous cannulation can sometimes be difficult due to different factors.

Obesity is commonly considered a complicating condition as it affects vein palpation and visualization [95]. The research by Brandt et al. showed that a higher BMI is associated with the absence of clinically detectable veins and that ultrasonography guarantees 100% success in finding a peripheral vein suitable for cannulation [95].

3.5.6. Intubation

Endotracheal intubation is commonly considered to be more difficult in patients with obesity; however, there is no clear evidence that difficult intubation is more frequent than in lean populations [96]. A large French cohort study reported an increased incidence of failed primary intubation and of difficult intubation in individuals with obesity compared to individuals without obesity, although the factors related to an increased risk of failed intubation did not differ from those seen in the normal weight population (Mallampati III/IV grade, cervical spine rigidity, OSAS) [97,98]. Bariatric patients frequently have an increased neck circumference and a neck circumference/thyromental distance ratio due to fat distribution which are associated with an increased Mallampati grade [99]. Moreover, the frequent association between obesity and diabetes adds another factor that can complicate the intubation, as it has been demonstrated that diabetic patients suffer from increased osteoarticular stiffness, which provokes cervical spine rigidity and reduction in consented motions during intubation [100]. A history of OSAS should always be investigated preoperatively as its incidence is elevated in the morbidly obese population (35–93%) and it can affect many aspects of anaesthesiologic perioperative management [101]. Videolaringoscopy could be employed to ease difficult intubations; however, there is still weak evidence regarding its actual benefits in this specific situation. On the other hand, preferring a ramped position to a flat supine position at the moment of induction and intubation eases the procedure [101].

3.5.7. Ventilation

Up to 20% of patients with morbid obesity are diagnosed with Obesity Hypoventilation Syndrome, which is defined as the coexistence of BMI $\geq$ 30 kg/m^2 and daytime hypercapnia with $PaCO_2$ > 45 mmHg during wakefulness in the absence of an alternative neuromuscular, mechanical, or metabolic explanation for hypoventilation, and its incidence reaches 50% in patients with BMI $\geq$ 50 kg/m^2 [102]. Different mechanisms are implicated: the obesity-related restrictive respiratory mechanic, the central respiratory drive depression determined by chronic hypercapnia and the consequently increased bicarbonate retention, and leptin resistance [103]. In these patients, bilateral pulmonary atelectasis frequently coexists, reducing respiratory reserve [103]. Obesity Hypoventilation Syndrome exposes the bariatric patient to perioperative desaturation and to an increased risk of respiratory complications, depending on the difficulty of reaching a balance between adequate oxygenation and the risk of pulmonary barotrauma [104]. In addition, the concurrence of OSAS, which delineates the so-called overlap syndrome, further accentuates the aforementioned issues. Moreover, the need to set the patient in a Trendellenburg position during certain technical surgical steps increases the pressure performed by the abdomen on the chest furtherly reducing respiratory volumes and reserves. Intraoperative pressure-controlled ventilation with low tidal volume, carefully titrated positive end-expiratory pressure, and lung recruitment manoeuvres result in better intraoperative oxygenation, atelectasis mitigation, and reduced postoperative respiratory complications after laparoscopic BS [104].

3.5.8. Extubation

The respiratory function alterations induced by obesity and its related medical issues in combination with the effects of anaesthetic drugs also exposes the bariatric patient to an increased risk of respiratory insufficiency from the moment of extubation [105]. To help avoid respiratory complications, bariatric patients should be as awake as possible prior to extubating in the operating room [105]. To achieve this, many attempts to modify anaesthetic drugs protocols have been carried out. Patients undergoing BS have different

pharmacokinetics compared to leaner populations, as liposoluble drugs are stocked in fat tissue, releasing them slowly, which in turn may create long-lasting residual effects [106]. Avoiding opioids or using short-acting opioids along with adjuvants and avoiding or minimizing the need for neuromuscular blocking agents can directly cut down the number of postoperative pulmonary complications in patients with obesity [106].

3.6. Very Low-Calorie Ketogenic Diet in Bariatric Surgery

3.6.1. The Use of Ketogenic Diet on Patients with Obesity Scheduled for Bariatric Surgery

BS is known to be the most effective and durable therapeutic means for the long-term treatment of morbid obesity [107]. Currently, laparoscopic surgery is the preferred method for BS in almost all cases. Patients who require BS often have a steatotic liver, which can make the surgery technically challenging [107]. This can lead to longer surgery times, an increased risk of bleeding during surgery, anastomotic complications, and in some cases, suboptimal bariatric anatomy, which can compromise long-term results [108,109]. Another challenge during bariatric surgery is increased intra-abdominal fat, especially in patients with central obesity. This can reduce the working space and make it difficult to expose anatomical landmarks, as well as impair complex surgical tasks, such as knotting and suturing [13,110,111]. Therefore, preoperative interventions to reduce body weight, hepatomegaly, and intra-abdominal fat before laparoscopic bariatric surgery could benefit both surgeons and patients by reducing surgical risk [13,110,111]. However, there is no clear consensus on the most effective dietary approach.

KDs have been used as a therapy for epilepsy since the 1920s and have been widely used for obesity treatment since the 1960s [112]. These diets are characterized by a high intake of fats and proteins, with a significant reduction in carbohydrate consumption, inducing a state of physiological ketosis [113]. For instance, a VLCKD involves a drastic reduction in carbohydrate intake (less than 50 g per day, providing about 13% of caloric intake), with adequate protein intake (about 0.8–1.2 g per kg of ideal body weight, providing about 45% of caloric intake) and a relatively high intake of fats (approximately 42% of caloric intake), with an average energy intake of 800 kcal per day [113]. Strong and supportive evidence suggests that KDs are effective for weight loss therapy, and they may be a valid option for patients at higher risk who need to achieve rapid weight loss [45,114]. Patients often report satisfaction with this nutritional approach, possibly due to the anorexigenic, euphoric, and mood-stabilizing effects of ketone bodies, which reduce hunger and promote a feeling of rapid satiety [112].

One of the first study addressing the effect of VLCKD on patients with obesity scheduled for BS was performed by Leonetti et al. [48]. The study evaluated the efficacy of a sequential diet regimen called OPOD, in 50 patients with a mean BMI of 53.5 $\pm$ 8.4 kg/m^2, with and without T2DM, who were scheduled for laparoscopic BS. The OPOD regimen consisted of a 10-day KD (600 kcal per day, 15 g of carbohydrates, 80 g of proteins, and 23 g of lipids), followed by a 10-day VLCD (800 kcal per day, 55 g carbohydrates, same proteins, and 30 g lipids), and finally an LCD (1100 kcal per day, with an increase in carbohydrates up to 145 g, 60 g proteins, and 33 g lipids) until the surgery. The OPOD regimen scheme used by Leonetti et al. is reported in Table 1.

The patients in the study were assessed at baseline (T0) and after 10 days (T1), 20 days (T2), and 30 days (T3). The results showed that body weight, BMI, waist circumference, and neck circumference were significantly lower at T1, T2, and T3 than at T0 in the 48 patients who completed the OPOD regimen. Additionally, in patients with T2DM, fasting plasma glucose levels decreased significantly, allowing for a reduction in diabetic medications. The study concluded that the OPOD, which includes 10 days of VLCKD, was safe and effective for patients with obesity with or without T2DM who were candidates for BS [48]. Similarly, Albanese et al. aimed to compare surgical outcomes and weight loss in two groups of patients who were offered two different pre-operative diets: VLCD and VLCKD. The study involved 178 patients, with VLCKD implemented for 72 patients and VLCD implemented for 106 patients. The mean age was 43 years, and the mean BMI before the diet was

46.3 ± 6.3 kg/m^2 for the VLCKD group and 43.1 ± 6.9 kg/m^2 for the VLCD group. The results showed that absolute weight loss was significantly better in the VLCKD group than in the VLCD group (5.8 ± 2.4 vs. 4.8 ± 2.5 kg; $p = 0.008$), while there were no significant differences in excess BMI loss (10.4 ± 4.0 vs. 10.0 ± 5.6%; $p = 0.658$). The VLCKD regimen consisted of 1.4 g of protein per kg of ideal body weight, <20–30 g of carbohydrates, and 15–20 g of lipids per day, divided into three main meals with a maximum caloric intake of 700 kcal per day. Breakfast and dinner were replaced by a diluted powder containing whey proteins enriched with amino acids, while lunch included animal or plant-derived protein natural food and 200 g of vegetables. The study recommended the integration of trace elements diluted in 2 L of water per day [36]. The VLKCD scheme used by Albanese et al. is reported in Table 2.

Table 1. The obese preoperative diet (OPOD) [48].

Regimen OPOD		
VLCKD (Days 1–10)	**VLCD (Days 11–20)**	**LCD (Days 21–30)**
Take 8–9 * scoops (one scoop = 10 g; 0.3 g of carbohydrates; 8.2 g of protein; 0.4 g of fats) of ketogenic powder per day each diluted in 100–200 mL of water and oral supplements as follows: • Breakfast—two scoops and two tablets of multimineral. • Lunch—two scoops and two tablets of multivitamins. • Dinner—two scoops and two tablets of omega 3 Snacks (mid-morning, mid-afternoon, after dinner)—one scoop. Drink each day at least 2 L of liquids (except sweetened drinks). Limit physical activity and excessive stress. Free consumption of vegetables at lunch and dinner (minimum 500 g day). Allowed—20 g of extra virgin olive oil per day. Daily energy intake 560–595 Kcal: ✓ Carbohydrates: 15 g, ✓ Proteins: 72–80 g, ✓ Lipids: 23–24 g.	Stop VLCKD treatment and oral supplements. Start a very low-calorie diet as follows: • Breakfast: Recommended food—200 g of semi- skimmed milk or low-fat yogurt or unsweetened orange juice, 20 g of rusks or 20 g of bread. Forbidden food—sweets or brioches. • Lunch—150 g of lean meat or 200 g of fish, free consumption of vegetables (minimum 250 g), 100 g of fruit. • Dinner—100 g of low-fat cheese, free consumption of vegetables (minimum 250 g), 100 g of fruit. Allowed—20 g of extra virgin olive oil per day. Daily energy intake 810 Kcal: ✓ Carbohydrates 55 g, ✓ Proteins 80 g, ✓ Lipids 30 g.	Increase the amount of carbohydrates as the following scheme: • Breakfast: Recommended food—200 g of semi- skimmed milk, or low-fat yogurt or unsweetened orange juice, 40 g of rusks or 50 g of bread. Forbidden sweets or brioches. • Lunch—80 g of pasta or bread, free consumption of vegetables (minimum 250 g), 100 g of fruit. • Dinner—150 g of lean meat or 200 g of fish or 100 g of low-fat cheese, free consumption of vegetables (minimum 250 g), 100 g of fruit. Allowed—20 g of extra virgin olive oil per day. Daily energy intake 1100 Kcal: ✓ Carbohydrates 145 g, ✓ Proteins 60 g, ✓ Lipids 33 g.

* Eight for females, nine for males. OPOD, obese preoperative diet; VLCKD, very low-calorie ketogenic diet; VLCD, very low-calorie diet; LCD, low-calorie diet.

While in the study by Albanese et al., VLCKD was developed using regular food, Pilone et al. proposed a sequential diet regimen consisting of a VLCKD for 10 days (referred to as the V-diet), followed by a hypocaloric scheme for the next 20 days (referred to as V-hypo), with a gradual increase in caloric intake [115]. Pilone et al. proposed a dedicated KetoStationkit for use during the first 10 days of the regimen, along with a hypocaloric scheme for the next 20 days. The KetoStationkit included a protein powder (82 g of protein from whey and caseinate for every 100 g of product) and nutritional supplements (multiminerals, multivitamins, and omega 3 fatty acids). During the V-diet, patients were advised to consume eight scoops of ketogenic powder per day for females and nine scoops per day for males, with each scoop diluted in 100–200 mL of water (one scoop containing 10 g, including 0.3 g of carbohydrate, 8.2 g of protein, and 0.4 g of fat). Patients could add vegetables to their regimen during lunch and dinner and were encouraged to consume at

least 2 L of fluids per day. Ketone body levels were measured in the plasma and urine, and routine laboratory tests and anthropometric measurements were conducted at enrolment (T0), after 10 days (T1), and after 30 days (T2). The results of the study showed a significant decrease in body weight, BMI, and waist circumference at T0 and T1, T0 and T2, and T1 and T2 ($p < 0.05$). Additionally, a bioelectrical impedance assay showed a significant reduction in visceral fat at T1 and T2. The study also observed a significant improvement in several clinical parameters, including glycaemic and lipid profile parameters, associated with a mean 30% reduction in liver volume. The study concluded that a VLCKD performed using a dedicated KetoStationkit was safe and effective in reducing weight and liver volume in patients with obesity who were candidates for BS [115].

Table 2. Very low-calorie ketogenic diet scheme used by Albanese et al. [36].

Meal	
Breakfast	Two measuring cups of protein powder in water or yogurt with a fat content of 0.1% (either plain or fruit-flavoured). Coffee is also acceptable.
Lunch*	A total of 180 g of animal proteins (such as beef, calf, rabbit meat, chicken, or turkey breast) or 200 g of fish proteins (such as anchovies, sardines, tuna, mackerel, lobster, shrimps, pike, cod, rhombus, sole, sea bass, grouper, snapper, sea bream, cuttlefish, squid, octopus, salmon, or swordfish) or 200 g of plant-based proteins (such as tofu, seitan, or tempeh), along with 200 g of vegetables (such as chard, chicory, zucchini, cauliflower, fennel, eggplant, broccoli, lettuce, radish, artichoke, or spinach).
Dinner *	Four measuring cups of protein powder in water or yogurt with a fat content of 0.1% (either plain or fruit-flavoured), along with 200 g of vegetables (such as chard, chicory, zucchini, cauliflower, fennel, eggplant, broccoli, lettuce, radish, artichoke, or spinach).

* the consumption of two small scoops of olive oil per day is allowed, but vinegar is not permitted.

Furthermore, Schiavo et al. investigated the clinical impact of a micronutrient-enriched ketogenic diet on patients with obesity who were candidates for BS [50]. The study involved a 4-week preoperative period during which the patients adhered to a ketogenic food plan, providing approximately 1200 calories per day, consisting of 4% carbohydrates, 71% fats, and 25% proteins. The food plan was supplemented with a composition of nutrients (Ketocompleat, MVMedical Solutions, Serravalle, Repubblica San Marino) [50].

An example of the preoperative KD daily plan used by Schiavo et al. is reported in Table 3.

Table 3. An example of preoperative ketogenic diet daily plan used by Schiavo et al. [50].

Meal	
Breakfast	Egg (100 g), salt (0.13 g), pepper (0.033 g), olive oil (5 g)
Snack	Nuts (30 g)
Lunch	Lamb loin 145 g), olive oil (10 g), salt (1.5 g), pepper (0.13 g), asparagus (143 g)
Snack	Cheddar cheese (30 g)
Dinner	Ketocompleat (40 g), water (250 mL)
Total calories 1215.4 kcal:	
✓	Fat: 71% (96.1 g),
✓	Carbs: 4% (14.2 g),
✓	Protein: 25% (76 g).

All subjects obtained a significant reduction in body weight (males 10.3%, $p < 0.001$ and females 8.2%, $p < 0.001$) and in left hepatic lobe volume (−19.8%; 503 ± 61 cm^3 vs. 627 ± 85 cm^3, $p < 0.001$) [50]. Furthermore, Schiavo et al., with the aim to prospectively compare the effects on weight loss, fat mass, fat free mass, and resting metabolic rate in two groups of patients with obesity scheduled for BS and who were randomized to two different diets (LCKD diet vs. LCD) after intragastric balloon placement, showed that the LCKD group displayed a significantly lower decrease in fat free mass and resting metabolic rate when compared with the LCD group (3.55 vs. 14.3%, $p < 0.001$; 9.79 vs.

11.4%, $p < 0.001$, respectively) [116]. Moreover, fat mass decreased more significantly with LCKD compared to LCD (41.6 vs. 33.1%, $p = 0.0606$). The authors concluded that, based on their findings, they were able to support the hypothesis that LCKD is associated with an increased fat mass loss while reducing the fat free mass loss and the resting metabolic rate [116]. In addition, in another study, Schiavo et al. were able to show in a pilot, prospective, randomized multicentre comparative study that LCKD associated with continuous positive airway pressure was able to alleviate OSAS in patients with obesity scheduled for bariatric/metabolic surgery [117].

3.6.2. Assessment of Surgical Outcomes

Many bariatric surgeons suggest an aggressive weight reduction regimen to patients before undergoing BS, as preoperative weight loss may improve patient outcomes. Some surgeons may even withhold surgery if a certain threshold of preoperative weight loss is not achieved, although the scientific evidence supporting this practice is unclear. However, in an effort to improve patient outcomes after bariatric procedures, many now insist that patients meet preoperative weight loss goals before undergoing surgery. The Canadian Clinical Guidelines recommend a preoperative weight loss of 10% of body weight within 6 months through dietary modification [118], while some insurance companies in the United States require a 5–10% preoperative weight loss and the attendance of multiple nutritionist consultations before surgery approval [119]. The purported benefits of preoperative weight loss include selecting the most motivated patients, acclimating patients to restricted intake, reducing perioperative morbidity, and decreasing liver volume, leading to shorter operative times [120]. However, the National Institutes of Health consensus statement does not mandate preoperative weight loss but rather evaluates patients based on BMI, co-morbidities, and previous weight loss attempts, without considering successful preoperative weight loss [121].

Bariatric surgeons commonly believe that weight loss before BS leads to technically simpler procedures. However, the evidence for mandatory preoperative weight reduction is limited and conflicting. While reducing liver volume and intra-abdominal fat may make surgery easier and decrease co-morbidities, this hypothesis has not been definitively established. The systematic review of 17 trials, encompassing approximately 4611 patients, found preoperative weight loss to be beneficial, while 10 studies, encompassing 2075 patients, found no benefit [45]. Laparoscopic RYGB patients who underwent preoperative weight loss experienced a 12.5-min shorter operative time. In terms of postoperative weight loss, nine studies (39%) reported a positive correlation, while fifteen (62.5%) reported no benefit. Nine studies reporting perioperative complications (852 patients) revealed no difference in complication rates, while two studies (1234 patients) suggested a significant decrease associated with preoperative weight loss [45]. Therefore, a large-scale, multicentre, randomized, controlled trial with sufficient power is necessary to determine the effectiveness of preoperative weight loss.

Up to this point, it has been difficult to determine whether the results of weight loss before BS are solely due to weight loss or whether a specific KD provides additional benefits. Albanese et al. sought to answer this question by comparing weight loss and surgical outcomes in two groups of patients who followed different diets for three weeks before surgery: a VLCKD and a VLCD [36]. A total of 178 patients were enrolled in the study, with 72 following VLCKD and 106 following VLCD. While both groups were informed that weight loss before surgery was mandatory, the patients' preferences influenced the type of diet they followed. After three weeks, the VLCKD group had a better absolute weight loss than the VLCD group (5.8 ± 2.4 kg vs. 4.8 ± 2.5 kg, $p = 0.008$), but there was no significant difference in the percentage of excess BMI loss (respectively, $10.4 \pm 4.0\%$ and $10.0 \pm 5.6\%$, $p = 0.658$). All patients underwent laparoscopic SG. While the mean operative times and hospital stays were comparable in both groups, the VLCKD group had lower drainage output (141.2 ± 72.8 mL vs. 190.7 ± 183.6 mL, $p = 0.032$), higher post-operative haemoglobin levels (13.1 ± 1.2 mg/dL vs. 12.7 ± 1.5 mg/dL, $p = 0.04$), and a lower percentage of patients

requiring prolonged hospital stays (2.8% vs. 10.4%, $p = 0.048$) compared to the VLCD group. The authors concluded that the advantages of VLCKD were not strictly related to surgical manoeuvres, as the operative time was comparable between the two groups but rather to a better metabolic and nutritional status that positively influenced tissue healing [36].

Table 4 summarises the main findings of studies on KDs before BS.

Table 4. Main findings of studies on ketogenic diet before bariatric surgery.

Reference	Population	Aim and Intervention	Findings
Leonetti et al. [108]	19 M; 31 F	Assessment of the effectiveness of a sequential diet regimen termed the OPOD in morbidly obese patients with and without type 2 diabetes mellitus scheduled for bariatric surgery. OPOD regimen: VLCKD for 10 days; VLCD for 10 days; LCD for 10 days.	Reduction in body weight, body mass index, waist circumference, and neck circumference; amelioration in fasting plasma glucose levels; reduction in liver volume; and improvement of liver steatosis.
Albanese et al. [30]	39 M; 139 F	Compared surgical outcome and weight loss in two groups of patients who were offered two different pre-operative diets: VLCD and VLCKD: 72 patients followed a pre-operative VLCKD and 106 a VLCD.	Absolute weight loss was significantly better in the VLCKD than in the VLCD group, while no significant differences were observed in % of excess body mass index loss. VLCKD showed better results than VLCD on surgical outcome, influencing drainage output, post-operative haemoglobin levels, and hospital stay.
Pilone et al. [109]	44 M; 75 F	Evaluation of safety, efficacy, and acceptability of a VLCKD in patients before bariatric surgery using a sequential diet regimen: VLCKD for 10 days, followed by a hypocaloric scheme for 20 days, with the progressive recovery of calorie levels.	Weight, body mass index, waist circumference, and visceral fat decreased significantly. Furthermore, a significant improvement in several clinical parameters, including liver volume and glycaemic and lipid profile parameters were observed. The majority of patients declared themselves satisfied or very satisfied. The adverse effects were mild, of short duration, and not clinically relevant.
Schiavo et al. [110]	10 M; 17 F	To assess the safety and the effectiveness of a 4-week preoperative KMED in reducing body weight and left hepatic lobe volume in patients scheduled for bariatric surgery. Ketogenic food plan (from 1150 to 1250 kcal/day) consisted of 4% carbohydrates, 71% fats, and 25% proteins. Dinner was substituted by Ketocompleat (MVMedical Solutions, Serravalle, Repubblica San Marino). Ketocompleat is a supplement included on the register of food supplements of the Italian Minister of Health (code number 94721), and due to its carbohydrate-free formulation, may be associated to a low-carbohydrate ketogenic diet.	The study indicates that a 4-week preoperative KMED is safe and effective in reducing body weight and left hepatic lobe volume in patients with obesity scheduled for bariatric surgery.

Table 4. *Cont.*

Reference	Population	Aim and Intervention	Findings
Schiavo et al. [111]	22 M; 26 F	To prospectively compare the effects on weight loss, fat mass, fat-free mass, and resting metabolic rate in two groups of patients who were randomized to two different diets: LCKD and a standard LCD after intragastric balloon placement. The macronutrients composition of the LCD and LCKD was 40% carbohydrates, 43% proteins, and 15% fats (~1200 kcal/day) and 4% carbohydrates, 25% proteins, and 71% fats (~1200 kcal/day), respectively.	The LCKD group showed a significantly lower decrease in free fat mass and resting metabolic rate when compared with the LCD group. Fat mass decreased more significantly with LCKD compared to LCD, without negative impact on renal function.
Schiavo et al. [112]	44 M; 26 F	To assess the clinical advantage of pre-bariatric surgery CPAP alone or in combination with a LCKD on apnoea–hypopnoea index and CRP levels in patients with obesity and obstructive sleep apnoea syndrome. The ketogenic food plan (from 1150 to 1250 kcal/day) consisted of 4% carbohydrates, 71% fats, and 25% proteins. Dinner was substituted by Ketocompleat (MVMedical Solutions, Serravalle, Repubblica San Marino)	Apnoea–hypopnea index scores improved significantly in both groups. Combining CPAP and LCKD registered no advantage on the apnoea–hypopnoea index score. Furthermore, CPAP + LCKD had a greater impact on CRP levels than CPAP alone demonstrating a positive impact on chronic inflammatory status.

OPOD, obese preoperative diet; VLCKD, very low-calorie ketogenic diet; VLCD, very low-calorie diet; LCD, low-calorie diet; MKED, ketogenic micronutrient-enriched diet; LCKD, low-calorie ketogenic diet; CPAP, continuous positive airway pressure; CRP, C reactive protein.

4. Conclusions

Weight loss before BS is crucial for patients, as it leads to various benefits, such as a decrease in liver volume and visceral fat, a lower risk of intra- and post-operative complications, shorter surgery times, and reduced hospital stays. VLCKDs have proven to be a safe and effective way to achieve weight loss and may be considered as an option in the pre-operative period of BS. However, larger RCTs with well-defined dietary protocols are necessary to make definitive conclusions. Additionally, a longer follow-up period is needed to evaluate the long-term effects of preoperative weight loss.

Author Contributions: Conceptualization, L.B. and G.M.; methodology, L.B. and G.M.; writing—original draft preparation, L.V., L.S., G.S., E.C., A.I., M.C. and V.P.; writing—review and editing, L.B., L.V. and G.M.; visualization, A.C.; supervision, A.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analysed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Flegal, K.M.; Kit, B.K.; Orpana, H.; Graubard, B.I. Association of all-cause mortality with overweight and obesity using standard body mass index categories: A systematic review and meta-analysis. *JAMA* **2013**, *309*, 71–82. [CrossRef] [PubMed]
2. Muscogiuri, G.; Verde, L.; Sulu, C.; Katsiki, N.; Hassapidou, M.; Frias-Toral, E.; Cucalon, G.; Pazderska, A.; Yumuk, V.D.; Colao, A.; et al. Mediterranean Diet and Obesity-related Disorders: What is the Evidence? *Curr. Obes. Rep.* **2022**, *11*, 287–304. [CrossRef] [PubMed]
3. Sjostrom, L. Review of the key results from the Swedish Obese Subjects (SOS) trial—A prospective controlled intervention study of bariatric surgery. *J. Intern. Med.* **2013**, *273*, 219–234. [CrossRef]

4. Sjostrom, L.; Peltonen, M.; Jacobson, P.; Sjostrom, C.D.; Karason, K.; Wedel, H.; Ahlin, S.; Anveden, A.; Bengtsson, C.; Bergmark, G.; et al. Bariatric surgery and long-term cardiovascular events. *JAMA* **2012**, *307*, 56–65. [CrossRef] [PubMed]
5. Perrone, F.; Bianciardi, E.; Ippoliti, S.; Nardella, J.; Fabi, F.; Gentileschi, P. Long-term effects of laparoscopic sleeve gastrectomy versus Roux-en-Y gastric bypass for the treatment of morbid obesity: A monocentric prospective study with minimum follow-up of 5 years. *Updates Surg.* **2017**, *69*, 101–107. [CrossRef] [PubMed]
6. Sundbom, M. Laparoscopic revolution in bariatric surgery. *World J. Gastroenterol.* **2014**, *20*, 15135–15143. [CrossRef]
7. Riess, K.P.; Baker, M.T.; Lambert, P.J.; Mathiason, M.A.; Kothari, S.N. Effect of preoperative weight loss on laparoscopic gastric bypass outcomes. *Surg. Obes. Relat. Dis.* **2008**, *4*, 704–708. [CrossRef] [PubMed]
8. Picot, J.; Jones, J.; Colquitt, J.L.; Gospodarevskaya, E.; Loveman, E.; Baxter, L.; Clegg, A.J. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: A systematic review and economic evaluation. *Health Technol. Assess* **2009**, *13*, 1–190. [CrossRef] [PubMed]
9. Schwartz, M.L.; Drew, R.L.; Chazin-Caldie, M. Laparoscopic Roux-en-Y gastric bypass: Preoperative determinants of prolonged operative times, conversion to open gastric bypasses, and postoperative complications. *Obes. Surg.* **2003**, *13*, 734–738. [CrossRef] [PubMed]
10. Gonzalez, H.; Minville, V.; Delanoue, K.; Mazerolles, M.; Concina, D.; Fourcade, O. The importance of increased neck circumference to intubation difficulties in obese patients. *Anesth. Analg.* **2008**, *106*, 1132–1136. [CrossRef] [PubMed]
11. Gerber, P.; Anderin, C.; Thorell, A. Weight loss prior to bariatric surgery: An updated review of the literature. *Scand. J. Surg.* **2015**, *104*, 33–39. [CrossRef]
12. Livhits, M.; Mercado, C.; Yermilov, I.; Parikh, J.A.; Dutson, E.; Mehran, A.; Ko, C.Y.; Gibbons, M.M. Does weight loss immediately before bariatric surgery improve outcomes: A systematic review. *Surg. Obes. Relat. Dis.* **2009**, *5*, 713–721. [CrossRef]
13. Schiavo, L.; Sans, A.; Scalera, G.; Barbarisi, A.; Iannelli, A. Why Preoperative Weight Loss in Preparation for Bariatric Surgery Is Important. *Obes. Surg.* **2016**, *26*, 2790–2792. [CrossRef] [PubMed]
14. Bettini, S.; Belligoli, A.; Fabris, R.; Busetto, L. Diet approach before and after bariatric surgery. *Rev. Endocr. Metab. Disord.* **2020**, *21*, 297–306. [CrossRef]
15. Fried, M.; Yumuk, V.; Oppert, J.M.; Scopinaro, N.; Torres, A.J.; Weiner, R.; Yashkov, Y.; Fruhbeck, G. International Federation for the Surgery of Obesity—European, C. Interdisciplinary European Guidelines on metabolic and bariatric surgery. *Obes. Facts* **2013**, *6*, 449–468. [CrossRef]
16. Mechanick, J.I.; Apovian, C.; Brethauer, S.; Garvey, W.T.; Joffe, A.M.; Kim, J.; Kushner, R.F.; Lindquist, R.; Pessah-Pollack, R.; Seger, J.; et al. Clinical Practice Guidelines for the Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures—2019 Update: Cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, the Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists—Executive Summary. *Endocr. Pract.* **2019**, *25*, 1346–1359. [CrossRef] [PubMed]
17. Tang, T.; Abbott, S.; le Roux, C.W.; Wilson, V.; Singhal, R.; Bellary, S.; Tahrani, A.A. Preoperative weight loss with glucagon-like peptide-1 receptor agonist treatment predicts greater weight loss achieved by the combination of medical weight management and bariatric surgery in patients with type 2 diabetes: A longitudinal analysis. *Diabetes Obes. Metab.* **2018**, *20*, 745–748. [CrossRef] [PubMed]
18. Adrianzen Vargas, M.; Cassinello Fernandez, N.; Ortega Serrano, J. Preoperative weight loss in patients with indication of bariatric surgery: Which is the best method? *Nutr. Hosp.* **2011**, *26*, 1227–1230. [CrossRef]
19. Busetto, L.; Segato, G.; De Luca, M.; Bortolozzi, E.; MacCari, T.; Magon, A.; Inelmen, E.M.; Favretti, F.; Enzi, G. Preoperative weight loss by intragastric balloon in super-obese patients treated with laparoscopic gastric banding: A case-control study. *Obes. Surg.* **2004**, *14*, 671–676. [CrossRef]
20. Baldry, E.L.; Leeder, P.C.; Idris, I.R. Pre-operative dietary restriction for patients undergoing bariatric surgery in the UK: Observational study of current practice and dietary effects. *Obes. Surg.* **2014**, *24*, 416–421. [CrossRef]
21. Holderbaum, M.S.; Buss, C. Dietary Management in the Immediate Preoperative Period of Bariatric Surgery: A National Overview: Bariatric Preoperative Diets. *Obes. Surg.* **2018**, *28*, 1688–1696. [CrossRef]
22. Erdem, N.Z.; Ozelgun, D.; Taskin, H.E.; Avsar, F.M. Comparison of a pre-bariatric surgery very low-calorie ketogenic diet and the Mediterranean diet effects on weight loss, metabolic parameters, and liver size reduction. *Sci. Rep.* **2022**, *12*, 20686. [CrossRef]
23. Gastaldo, I.; Casas, R.; Moize, V. Clinical Impact of Mediterranean Diet Adherence before and after Bariatric Surgery: A Narrative Review. *Nutrients* **2022**, *14*, 393. [CrossRef]
24. Schiavo, L.; Scalera, G.; Sergio, R.; De Sena, G.; Pilone, V.; Barbarisi, A. Clinical impact of Mediterranean-enriched-protein diet on liver size, visceral fat, fat mass, and fat-free mass in patients undergoing sleeve gastrectomy. *Surg. Obes. Relat. Dis.* **2015**, *11*, 1164–1170. [CrossRef]
25. Hollis, G.; Franz, R.; Bauer, J.; Bell, J. Implementation of a very low calorie diet program into the pre-operative model of care for obese general elective surgery patients: Outcomes of a feasibility randomised control trial. *Nutr. Diet.* **2020**, *77*, 490–498. [CrossRef]
26. Benjaminov, O.; Beglaibter, N.; Gindy, L.; Spivak, H.; Singer, P.; Wienberg, M.; Stark, A.; Rubin, M. The effect of a low-carbohydrate diet on the nonalcoholic fatty liver in morbidly obese patients before bariatric surgery. *Surg. Endosc.* **2007**, *21*, 1423–1427. [CrossRef] [PubMed]

27. Browning, J.D.; Baker, J.A.; Rogers, T.; Davis, J.; Satapati, S.; Burgess, S.C. Short-term weight loss and hepatic triglyceride reduction: Evidence of a metabolic advantage with dietary carbohydrate restriction. *Am. J. Clin. Nutr.* **2011**, *93*, 1048–1052. [CrossRef]
28. Trimboli, P.; Castellana, M.; Bellido, D.; Casanueva, F.F. Confusion in the nomenclature of ketogenic diets blurs evidence. *Rev. Endocr. Metab. Disord.* **2020**, *21*, 1–3. [CrossRef]
29. Muscogiuri, G.; Barrea, L.; Laudisio, D.; Pugliese, G.; Salzano, C.; Savastano, S.; Colao, A. The management of very low-calorie ketogenic diet in obesity outpatient clinic: A practical guide. *J. Transl. Med.* **2019**, *17*, 356. [CrossRef]
30. Muscogiuri, G.; El Ghoch, M.; Colao, A.; Hassapidou, M.; Yumuk, V.; Busetto, L.; Obesity Management Task Force (OMTF) of the European Association for the Study of Obesity (EASO). European Guidelines for Obesity Management in Adults with a Very Low-Calorie Ketogenic Diet: A Systematic Review and Meta-Analysis. *Obes. Facts* **2021**, *14*, 222–245. [CrossRef]
31. Freeman, J.M.; Kossoff, E.H.; Hartman, A.L. The ketogenic diet: One decade later. *Pediatrics* **2007**, *119*, 535–543. [CrossRef] [PubMed]
32. Barrea, L.; Caprio, M.; Watanabe, M.; Cammarata, G.; Feraco, A.; Muscogiuri, G.; Verde, L.; Colao, A.; Savastano, S. Could very low-calorie ketogenic diets turn off low grade inflammation in obesity? Emerging evidence. *Crit. Rev. Food Sci. Nutr.* **2022**, 1–17. [CrossRef]
33. Barrea, L.; de Alteriis, G.; Muscogiuri, G.; Vetrani, C.; Verde, L.; Camajani, E.; Aprano, S.; Colao, A.; Savastano, S. Impact of a Very Low-Calorie Ketogenic Diet (VLCKD) on Changes in Handgrip Strength in Women with Obesity. *Nutrients* **2022**, *14*, 4213. [CrossRef]
34. Barrea, L.; Megna, M.; Cacciapuoti, S.; Frias-Toral, E.; Fabbrocini, G.; Savastano, S.; Colao, A.; Muscogiuri, G. Very low-calorie ketogenic diet (VLCKD) in patients with psoriasis and obesity: An update for dermatologists and nutritionists. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 398–414. [CrossRef]
35. Moriconi, E.; Camajani, E.; Fabbri, A.; Lenzi, A.; Caprio, M. Very-Low-Calorie Ketogenic Diet as a Safe and Valuable Tool for Long-Term Glycemic Management in Patients with Obesity and Type 2 Diabetes. *Nutrients* **2021**, *13*, 758. [CrossRef] [PubMed]
36. Albanese, A.; Prevedello, L.; Markovich, M.; Busetto, L.; Vettor, R.; Foletto, M. Pre-operative Very Low Calorie Ketogenic Diet (VLCKD) vs. Very Low Calorie Diet (VLCD): Surgical Impact. *Obes. Surg.* **2019**, *29*, 292–296. [CrossRef] [PubMed]
37. Cappello, G.; Franceschelli, A.; Cappello, A.; De Luca, P. Ketogenic enteral nutrition as a treatment for obesity: Short term and long term results from 19,000 patients. *Nutr. Metab.* **2012**, *9*, 96. [CrossRef]
38. Manninen, A.H. Metabolic effects of the very-low-carbohydrate diets: Misunderstood "villains" of human metabolism. *J. Int. Soc. Sports Nutr.* **2004**, *1*, 7–11. [CrossRef]
39. Moreno, O.; Meoro, A.; Martinez, A.; Rodriguez, C.; Pardo, C.; Aznar, S.; Lopez, P.; Serrano, J.; Boix, E.; Martin, M.D.; et al. Comparison of two low-calorie diets: A prospective study of effectiveness and safety. *J. Endocrinol. Invest.* **2006**, *29*, 633–640. [CrossRef]
40. Caprio, M.; Infante, M.; Moriconi, E.; Armani, A.; Fabbri, A.; Mantovani, G.; Mariani, S.; Lubrano, C.; Poggiogalle, E.; Migliaccio, S.; et al. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: Systematic review and consensus statement from the Italian Society of Endocrinology (SIE). *J. Endocrinol. Invest.* **2019**, *42*, 1365–1386. [CrossRef]
41. Goday, A.; Bellido, D.; Sajoux, I.; Crujeiras, A.B.; Burguera, B.; Garcia-Luna, P.P.; Oleaga, A.; Moreno, B.; Casanueva, F.F. Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. *Nutr. Diabetes* **2016**, *6*, e230. [CrossRef]
42. Romano, L.; Marchetti, M.; Gualtieri, P.; Di Renzo, L.; Belcastro, M.; De Santis, G.L.; Perrone, M.A.; De Lorenzo, A. Effects of a Personalized VLCKD on Body Composition and Resting Energy Expenditure in the Reversal of Diabetes to Prevent Complications. *Nutrients* **2019**, *11*, 1526. [CrossRef] [PubMed]
43. SICOB. Linee Guida di Chirurgia Dell'Obesità. Available online: https://www.sicob.org/00_materiali/linee_guida_2016.pdf (accessed on 3 April 2023).
44. Fris, R.J. Preoperative low energy diet diminishes liver size. *Obes. Surg.* **2004**, *14*, 1165–1170. [CrossRef]
45. Cassie, S.; Menezes, C.; Birch, D.W.; Shi, X.; Karmali, S. Effect of preoperative weight loss in bariatric surgical patients: A systematic review. *Surg. Obes. Relat. Dis.* **2011**, *7*, 760–767; discussion 767. [CrossRef]
46. Stephens, D.J.; Saunders, J.K.; Belsley, S.; Trivedi, A.; Ewing, D.R.; Iannace, V.; Capella, R.F.; Wasielewski, A.; Moran, S.; Schmidt, H.J.; et al. Short-term outcomes for super-super obese (BMI > or =60 kg/m^2) patients undergoing weight loss surgery at a high-volume bariatric surgery center: Laparoscopic adjustable gastric banding, laparoscopic gastric bypass, and open tubular gastric bypass. *Surg. Obes. Relat. Dis.* **2008**, *4*, 408–415. [CrossRef] [PubMed]
47. Colles, S.L.; Dixon, J.B.; Marks, P.; Strauss, B.J.; O'Brien, P.E. Preoperative weight loss with a very-low-energy diet: Quantitation of changes in liver and abdominal fat by serial imaging. *Am. J. Clin. Nutr.* **2006**, *84*, 304–311. [CrossRef] [PubMed]
48. Leonetti, F.; Campanile, F.C.; Coccia, F.; Capoccia, D.; Alessandroni, L.; Puzziello, A.; Coluzzi, I.; Silecchia, G. Very low-carbohydrate ketogenic diet before bariatric surgery: Prospective evaluation of a sequential diet. *Obes. Surg.* **2015**, *25*, 64–71. [CrossRef] [PubMed]
49. Hession, M.; Rolland, C.; Kulkarni, U.; Wise, A.; Broom, J. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obes. Rev.* **2009**, *10*, 36–50. [CrossRef]

50. Schiavo, L.; Pilone, V.; Rossetti, G.; Barbarisi, A.; Cesaretti, M.; Iannelli, A. A 4-Week Preoperative Ketogenic Micronutrient-Enriched Diet Is Effective in Reducing Body Weight, Left Hepatic Lobe Volume, and Micronutrient Deficiencies in Patients Undergoing Bariatric Surgery: A Prospective Pilot Study. *Obes. Surg.* **2018**, *28*, 2215–2224. [CrossRef]
51. Paoli, A.; Bosco, G.; Camporesi, E.M.; Mangar, D. Ketosis, ketogenic diet and food intake control: A complex relationship. *Front. Psychol.* **2015**, *6*, 27. [CrossRef]
52. Koutnik, A.P.; D'Agostino, D.P.; Egan, B. Anticatabolic Effects of Ketone Bodies in Skeletal Muscle. *Trends Endocrinol. Metab.* **2019**, *30*, 227–229. [CrossRef]
53. Marinari, G.; Foletto, M.; Nagliati, C.; Navarra, G.; Borrelli, V.; Bruni, V.; Fantola, G.; Moroni, R.; Tritapepe, L.; Monzani, R.; et al. Enhanced recovery after bariatric surgery: An Italian consensus statement. *Surg. Endosc.* **2022**, *36*, 7171–7186. [CrossRef] [83PubMed]
54. Di Lorenzo, N.; Antoniou, S.A.; Batterham, R.L.; Busetto, L.; Godoroja, D.; Iossa, A.; Carrano, F.M.; Agresta, F.; Alarcon, I.; Azran, C.; et al. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: Update 2020 endorsed by IFSO-EC, EASO and ESPCOP. *Surg. Endosc.* **2020**, *34*, 2332–2358. [CrossRef]
55. Anderin, C.; Gustafsson, U.O.; Heijbel, N.; Thorell, A. Weight loss before bariatric surgery and postoperative complications: Data from the Scandinavian Obesity Registry (SOReg). *Ann. Surg.* **2015**, *261*, 909–913. [CrossRef]
56. Carron, M.; Safaee Fakhr, B.; Iepparіello, G.; Foletto, M. Perioperative care of the obese patient. *Br. J. Surg.* **2020**, *107*, e39–e55. [CrossRef]
57. Basciani, S.; Camajani, E.; Contini, S.; Persichetti, A.; Risi, R.; Bertoldi, L.; Strigari, L.; Prossomariti, G.; Watanabe, M.; Mariani, S.; et al. Very-Low-Calorie Ketogenic Diets With Whey, Vegetable, or Animal Protein in Patients With Obesity: A Randomized Pilot Study. *J. Clin. Endocrinol. Metab.* **2020**, *105*, 2939–2949. [CrossRef]
58. Barrea, L.; Verde, L.; Vetrani, C.; Marino, F.; Aprano, S.; Savastano, S.; Colao, A.; Muscogiuri, G. VLCKD: A real time safety study in obesity. *J. Transl. Med.* **2022**, *20*, 23. [CrossRef] [PubMed]
59. Hess, D.S.; Hess, D.W. Biliopancreatic diversion with a duodenal switch. *Obes. Surg.* **1998**, *8*, 267–282. [CrossRef]
60. Regan, J.P.; Inabnet, W.B.; Gagner, M.; Pomp, A. Early experience with two-stage laparoscopic Roux-en-Y gastric bypass as an alternative in the super-super obese patient. *Obes. Surg.* **2003**, *13*, 861–864. [CrossRef] [PubMed]
61. Ali, M.; El Chaar, M.; Ghiassi, S.; Rogers, A.M.; American Society for Metabolic and Bariatric Surgery Clinical Issues Committee. American Society for Metabolic and Bariatric Surgery updated position statement on sleeve gastrectomy as a bariatric procedure. *Surg. Obes. Relat. Dis.* **2017**, *13*, 1652–1657. [CrossRef]
62. Benaiges, D.; Mas-Lorenzo, A.; Goday, A.; Ramon, J.M.; Chillaron, J.J.; Pedro-Botet, J.; Flores-Le Roux, J.A. Laparoscopic sleeve gastrectomy: More than a restrictive bariatric surgery procedure? *World J. Gastroenterol.* **2015**, *21*, 11804–11814. [CrossRef] [PubMed]
63. Diamantis, T.; Apostolou, K.G.; Alexandrou, A.; Griniatsos, J.; Felekouras, E.; Tsigris, C. Review of long-term weight loss results after laparoscopic sleeve gastrectomy. *Surg. Obes. Relat. Dis.* **2014**, *10*, 177–183. [CrossRef] [PubMed]
64. Madadi, F.; Jawad, R.; Mousati, I.; Plaeke, P.; Hubens, G. Remission of Type 2 Diabetes and Sleeve Gastrectomy in Morbid Obesity: A Comparative Systematic Review and Meta-analysis. *Obes. Surg.* **2019**, *29*, 4066–4076. [CrossRef]
65. Han, Y.; Jia, Y.; Wang, H.; Cao, L.; Zhao, Y. Comparative analysis of weight loss and resolution of comorbidities between laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass: A systematic review and meta-analysis based on 18 studies. *Int. J. Surg.* **2020**, *76*, 101–110. [CrossRef]
66. Gu, L.; Huang, X.; Li, S.; Mao, D.; Shen, Z.; Khadaroo, P.A.; Ng, D.M.; Chen, P. A meta-analysis of the medium- and long-term effects of laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass. *BMC Surg.* **2020**, *20*, 30. [CrossRef] [PubMed]
67. Lee, Y.; Doumouras, A.G.; Yu, J.; Aditya, I.; Gmora, S.; Anvari, M.; Hong, D. Laparoscopic Sleeve Gastrectomy Versus Laparoscopic Roux-en-Y Gastric Bypass: A Systematic Review and Meta-analysis of Weight Loss, Comorbidities, and Biochemical Outcomes From Randomized Controlled Trials. *Ann. Surg.* **2021**, *273*, 66–74. [CrossRef] [PubMed]
68. Yeung, K.T.D.; Penney, N.; Ashrafian, L.; Darzi, A.; Ashrafian, H. Does Sleeve Gastrectomy Expose the Distal Esophagus to Severe Reflux?: A Systematic Review and Meta-analysis. *Ann. Surg.* **2020**, *271*, 257–265. [CrossRef]
69. Clapp, B.; Wynn, M.; Martyn, C.; Foster, C.; O'Dell, M.; Tyroch, A. Long term (7 or more years) outcomes of the sleeve gastrectomy: A meta-analysis. *Surg. Obes. Relat. Dis.* **2018**, *14*, 741–747. [CrossRef]
70. Angrisani, L.; Santonicola, A.; Iovino, P.; Vitiello, A.; Zundel, N.; Buchwald, H.; Scopinaro, N. Bariatric Surgery and Endoluminal Procedures: IFSO Worldwide Survey 2014. *Obes. Surg.* **2017**, *27*, 2279–2289. [CrossRef]
71. Magema, J.; Himpens, J. "What Really Matters When Performing a Laparoscopic Roux-en Y Gastric Bypass?" Literature-Based Key Steps Towards Success and Standardization of the Procedure. *Obes. Surg.* **2021**, *31*, 5441–5445. [CrossRef]
72. Mahawar, K.K.; Sharples, A.J. Contribution of Malabsorption to Weight Loss After Roux-en-Y Gastric Bypass: A Systematic Review. *Obes. Surg.* **2017**, *27*, 2194–2206. [CrossRef] [PubMed]
73. Golzarand, M.; Toolabi, K.; Farid, R. The bariatric surgery and weight losing: A meta-analysis in the long- and very long-term effects of laparoscopic adjustable gastric banding, laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy on weight loss in adults. *Surg. Endosc.* **2017**, *31*, 4331–4345. [CrossRef]
74. O'Brien, P.E.; Hindle, A.; Brennan, L.; Skinner, S.; Burton, P.; Smith, A.; Crosthwaite, G.; Brown, W. Long-Term Outcomes After Bariatric Surgery: A Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. *Obes. Surg.* **2019**, *29*, 3–14. [CrossRef] [PubMed]

75. Yan, Y.; Sha, Y.; Yao, G.; Wang, S.; Kong, F.; Liu, H.; Zhang, G.; Zhang, H.; Hu, C.; Zhang, X. Roux-en-Y Gastric Bypass Versus Medical Treatment for Type 2 Diabetes Mellitus in Obese Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicine* **2016**, *95*, e3462. [CrossRef]
76. Yu, Z.; Li, P.; Li, P.; Zhang, H.; Zhang, Y. Meta-analysis of Long-Term Relapse Rate of Type 2 Diabetes Following Initial Remission After Roux-en-Y Gastric Bypass. *Obes. Surg.* **2021**, *31*, 5034–5043. [CrossRef] [PubMed]
77. Lupoli, R.; Lembo, E.; Saldalamacchia, G.; Avola, C.K.; Angrisani, L.; Capaldo, B. Bariatric surgery and long-term nutritional issues. *World J. Diabetes* **2017**, *8*, 464–474. [CrossRef]
78. Christou, N.V.; Look, D.; Maclean, L.D. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. *Ann. Surg.* **2006**, *244*, 734–740. [CrossRef]
79. Carbajo, M.; Garcia-Caballero, M.; Toledano, M.; Osorio, D.; Garcia-Lanza, C.; Carmona, J.A. One-anastomosis gastric bypass by laparoscopy: Results of the first 209 patients. *Obes. Surg.* **2005**, *15*, 398–404. [CrossRef]
80. De Luca, M.; Piatto, G.; Merola, G.; Himpens, J.; Chevallier, J.M.; Carbajo, M.A.; Mahawar, K.; Sartori, A.; Clemente, N.; Herrera, M.; et al. IFSO Update Position Statement on One Anastomosis Gastric Bypass (OAGB). *Obes. Surg.* **2021**, *31*, 3251–3278. [CrossRef]
81. Parikh, M.; Eisenberg, D.; Johnson, J.; El-Chaar, M.; American Society for Metabolic and Bariatric Surgery Clinical Issues Committee. American Society for Metabolic and Bariatric Surgery review of the literature on one-anastomosis gastric bypass. *Surg. Obes. Relat. Dis.* **2018**, *14*, 1088–1092. [CrossRef] [PubMed]
82. Keleidari, B.; Dehkordi, M.M.; Shahraki, M.S.; Ahmadi, Z.S.; Heidari, M.; Hajian, A.; Nasaj, H.T. Bile reflux after one anastomosis gastric bypass surgery: A review study. *Ann. Med. Surg.* **2021**, *64*, 102248. [CrossRef] [PubMed]
83. Tourky, M.; Issa, M.; Salman, M.A.; Salman, A.; Shaaban, H.E.; Safina, A.; Elias, A.A.; Elewa, A.; Noureldin, K.; Mahmoud, A.A.; et al. Nutritional Complications After Laparoscopic Roux-en-Y Gastric Bypass and One-Anastomosis Gastric Bypass: A Comparative Systematic Review and Meta-Analysis. *Cureus* **2022**, *14*, e21114. [CrossRef] [PubMed]
84. Sanchez-Pernaute, A.; Rubio Herrera, M.A.; Perez-Aguirre, E.; Garcia Perez, J.C.; Cabrerizo, L.; Diez Valladares, L.; Fernandez, C.; Talavera, P.; Torres, A. Proximal duodenal-ileal end-to-side bypass with sleeve gastrectomy: Proposed technique. *Obes. Surg.* **2007**, *17*, 1614–1618. [CrossRef]
85. Verhoeff, K.; Mocanu, V.; Zalasky, A.; Dang, J.; Kung, J.Y.; Switzer, N.J.; Birch, D.W.; Karmali, S. Evaluation of Metabolic Outcomes Following SADI-S: A Systematic Review and Meta-analysis. *Obes. Surg.* **2022**, *32*, 1049–1063. [CrossRef]
86. Sanchez-Pernaute, A.; Herrera, M.A.R.; Ferre, N.P.; Rodriguez, C.S.; Marcuello, C.; Panella, C.; Antonanzas, L.L.; Torres, A.; Perez-Aguirre, E. Long-Term Results of Single-Anastomosis Duodeno-ileal Bypass with Sleeve Gastrectomy (SADI-S). *Obes. Surg.* **2022**, *32*, 682–689. [CrossRef]
87. Chierici, A.; Chevalier, N.; Iannelli, A. Postoperative morbidity and weight loss after revisional bariatric surgery for primary failed restrictive procedure: A systematic review and network meta-analysis. *Int. J. Surg.* **2022**, *102*, 106677. [CrossRef]
88. Wehrtmann, F.S.; de la Garza, J.R.; Kowalewski, K.F.; Schmidt, M.W.; Muller, K.; Tapking, C.; Probst, P.; Diener, M.K.; Fischer, L.; Muller-Stich, B.P.; et al. Learning Curves of Laparoscopic Roux-en-Y Gastric Bypass and Sleeve Gastrectomy in Bariatric Surgery: A Systematic Review and Introduction of a Standardization. *Obes. Surg.* **2020**, *30*, 640–656. [CrossRef]
89. Hasson, H.M. A modified instrument and method for laparoscopy. *Am. J. Obstet. Gynecol.* **1971**, *110*, 886–887. [CrossRef]
90. Kassir, R.; Blanc, P.; Lointier, P.; Tiffet, O.; Berger, J.L.; Amor, I.B.; Gugenheim, J. Laparoscopic entry techniques in obese patient: Veress needle, direct trocar insertion or open entry technique? *Obes. Surg.* **2014**, *24*, 2193–2194. [CrossRef]
91. Deffieux, X.; Ballester, M.; Collinet, P.; Fauconnier, A.; Pierre, F. Risks associated with laparoscopic entry: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2011**, *158*, 159–166. [CrossRef]
92. Shahabi, S.; Carbajo, M.; Nimeri, A.; Kermansaravi, M.; Jazi, A.H.D.; Pazouki, A.; Mahawar, K. Factors that make Bariatric Surgery Technically Challenging: A Survey of 370 Bariatric Surgeons. *World J. Surg.* **2021**, *45*, 2521–2528. [CrossRef] [PubMed]
93. Ertugrul, I.; Kayaalp, C.; Yagci, M.A.; Sumer, F.; Karagul, S.; Tolan, K. Comparison of Direct Trocar Entry and Veress Needle Entry in Laparoscopic Bariatric Surgery: Randomized Controlled Trial. *J. Laparoendosc. Adv. Surg. Tech. A* **2015**, *25*, 875–879. [CrossRef]
94. Ikechebelu, J.I.; Eleje, G.U.; Joe-Ikechebelu, N.N.; Okafor, C.D.; Okpala, B.C.; Ugwu, E.O.; Nwachukwu, C.E.; Okoro, C.C.; Okam, P.C. Randomized control trial on effectiveness and safety of direct trocar versus Veress needle entry techniques in obese women during diagnostic laparoscopy. *Arch. Gynecol. Obstet.* **2021**, *304*, 815–822. [CrossRef]
95. Brandt, H.G.; Jepsen, C.H.; Hendriksen, O.M.; Lindekaer, A.; Skjonnemand, M. The use of ultrasound to identify veins for peripheral venous access in morbidly obese patients. *Dan. Med. J.* **2016**, *63*, A5191.
96. Wang, T.; Sun, S.; Huang, S. The association of body mass index with difficult tracheal intubation management by direct laryngoscopy: A meta-analysis. *BMC Anesthesiol.* **2018**, *18*, 79. [CrossRef]
97. De Jong, A.; Molinari, N.; Pouzeratte, Y.; Verzilli, D.; Chanques, G.; Jung, B.; Futier, E.; Perrigault, P.F.; Colson, P.; Capdevila, X.; et al. Difficult intubation in obese patients: Incidence, risk factors, and complications in the operating theatre and in intensive care units. *Br. J. Anaesth.* **2015**, *114*, 297–306. [CrossRef] [PubMed]
98. Galinski, M.; Chouteau, M.; Lunghi, G.; Vinurel, M.; Blazy, B.; Cher, M.; Alouane, B.; Bento, H.; Germain, J.L.; Barrat, C.; et al. Multivariate Analysis of the Failure Risk of First Tracheal Intubation Attempt in a Population of Patients Scheduled for Bariatric Surgery. *Obes. Surg.* **2021**, *31*, 4392–4398. [CrossRef]

99. Hashim, M.M.; Ismail, M.A.; Esmat, A.M.; Adeel, S. Difficult tracheal intubation in bariatric surgery patients, a myth or reality? *Br. J. Anaesth.* **2016**, *116*, 557–558. [CrossRef]
100. Lekkala, S.; Taylor, E.A.; Hunt, H.B.; Donnelly, E. Effects of Diabetes on Bone Material Properties. *Curr. Osteoporos Rep.* **2019**, *17*, 455–464. [CrossRef]
101. de Raaff, C.A.L.; Gorter-Stam, M.A.W.; de Vries, N.; Sinha, A.C.; Jaap Bonjer, H.; Chung, F.; Coblijn, U.K.; Dahan, A.; van den Helder, R.S.; Hilgevoord, A.A.J.; et al. Perioperative management of obstructive sleep apnea in bariatric surgery: A consensus guideline. *Surg. Obes. Relat. Dis.* **2017**, *13*, 1095–1109. [CrossRef] [PubMed]
102. Raveendran, R.; Wong, J.; Singh, M.; Wong, D.T.; Chung, F. Obesity hypoventilation syndrome, sleep apnea, overlap syndrome: Perioperative management to prevent complications. *Curr. Opin. Anaesthesiol.* **2017**, *30*, 146–155. [CrossRef]
103. Bazurro, S.; Ball, L.; Pelosi, P. Perioperative management of obese patient. *Curr. Opin. Crit. Care* **2018**, *24*, 560–567. [CrossRef] [PubMed]
104. Kaw, R.; Wong, J.; Mokhlesi, B. Obesity and Obesity Hypoventilation, Sleep Hypoventilation, and Postoperative Respiratory Failure. *Anesth. Analg.* **2021**, *132*, 1265–1273. [CrossRef]
105. Singh, P.M.; Panwar, R.; Borle, A.; Goudra, B.; Trikha, A.; van Wagensveld, B.A.; Sinha, A. Efficiency and Safety Effects of Applying ERAS Protocols to Bariatric Surgery: A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Evidence. *Obes. Surg.* **2017**, *27*, 489–501. [CrossRef]
106. Smit, C.; De Hoogd, S.; Bruggemann, R.J.M.; Knibbe, C.A.J. Obesity and drug pharmacology: A review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. *Expert. Opin. Drug. Metab. Toxicol.* **2018**, *14*, 275–285. [CrossRef]
107. Eisenberg, D.; Shikora, S.A.; Aarts, E.; Aminian, A.; Angrisani, L.; Cohen, R.V.; De Luca, M.; Faria, S.L.; Goodpaster, K.P.S.; Haddad, A.; et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery. *Surg. Obes. Relat. Dis.* **2022**, *18*, 1345–1356. [CrossRef] [PubMed]
108. Drai, C.; Chierici, A.; Schiavo, L.; Mazahreh, T.S.; Schneck, A.S.; Iannelli, A. Long-Term Results at 10 Years of Pouch Resizing for Roux-en-Y Gastric Bypass Failure. *Nutrients* **2022**, *14*, 4035. [CrossRef]
109. Iannelli, A.; Schneck, A.S.; Hebuterne, X.; Gugenheim, J. Gastric pouch resizing for Roux-en-Y gastric bypass failure in patients with a dilated pouch. *Surg. Obes. Relat. Dis.* **2013**, *9*, 260–267. [CrossRef]
110. Sarno, G.; Calabrese, P.; Frias-Toral, E.; Ceriani, F.; Fuchs-Tarlovsky, V.; Spagnuolo, M.; Cucalon, G.; Cordova, L.A.; Schiavo, L.; Pilone, V. The relationship between preoperative weight loss and intra and post-bariatric surgery complications: An appraisal of the current preoperative nutritional strategies. *Crit. Rev. Food Sci. Nutr.* **2022**, 1–9. [CrossRef]
111. Schiavo, L.; Pilone, V.; Rossetti, G.; Iannelli, A. The Role of the Nutritionist in a Multidisciplinary Bariatric Surgery Team. *Obes. Surg.* **2019**, *29*, 1028–1030. [CrossRef]
112. Paoli, A.; Rubini, A.; Volek, J.S.; Grimaldi, K.A. Beyond weight loss: A review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur. J. Clin. Nutr.* **2013**, *67*, 789–796. [CrossRef]
113. Colangeli, L.; Gentileschi, P.; Sbraccia, P.; Guglielmi, V. Ketogenic Diet for Preoperative Weight Reduction in Bariatric Surgery: A Narrative Review. *Nutrients* **2022**, *14*, 3610. [CrossRef]
114. Carter, J.; Chang, J.; Birriel, T.J.; Moustarah, F.; Sogg, S.; Goodpaster, K.; Benson-Davies, S.; Chapmon, K.; Eisenberg, D. ASMBS position statement on preoperative patient optimization before metabolic and bariatric surgery. *Surg. Obes. Relat. Dis.* **2021**, *17*, 1956–1976. [CrossRef]
115. Pilone, V.; Tramontano, S.; Renzulli, M.; Romano, M.; Cobellis, L.; Berselli, T.; Schiavo, L. Metabolic effects, safety, and acceptability of very low-calorie ketogenic dietetic scheme on candidates for bariatric surgery. *Surg. Obes. Relat. Dis.* **2018**, *14*, 1013–1019. [CrossRef] [PubMed]
116. Schiavo, L.; De Stefano, G.; Persico, F.; Gargiulo, S.; Di Spirito, F.; Griguolo, G.; Petrucciani, N.; Fontas, E.; Iannelli, A.; Pilone, V. A Randomized, Controlled Trial Comparing the Impact of a Low-Calorie Ketogenic vs a Standard Low-Calorie Diet on Fat-Free Mass in Patients Receiving an Elipse Intragastric Balloon Treatment. *Obes. Surg.* **2021**, *31*, 1514–1523. [CrossRef] [PubMed]
117. Schiavo, L.; Pierro, R.; Asteria, C.; Calabrese, P.; Di Biasio, A.; Coluzzi, I.; Severino, L.; Giovanelli, A.; Pilone, V.; Silecchia, G. Low-Calorie Ketogenic Diet with Continuous Positive Airway Pressure to Alleviate Severe Obstructive Sleep Apnea Syndrome in Patients with Obesity Scheduled for Bariatric/Metabolic Surgery: A Pilot, Prospective, Randomized Multicenter Comparative Study. *Obes. Surg.* **2022**, *32*, 634–642. [CrossRef] [PubMed]
118. Lau, D.C.; Douketis, J.D.; Morrison, K.M.; Hramiak, I.M.; Sharma, A.M.; Ur, E.; Obesity Canada Clinical Practice Guidelines Expert, P. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *CMAJ* **2007**, *176*, S1–S13. [CrossRef]
119. Sadhasivam, S.; Larson, C.J.; Lambert, P.J.; Mathiason, M.A.; Kothari, S.N. Refusals, denials, and patient choice: Reasons prospective patients do not undergo bariatric surgery. *Surg. Obes. Relat. Dis.* **2007**, *3*, 531–535; discussion 535–536. [CrossRef]

120. van de Weijgert, E.J.; Ruseler, C.H.; Elte, J.W. Long-term follow-up after gastric surgery for morbid obesity: Preoperative weight loss improves the long-term control of morbid obesity after vertical banded gastroplasty. *Obes. Surg.* **1999**, *9*, 426–432. [CrossRef]
121. Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement. *Am. J. Clin. Nutr.* **1992**, *55*, 615S–619S. [CrossRef]

Review

The Evolution of Very-Low-Calorie Diets: An Update and Meta-analysis

Adam Gilden Tsai and Thomas A. Wadden

Abstract

TSAI, ADAM GILDEN AND THOMAS A. WADDEN. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity.* 2006;14:1283–1293.

Objective: Very-low-calorie diets (VLCDs), providing <800 kcal/d, have been used since the 1970s to induce rapid weight loss. Previous reviews of the literature have disagreed concerning the relative efficacy of VLCDs vs. conventional low-calorie diets (LCDs) for achieving long-term weight loss.

Research Methods and Procedures: We sought to update findings on the clinical use, safety, and efficacy of VLCDs and to perform a meta-analysis of randomized trials that compared the long-term efficacy of LCDs and VLCDs. Original research articles were retrieved by a Medline search and from prior reviews of VLCDs. Trials were included only if they were randomized comparisons of LCDs and VLCDs and included a follow-up assessment at least 1 year after maximum weight loss. Data were abstracted by both authors regarding: duration of VLCD, total length of treatment, attrition, short- and long-term weight loss, changes in weight-related comorbidities, and adverse effects.

Results: Six randomized trials were found that met inclusion criteria. VLCDs, compared with LCDs, induced significantly greater short-term weight losses (16.1 ± 1.6% vs. 9.7 ± 2.4% of initial weight, respectively; $p = 0.0001$) but similar long-term losses (6.3 ± 3.2% vs. 5.0 ± 4.0%, respectively; $p > 0.2$). Attrition was similar with VLCD and LCD regimens.

Discussion: VLCDs did not produce greater long-term weight losses than LCDs. In the United States, the use of liquid meal replacements as part of a 1000 to 1500 kcal/d diet may provide an effective and less expensive alternative to VLCDs. In Europe, VLCDs are used with less intensive medical supervision than in the United States, which reduces the cost of this approach.

Key words: diet, reducing; energy intake; weight loss; very-low-calorie diet; meta-analysis

Introduction

Very-low-calorie diets (VLCDs)[1] reached the height of their popularity in the United States in 1988 when Oprah Winfrey announced to her television audience that she had lost 67 pounds by consuming a liquid diet. Interest in this approach declined sharply in 1990 when Winfrey reported that she had regained her lost weight and would "never diet again." Despite these market ups and downs, >200,000 Americans used VLCDs in 2004 (personal communication, J. LaRosa, Marketdata Enterprises, July 20, 2005). Similarly, an estimated 67,800 months' supply of VLCD products was sold in the European Union in 2000 (1). In addition, three recent reviews concluded that VLCDs are associated with greater long-term weight losses than are conventional reducing diets (2–4).

This article updates a prior review of the use of VLCDs (5) and presents a meta-analysis of randomized trials that compared the long-term efficacy of VLCDs with low-calorie diets (LCDs) comprised of conventional foods. The review concludes by examining the use of meal replacement plans that have evolved from VLCDs over the past decade.

VLCDs: An Overview

An expert panel convened by the National Heart, Lung, and Blood Institute (NHLBI) defined VLCDs as diets providing fewer than 800 kcal/d (6), the same definition used

Received for review December 6, 2005.
Accepted in final form June 1, 2006.
The costs of publication of this article were defrayed, in part, by the payment of page charges. This article must, therefore, be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Department of Psychiatry, Center for Weight and Eating Disorders, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.
Address correspondence to Thomas A. Wadden, Department of Psychiatry, Center for Weight and Eating Disorders, University of Pennsylvania School of Medicine, 3535 Market Street, Suite 3029; Philadelphia, PA 19104.
E-mail: wadden@mail.med.upenn.edu

[1] Nonstandard abbreviations: VLCD, very-low-calorie diet; LCD, low-calorie diet; NHLBI, National Heart, Lung, and Blood Institute; REE, resting energy expenditure; SD, standard deviation; HbA_{1c}, hemoglobin A_{1c}.

by a recent European expert panel (1). The diets are designed to produce rapid weight loss while preserving lean body mass. This is accomplished by providing large amounts of dietary protein, typically 70 to 100 g/d or 0.8 to 1.5 g protein/kg ideal body weight (5,7). Protein may be obtained from a milk-, soy-, or egg-based powder, which is mixed with water and consumed as a liquid diet. Such diets may provide up to 80 g carbohydrate/d and 15 g fat/d, and they include 100% of the recommended daily allowance for essential vitamins and minerals. Alternatively, protein may be obtained from a protein-sparing modified fast, consisting of servings of lean meat, fish, and fowl (8,9). The modified fast must be supplemented with a multivitamin and 2 to 3 g/d potassium. Both diets require patients to drink 2 L/d non-caloric fluids (5). The two approaches produce comparable short-term weight losses (10). Thus, the choice of diet may be left to patient preference. Some investigators severely restrict carbohydrate to induce ketosis, which is thought to reduce hunger (8–10). However, comparable hunger ratings have been reported with ketotic and non-ketotic VLCDs (11).

We note that the definition of a VLCD is arbitrary. A 700 kcal/d diet, for example, would induce a relatively modest energy deficit in a short, sedentary woman with a resting energy expenditure (REE) of 1100 kcal/d. In contrast, a 1200 kcal/d diet would induce a substantial energy deficit in a tall man with an REE of 2500 kcal/d. The man would seem to have a greater risk of adverse metabolic effects (described later), even though technically he was prescribed an LCD and the woman a VLCD. Thus, an alternative definition of a VLCD is a diet that provides $<$50% of an individual's predicted REE (12).

Clinical Use of VLCDs

In the United States, VLCDs are generally used as part of a comprehensive intervention that includes medical monitoring and a program of lifestyle modification. Care is provided by a physician, often in conjunction with a dietitian, psychologist, and/or exercise physiologist (5,6,13). Treatment, including the cost of the VLCD, is typically $1800 to $2200 for the first 12 weeks, during the period of rapid weight loss (14). An additional 12 to 14 weeks of refeeding (in which conventional foods are reintroduced) and weight stabilization bring total costs for 6 months to $3000 to $3500 (5).

In European Union nations, VLCDs are frequently used with less medical supervision than provided in the United States (1,15,16). In most countries, diet products can be purchased over-the-counter or from a pharmacist without a prescription (except in France). As recommended by the SCOOP-VLCD report, prepared by an expert European panel, consumers may use a VLCD as a sole source of nutrition for 3 weeks before seeking medical supervision (1). (SCOOP refers to Scientific Co-Operation on Questions Relating to Food.) The report, however, also states that persons with obesity-related conditions should consult their physician before starting a VLCD. Thus, although physicians may be involved in identifying appropriate persons for treatment with a VLCD and for providing medical monitoring after the first 3 weeks, they do not have the same gatekeeping role as their U.S. counterparts. Rossner and Torgerson (17) have reviewed the Swedish experience with VLCDs and concluded that such programs can be provided largely by dietitians and nurses, lessening the need for physician involvement. We note that some companies in the United States sell VLCDs directly to consumers (14), whom they tell to consult with their physician before dieting. However, medically unsupervised use of these diets falls outside the guidelines recommended by expert panels in the United States.

Safety

VLCDs are considered safe and effective when used by appropriately selected individuals under careful medical supervision (5). The diets are designed for patients with a BMI $\geq$ 30 kg/m^2, a group at increased risk of cardiovascular morbidity and mortality and that also may derive the most benefit from substantial weight loss. In the United States, all candidates for a VLCD are expected to undergo a history and physical examination to determine medical and behavioral contraindications to treatment, as described in previous reviews (5,7). As noted previously, a similar recommendation applies in Europe to individuals who have significant comorbidities (1).

Patients in medically supervised VLCD programs in the U.S. are monitored by a physician approximately every 2 weeks during the period of rapid weight loss (i.e., 1.5 to 2.5 kg/wk). During this time, they are at increased risk of gallstones, cold intolerance, hair loss, headache, fatigue, dizziness, volume depletion (with electrolyte abnormalities), muscle cramps, and constipation (5,15,16,18). These side effects are usually mild and easily managed.

Cholelithiasis has been studied in detail (19–25). In an early study, gallstones developed in 25% of patients during 8 weeks of VLCD, and 6% of patients eventually required cholecystectomy (19). In a second trial, asymptomatic gallstones occurred in ~12% of patients within 6 months of starting a VLCD, and approximately one-half of these individuals eventually became symptomatic, requiring cholecystectomy (20). The risk of cholelithiasis can be decreased by administration of ursodeoxycholic acid (21,22), including a moderate amount of fat in the diet (23,24), and limiting the rate of weight loss to 1.5 kg/wk (25).

In Europe, VLCDs apparently have not been associated with a higher than expected rate of cholelithiasis. This has been attributed to the inclusion of at least 7 grams of fat in meal replacement regimens sold in Europe, as reported by Festi et al. (23).

Unsupervised use of VLCDs can result in serious complications, including death (18,26). The great majority of fatalities related to VLCDs occurred in the 1970s when dieters consumed products that contained low-quality protein (i.e., hydrolyzed collagen) and were deficient in vitamins and minerals. Of 60 persons who died in the United States, most developed cardiac complications after a loss of ~30% of initial weight, achieved in an average of 4 months. No deaths were reported in persons who dieted for 8 weeks or fewer (for a full review of this issue, see 26–28).

The SCOOP-VLCD report (1) noted that there have been no documented deaths attributable to VLCDs since their inclusion in the early 1980s of high-quality proteins (i.e., milk, egg, or soy). Nonetheless, in the United States, there were six reports of death during this time in persons who consumed the Cambridge Diet (which provided 330 kcal/d at the time) (26). Observational data clearly can lead to different conclusions about the safety of a product because of differences in the way the product is used (e.g., duration of use) or in the populations that use it (e.g., lean vs. obese individuals). As used in European Union nations, for example, dexfenfluramine appeared to be safe, whereas in the United States, where dexfenfluramine and fenfluramine were used for longer periods than in Europe, these medications were found to be associated with valvular heart disease (29). Thus, although VLCDs seem to be safe when consumed for brief periods without medical supervision, long-term unsupervised use of a VLCD could be associated with significant health complications (as could any hypocaloric, reducing diet).

Efficacy of VLCDs for Weight Loss

Most evaluations of VLCDs have consisted of single-site case series conducted at academic medical centers or in individual physician practices. Most studies found that patients who completed a comprehensive VLCD program (that included lifestyle modification) generally lost 15% to 25% of initial weight in 3 to 4 months (2,3,15,16,30–32). Attrition in these programs typically ranged from 25% to 50% during the first 3 to 6 months, and patients generally regained 40% to 50% of lost weight 1 to 2 years after treatment, in the absence of follow-up care (30–32).

The NHLBI expert panel did not recommend the use of VLCDs over LCDs providing 1000 to 1500 kcal/d of conventional foods (6). The panel's conclusion was based on data from randomized trials that showed no differences in long-term weight losses between VLCDs and LCDs, principally because of greater weight regain after VLCDs (6).

Despite this expert panel's conclusion, the majority of individual randomized trials showed slightly larger long-term weight losses for persons prescribed VLCDs. Anderson and colleagues, in a meta-analysis of long-term studies, concluded that VLCDs were associated with greater long-term weight reductions than LCDs (2). The studies included in that review, however, were mostly case series, and the meta-analysis did not account for the possibility of differential attrition among patients consuming either a LCD or a VLCD. Astrup and Rossner (3), in a qualitative review of several studies, also concluded that the larger initial weight losses induced by VLCDs were associated with greater long-term weight losses. Their conclusion assumed that patients participated in a weight maintenance intervention that included lifestyle modification. In addition, the European SCOOP-VLCD report noted that long-term weight losses may be greater after larger initial reductions in weight (1). Given the conflicting conclusions of these reviews, we performed a meta-analysis of randomized trials that compared VLCDs and LCDs to determine whether combining study results would reveal any incremental long-term benefit of VLCDs.

Research Methods and Procedures

Data Sources and Study Selection

A Medline search from 1966 to the present was performed using multiple combinations of the MeSH terms reducing diet, obesity, energy intake, and weight loss. Bibliographies of relevant articles and one quantitative review (2) and three recent qualitative reviews (3,15,16) were also searched for additional references. We selected only randomized controlled trials that compared VLCDs and LCDs and included at least a 1-year follow-up assessment after maximum initial weight loss was achieved. An exception was made for a study by Wing et al. (33), in which patients consumed a VLCD for two separate 12-week periods during a year. We used weight loss after the second 12-week trial. Studies that used weight loss medication were excluded.

VLCDs were defined as diets providing <800 kcal/d and LCDs as those providing 800 to 1800 kcal/d. Over 1000 titles or abstracts were examined, including 16 original research papers that included long-term comparisons of VLCDs and LCDs. Of these 16 reports, 14 were randomized trials. Of the 14 randomized studies, seven were excluded because they did not include a 1-year follow-up assessment (after maximum weight loss) (34–40). An eighth study was excluded because both VLCD and LCD patients were treated concomitantly with weight loss medication (ephedrine and caffeine) (41). Thus, six studies were included in the meta-analysis (Figure 1) (33,42–46). Two additional studies were identified that included long-term follow-up comparisons of LCD and VLCD programs (47,48). However, neither of these studies was a randomized trial, as was determined by contacting the investigators. There were no disagreements between the two authors regarding inclusion/exclusion of individual trials.

For the six studies selected, data were extracted for: length of treatment with VLCD, total length of therapy, attrition, short- and long-term weight loss as a percentage of

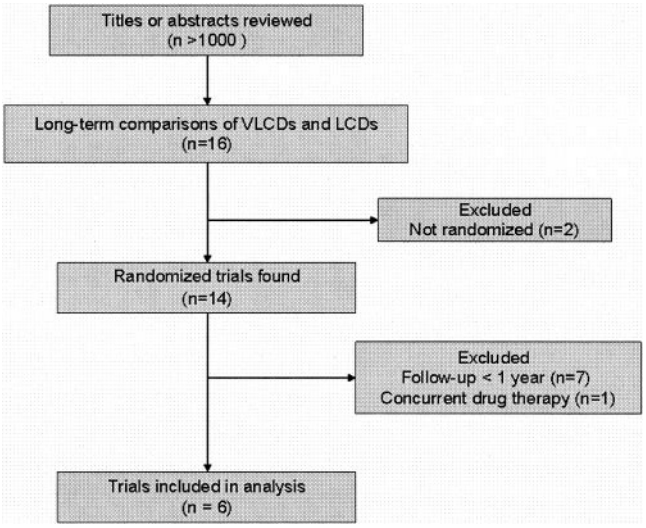


Figure 1: Flowchart for conducting the literature review.

initial weight, and changes in obesity-related comorbidities. Data were extracted independently by both authors and then compared for any discrepancies.

Statistical Analyses

Differences between the two dietary regimens in both short- and long-term weight loss were computed as: (percentage of initial weight lost for VLCD) − (percentage of initial weight lost for LCD). Analyses using weight loss in kilograms also were conducted and yielded the same statistical conclusions. Differences in attrition also were computed as: (VLCD − LCD). Given the varying lengths of follow-up, attrition was standardized as the percentage of the sample that dropped out per month. In one trial (42), there were three treatment groups, but data were analyzed only for the two groups that received the same behavioral counseling with and without VLCD. This was done to assess the true incremental effect of a VLCD when added to a standard behavioral intervention. All data were subjected to heterogeneity testing using the Q statistic (49). Heterogeneity was found for most comparisons; thus, a random effects model was used (50). Regression analysis was used to test for associations between study characteristics and the between-group difference in weight loss. All analyses were conducted using Stata version 8.2 SE (Stata Corporation, College Station, TX).

Data Imputation

In one study, the standard deviations (SDs) of the long-term weight losses were not given (43). Thus, using the other five studies, we calculated the SD as a percentage of the mean weight loss. We then used this percentage to impute an SD for the study with missing data.

Results

Sample

The six randomized controlled trials were published between 1989 and 1997 (33,42–46). Four of the studies were conducted in the U.S., one in Sweden, and one in multiple countries (i.e., Sweden, Norway, and Denmark). Individual level data were not available from these studies. Therefore, although the combined number of participants in these trials was 314, the *N* for our analysis was 6.

As shown in Table 1, the majority of studies enrolled patients with a BMI of 35 to 40 kg/m^2. Two studies enrolled only women (42,45), and two other trials enrolled only patients with type 2 diabetes (33,44). Participants were prescribed VLCDs for 8 to 24 weeks, and the total length of treatment ranged from 6 to 26 months. Three studies used liquid meal replacements (43,45,46), one used a protein-sparing modified fast (42), and two studies used a combination of the two approaches (33,44). In three studies, patients were provided with exercise goals, which consisted of daily walking (33,42,43). For the LCD group, all six studies prescribed hypocaloric diets comprised of conventional foods, with energy goals ranging from 1000 to 1800 kcal/d.

Attrition

Attrition per month across the six studies was 0.8 ± 0.7% for the VLCD group and 0.9 ± 0.4% for the LCD group ($p > 0.2$). Overall attrition in the six studies was 22.3% for VLCD groups (range, 14.6% to 40.7%) and 22.6% for LCD groups (range, 0% to 51.9%) over a mean of 29 ± 18 months.

Short-Term Weight Loss

Participants in the VLCD and LCD arms of the studies lost a mean of 16.1 ± 1.6% and 9.7 ± 2.4% of initial weight, respectively. The mean difference of 6.4 ± 2.7% was highly significant ($p = 0.0001$), revealing the short-term superiority of the VLCD regimen, which was prescribed for a mean of 12.7 ± 6.4 weeks. Figure 2 shows the difference in weight loss between groups (i.e., VLCD − LCD) for each of the six studies. Five of the six studies reported data for completers only, whereas one study used an intention-to-treat analysis, with the last observation carried forward for dropouts. Our analysis is based on the data provided in the reports. (We did not have access to the raw data to reexamine the findings using a last-observation-carried forward or baseline-carried forward analysis.)

Long-Term Weight Loss

At follow-up assessment, which ranged from 1 to 5 years (mean = 1.9 ± 1.6 years) after completing the VLCD, mean weight losses in the VLCD and LCD groups were 6.3 ± 3.2% and 5.0 ± 4.0% of initial weight, respectively. As shown in Figure 3, the difference between groups was 1.3 ±

Table 1. Summary of results for the six randomized trials that compared a VLCD with an LCD

Study	Treatment regimen	*N*	BMI (kg/m^2)	Treatment duration (weeks)	Maximal mean weight loss ± SD (percentage initial weight)	Follow-up weight loss ± SD (percentage initial weight)	Attrition (percentage per month)
Ryttig et al. (43)*	1. LCD, 1600 kcal/d, 112 weeks + BT	27	37.6	112	Week 8: 6.2 ± 4.1	26 Months: 4.7 ± 7.3 (n = 16)	26 months: 1.6
	2. VLCD, 420 kcal/d, 8 weeks + LCD 104 weeks + BT	54	37.7	112	Week 8: 16.7 ± 6.3	26 Months: 5.1 ± 8.5 (n = 26)	26 Months: 2
Torgerson et al. (46)†	1. LCD, 1200 to 1800 kcal/d, 104 weeks + BT	55	40.5	104	Week 26: 7.3 ± 6.0	24 Months: 5.4 ± 8.1 (n = 45)	24 Months: 0.8
	2. VLCD, 456 to 608 kcal/d, 12 weeks + LCD 92 weeks + BT	58	40.2	104	Week 26: 14.6 ± 9.0	24 Months: 7.9 ± 12.3 (n = 45)	24 Months: 0.9
Wadden et al. (42)‡	1. LCD, 1200 kcal/d, 26 weeks + BT	22	39.4 (both groups)	26	Week 26: 12.3 ± 6.2	66 Months: +2.9 ± 1.7 (n = 16)	66 Months: 0.4
	2. VLCD, 400 to 500 kcal/d, 8 weeks + LCD 18 weeks + BT	31		26	Week 26: 15.8 ± 6.3	66 Months: +0.8 ± 2.4 (n = 23)	66 Months: 0.4
Wadden et al. (45)	1. LCD, 1200 kcal/d, 78 weeks + BT	21	38.8	78	Week 26: 11.2 ± 5.9	18 months: 11.5 ± 7.8 (n = 17)	18 months: 1.1
	2. VLCD, 420 kcal/d, 16 weeks + LCD 62 weeks + BT	28	40.0	78	Week 26: 19.9 ± 8.9	18 months: 10.1 ± 9.3 (n = 23)	18 months: 1
Wing et al. (44)	1. LCD, 1000 to 1500 kcal/d, 20 weeks + BT	19	38.1	72	Week 20: 9.7 ± 4.1	18 months: 6.5 ± 6.6 (n = 16)	18 months: 0.9
	2. VLCD, 400 kcal/d, 8 weeks + LCD 12 weeks + BT	17	37.3	72	Week 20: 18.2 ± 9.3	18 months: 8.4 ± 9.0 (n = 17)	18 months: 0
Wing et al. (33)	1. LCD, 1000 to 1200 kcal/d, 50 weeks + BT	48	38.3	50	Week 50: 9.7 ± 10.8	24 months: 5.3 ± 7.3 (n = 41)	24 months: 0.6
	2. VLCD, 400 to 500 kcal/d, for two 12-week trials + LCD 26 weeks + BT	45	37.4	50	Week 50: 13.4 ± 9.7	24 months: 6.8 ± 7.6 (n = 38)	24 months: 0.7

VLCD, very-low-calorie diet; LCD, low-calorie diet; SD, standard deviation; BT, behavior therapy.

* Groups 2 and 3 from the original study were combined in the analysis; both groups consumed an LCD after 8 weeks of VLCD, with one group including meal replacements in their diet. The SDs for long-term weight loss were imputed, as described in the text.

† Weight loss and its SD were estimated from the figure in the manuscript.

‡ As described in the text, only Groups 2 and 3 were compared to evaluate the effect of VLCD when added to maximal therapy.

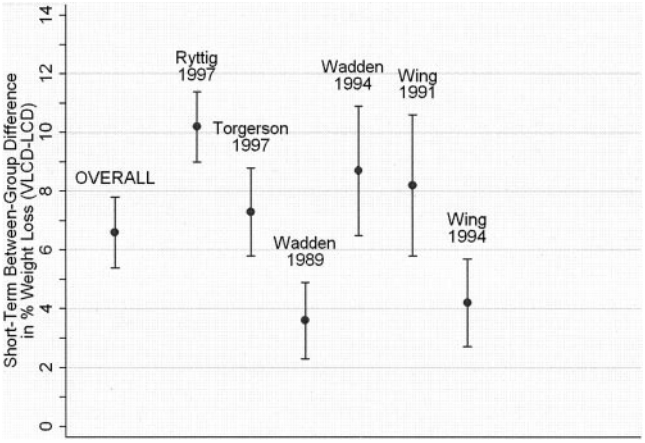


Figure 2: Differences between the VLCD and LCD groups (i.e., VLCD − LCD) in short-term percentage reduction in initial weight. All values are mean ± standard error. Results shown are from references 33 and 42 to 46.

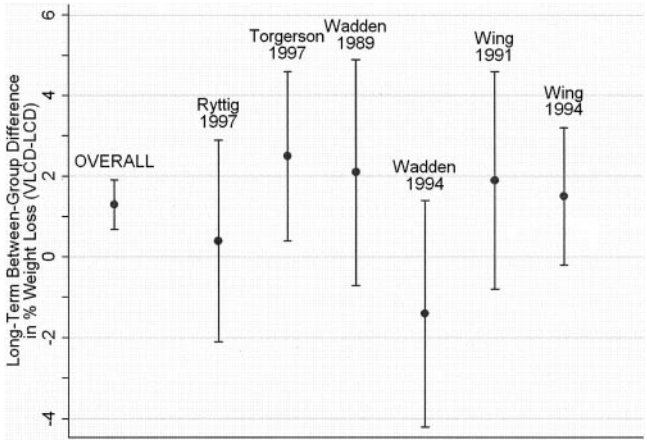


Figure 3: Differences between the VLCD and LCD groups (i.e., VLCD − LCD) in the long-term percentage reduction in initial weight. All values are mean ± standard error. Results shown are from references 33 and 42 to 46.

5.1%, which was not statistically significant ($p > 0.2$). VLCD and LCD patients regained 62% and 41% of lost weight, respectively.

Changes in Weight-Related Comorbidities

Four studies assessed changes in comorbid conditions at long-term follow-up (33,43–45). In a study by Wing et al. (44), participants in both dietary groups began treatment with a hemoglobin A_{1c} (HbA_{1c}) value of 10.4%. At Week 72 (1 year after a 20-week program), a decrease of 1.2 percentage points was observed in VLCD patients, compared with an increase of 1.4 points in the LCD group ($p = 0.01$). This difference in HbA_{1c} was observed despite comparable weight losses in the two groups of 8.4% and 6.5%, respectively, at Week 72. (Changes in lipids in the two groups did not differ significantly.) A second study, however, by the same investigators, failed to replicate the difference in glycemic control at a 2-year follow-up (33). HbA_{1c} increased by 0.1 and 0.2 percentage points in the VLCD and LCD groups, respectively, with weight losses of 6.8% and 5.3%. There also were no significant differences between groups in changes in lipids or systolic blood pressure (33). Diastolic blood pressure fell by 8 mm Hg in the VLCD group, compared with a 3 mm Hg reduction in the LCD group ($p = 0.03$), but this finding was not observed in the first study by Wing et al. (44). Ryttig et al. (43) found no significant changes within groups in glycemic control, blood pressure, or lipids for either group at 2 years, despite weight losses of 5.1% and 4.7% for the VLCD and LCD groups, respectively. Wadden et al. (45) reported greater decreases in binge eating among LCD- as compared with VLCD-treated patients, with similar weight losses at long-term follow-up. Changes in cardiovascular disease risk factors were not measured.

Adverse Events

No study reported any serious adverse events attributable to the VLCD. No symptomatic cholelithiasis was reported among VLCD participants in any of the trials. Ryttig et al. reported mild reversible alopecia in 35% of VLCD patients, compared with 2% of LCD participants (43). In the first study by Wing et al. (44), an increase in uric acid was seen in the VLCD group, although no patients developed clinical symptoms of gout. In the second study by Wing (33), transient cold intolerance, constipation, and alopecia were common in the VLCD group.

Study Characteristics and Weight Loss

The difference between groups in weight loss (i.e., VLCD − LCD) was not associated with the length of time the VLCD was used or with the total length of therapy. This was true for both short- and long-term weight loss. Even within the VLCD group, duration of VLCD use and total length of therapy were not associated with greater weight loss. There also were no associations between demographic variables, such as BMI or gender, and the difference between groups in weight loss. There were no differences in weight loss for the two studies that received partial support from industry, as compared with the four studies that were not industry-funded.

Discussion

This meta-analysis of six studies showed that VLCDs induced significantly greater short-term weight losses than LCDs but comparable long-term changes in weight. The equivalence of long-term losses was attributable to greater weight regain among the VLCD-treated patients. The present findings support the conclusion of the NHLBI ex-

pert panel that VLCDs not be recommended in lieu of LCDs comprised of conventional foods (6). The strength of the present conclusion resides in the examination of studies that directly compared VLCDs and LCDs, in head-to-head trials, rather than extrapolating across investigations, in which only one or the other diet was used (2). Results of this analysis should resolve the conflicting conclusions of prior reviews (1–5). We note that the present findings represent a best case scenario for both dietary approaches because data were provided for treatment completers only in five of six studies. Also, the relative absence of adverse events reported in VLCD participants in these six trials (particularly that no patient developed symptomatic cholelithiasis) may have been attributable to lack of detailed assessment.

The short-term weight losses clearly favored the use of VLCDs. Thus, these diets potentially would be a more attractive option if there were effective methods of maintaining lost weight. Several studies have addressed this issue using medications or behavioral weight maintenance counseling. Apfelbaum et al. (51) showed that, after 4 initial weeks of a VLCD, during which patients lost 7.6 kg, those randomized to 1 year of treatment with sibutramine achieved a cumulative loss of 12.8 kg at the end of this time, compared with a loss of 7.1 kg for placebo-treated individuals ($p = 0.004$). Mathus-Vliegen (52) prescribed a VLCD for 3 months, which induced an initial weight loss of 15.2 kg. Participants were then randomly assigned to sibutramine (10 mg/d) or placebo for an additional 15 months. At month 18, patients in the sibutramine group maintained a loss of 10.7 kg, compared with 8.5 kg for those prescribed placebo ($p < 0.008$). Thus, sibutramine slowed but did not prevent weight regain after a 15-kg loss. A study that combined the use of a VLCD with dexfenfluramine revealed similar findings. Patients lost 15% of initial weight in the first 6 months but maintained a loss of only 10% at 1 year, despite remaining on medication the entire time (53). Dexfenfluramine was removed from the market in 1997 because of its association with valvulopathy (54). Further studies are needed of medications on the horizon, such as rimonabant (55), to determine whether they can sustain the 15% to 25% reductions in initial weight achieved with VLCDs.

Several studies have investigated the benefits of behavioral weight maintenance therapy after the period of rapid weight loss with a VLCD. Such treatment provides weekly or biweekly group meetings, training in relapse prevention, and encouragement to adhere to diet and exercise recommendations. In a non-randomized study, patients with extreme obesity who attended weekly small group meetings for 2 years maintained a loss of 15.2% at the end of this time, after losing a maximum of 27.3% (32). In a randomized trial, patients who lost 11.9 kg in 6 months by consuming a 1200 kcal/d diet of conventional foods maintained a loss of 12.2 kg a year later while attending 39 group behavioral maintenance sessions (45). In contrast, persons who lost 21.5 kg (during the first 6 months) by adhering to a VLCD maintained a loss of only 10.9 kg, despite receiving the same 39 maintenance sessions. Poor maintenance of weight loss was also observed in a follow-up trial in which patients, after a loss of ~20 kg, received biweekly maintenance sessions combined with either placebo or sertraline (56). An additional randomized trial showed that VLCD-treated patients who lost 14.8 kg regained 50% to 80% of lost weight 18 months after the end of treatment and did not benefit from individualizing the rate of refeeding or using meal replacements during maintenance (57). Two studies of exercise to facilitate weight maintenance after a VLCD yielded mixed results (58,59).

Together, these findings suggest that efforts to maintain mean weight losses of 15% to 25% of initial weight are unlikely to be successful in a majority of patients, given current behavioral therapy and behavioral and pharmacologic therapies (i.e., sibutramine and orlistat). Factors responsible for weight regain after treatment with VLCD may include behavioral fatigue (60) in adhering to rigorous diet and exercise regimens in the presence of a toxic environment, as well as compensatory changes in peripheral and central hormones that regulate appetite and energy expenditure (61–63). At present, bariatric surgery appears to be the only reliable method of sustaining weight losses of 20% or more of initial weight (64).

Cycles of weight loss and regain do not seem to have the adverse health and metabolic consequences once feared (65). Thus, patients potentially could be encouraged to lose as much weight as possible through aggressive dieting, even if weight regain were likely (as indicated by the present meta-analysis). This approach, however, overlooks the substantial costs of medically supervised VLCDs in the United States. Even if the costs of meal replacements during a VLCD (i.e., about $10 a day) were canceled out by the usual costs of food, a 12-week program would still run approximately $1000 because of the extensive medical supervision required during rapid weight loss (14). These costs make VLCDs impractical for persons of low socioeconomic status, including minority members, in whom the rates of obesity are disproportionately high (66,67). As described previously, the European experience differs because the lack of mandatory medical supervision decreases the cost of using a VLCD. The cost of medical monitoring after the 3rd week on a VLCD probably varies from country to country within the European Union and may not result in significant out-of-pocket expenses for patients in some nations.

In the United States, one solution to the high costs and rapid weight regain associated with VLCDs is the use of liquid meal replacements as part of a 1000 to 1500 kcal/d diet that includes conventional foods. This latter regimen is designed to induce a mean loss of ~10% to 12% of initial weight (68,69). The higher calorie level reduces the need for intensive medical monitoring and, thus, should decrease

costs. Although the use of a 1000 to 1500 kcal/d partial meal replacement plan will not induce initial losses as great as those produced by all-liquid VLCDs, these greater losses presently cannot be maintained.

As used on an outpatient basis, partial meal replacement plans facilitate greater weight loss than the prescription of equivalent-calorie diets comprised solely of conventional foods. Heymsfield et al. (70) performed a meta-analysis of six randomized trials (71–76) that compared traditional LCDs (comprised of conventional foods) with isocaloric diets in which two meals and two snacks per day were replaced with a liquid diet and/or meal bars. They found significantly greater weight loss (of ~2.5 kg) at 3 months and at 1 year among participants who used the partial meal replacement plans (70). Since the publication of the meta-analysis, one additional randomized trial found greater weight loss with a meal replacement plan than with a conventional diet (77). A second randomized study found equal weight losses among the two groups (78).

How do meal replacements induce greater weight loss? Obese individuals typically underestimate their calorie intake by 40% to 50% when consuming a diet of conventional foods (79) because of difficulty in estimating portion sizes, macronutrient composition, and calorie content and in remembering all foods consumed. Meal replacements seem to decrease these difficulties and simplify food choices (7). Portion-controlled servings of conventional foods similarly facilitate weight loss, as shown by Jeffery et al. (80) and other investigators (81,82).

Further research is needed to determine the optimal macronutrient composition of meal replacements for treating obese persons with different weight-related conditions including type 2 diabetes, hypertension, and hyperlipidemia. Preliminary findings, for example, suggest that high-protein, low-carbohydrate diets may substantially improve glycemic control in obese patients with type 2 diabetes (83) and may be more effective, in this regard, than traditional, low-fat reducing diets (84). The first of two studies conducted by Wing et al. (44) similarly observed superior glycemic control among patients treated with a high-protein VLCD than with a more traditional, low-fat LCD, despite comparable weight losses. However, widespread adoption of the low-carbohydrate approach for diabetic patients should await further long-term safety data concerning lipids, cardiovascular and renal disease, and bone mineral density.

Persons prescribed a 1000 to 1500 kcal/d partial meal replacement plan as part of a comprehensive behavioral approach are likely to lose 10% to 12% of initial weight in the first 12 to 16 weeks (68,69). A minority of individuals may continue to lose substantially larger amounts of weight, an occurrence that need not be discouraged. The National Weight Control Registry has shown that some obese individuals can lose and maintain reductions of 25% to 30% of initial weight (achieved by a variety of different approaches) (85). However, except in highly selected cases, we do not recommend the use of expensive VLCDs to induce losses of 15% to 25% of initial weight, when the present findings indicate that few patients will be able to maintain these losses, even under the best of circumstances. In contrast, numerous studies have shown that obese individuals can maintain (for 1 year or more) mean losses of 10% to 12% of initial weight when provided behavioral weight maintenance therapy (45,86–88) or pharmacotherapy (89,90). Weight losses of this size clearly are associated with significant improvements in health and well being (6), including a reduction in the risk of developing type 2 diabetes (91,92).

Acknowledgments

We thank Myles Faith, Moonseong Heo, and Jesse Berlin for statistical advice. We acknowledge Johanna Brock and Rebecca Stack for editorial assistance. This work was supported, in part, by NIH Grant K24-DK-065018 (to T.A.W.). The funding body had no role in the design or conduct of the study, the collection, management, or analysis of the data, or the preparation, review, or approval of the manuscript. T.A.W. served until December 2004 as a consultant to Novartis Nutrition, which markets comprehensive weight loss programs that include low-calorie and very-low-calorie meal replacement plans.

References

1. **SCOOP-VLCD Working Group.** *Scientific Co-operation on Questions Relating to Food: Directorate-General Health and Consumer Protection, European Union.* http://www.foodedsoc.org/scoop.pdf (Accessed February 24, 2006).
2. **Anderson JW, Konz EC, Frederich RC, Wood CL.** Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr.* 2001;74:579–84.
3. **Astrup A, Rossner S.** Lessons from obesity management programmes: greater initial weight loss improves long-term maintenance. *Obes Rev.* 2000;1:17–9.
4. **Ayyad C, Andersen T.** Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. *Obes Rev.* 2000;1:113–39.
5. **National Task Force on the Prevention and Treatment of Obesity, National Institutes of Health.** Very low-calorie diets. *JAMA.* 1993;270:967–74.
6. **National Heart Lung and Blood Institute.** Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report: National Institutes of Health/National Heart Lung and Blood Institute. *Obes Res.* 1998;6:51–209S.
7. **Wadden TA, Berkowitz RI.** Very-low-calorie diets. In: Fairburn CG, Brownell KD, eds. *Eating Disorders and Obesity: A Comprehensive Handbook.* 2nd ed. New York: Guilford Press; 2002, pp. 534–8.
8. **Blackburn GL, Bistrian BR, Flatt JP.** Role of a protein-sparing modified fast in a comprehensive weight reduction

program. In: Howard AN, ed. *Recent Advances in Obesity Research.* London, UK: Newman Publishing; 1975, pp. 279–81.
9. **Blackburn GL, Greenberg I.** Multidisciplinary approach to adult obesity therapy. *Int J Obes.* 1978;2:133–42.
10. **Wadden TA, Stunkard AJ, Brownell KD, Day SC.** A comparison of two very-low-calorie diets: protein-sparing-modified fast versus protein-formula-liquid diet. *Am J Clin Nutr.* 1985;4:533–9.
11. **Rosen JC, Gross J, Loew D, Sims EA.** Mood and appetite during minimal-carbohydrate and carbohydrate-supplemented hypocaloric diets. *Am J Clin Nutr.* 1985;42:371–9.
12. **Atkinson RL.** Low and very low calorie diets. *Med Clin North Am.* 1989;73:203–15.
13. **Wadden TA, Van Itallie TB, Blackburn GL.** Responsible and irresponsible use of very-low-calorie diets in the treatment of obesity. *JAMA.* 1990;263:83–5.
14. **Tsai AG, Wadden TA.** Systematic review: an evaluation of major commercial weight loss programs in the United States. *Ann Intern Med.* 2005;142:56–66.
15. **Mustajoki P, Pekkarinen T.** Very low energy diets in the treatment of obesity. *Obes Rev.* 2001;2:61–72.
16. **Saris WH.** Very-low-calorie diets and sustained weight loss. *Obes Res.* 2001;9:295–301S.
17. **Rossner S, Torgerson JS.** VLCD a safe and simple treatment of obesity. *Lakartidningen.* 2000;97:3876–9.
18. **Wadden TA, Stunkard AJ, Brownell KD.** Very low calorie diets: their efficacy, safety, and future. *Ann Intern Med.* 1983; 99:675–84.
19. **Liddle RA, Goldstein RB, Saxton J.** Gallstone formation during weight-reduction dieting. *Arch Intern Med.* 1989;149: 1750–3.
20. **Kamrath RO, Plummer LJ, Sadur CN, et al.** Cholelithiasis in patients treated with a very-low-calorie diet. *Am J Clin Nutr.* 1992;56:255–7S.
21. **Shiffman ML, Kaplan GD, Brinkman-Kaplan V, Vickers FF.** Prophylaxis against gallstone formation with ursodeoxycholic acid in patients participating in a very-low-calorie diet program. *Ann Intern Med.* 1995;122:899–905.
22. **Broomfield PH, Chopra R, Sheinbaum RC, et al.** Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. *N Engl J Med.* 1988;319:1567–72.
23. **Festi D, Colecchia A, Orsini M, et al.** Gallbladder motility and gallstone formation in obese patients following very low calorie diets: use it (fat) to lose it (well). *Int J Obes.* 1998;22: 592–600.
24. **Hoy MK, Heshka S, Allison DB, et al.** Reduced risk of liver-function-test abnormalities and new gallstone formation with weight loss on 3350-kJ (800-kcal) formula diets. *Am J Clin Nutr.* 1994;6:249–54.
25. **Weinsier RL, Wilson LJ, Lee J.** Medically safe rate of weight loss for the treatment of obesity: a guideline based on risk of gallstone formation. *Am J Med.* 1995;98:115–7.
26. **Wadden TA, Stunkard AJ, Brownell KD, Van Itallie TB.** The Cambridge diet: more mayhem? *JAMA.* 1983;250: 2833–4.
27. **Heymsfield SB, Jain P, Ortiz O, Waki M.** Cardiac structure and function in markedly obese patients before and after weight loss. In: Wadden TA, VanItallie TB, eds, *Treatment of the Seriously Obese Patient.* New York: The Guilford Press; 1992, pp. 136–62.
28. **Sours HE, Frattali VP, Brand CD, et al.** Sudden death associated with very low calorie weight reduction regimens. *Am J Clin Nutr.* 1981;34:453–61.
29. **Connolly HM, Crary JL, McGoon MD, et al.** Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med.* 1997;337:581–8.
30. **Wadden TA, Foster GD, Letizia KA, Stunkard AJ.** A multicenter evaluation of a proprietary weight reduction program for the treatment of marked obesity. *Arch Intern Med.* 1992;152:961–6.
31. **Anderson JW, Brinkman-Kaplan V, Hamilton CC, Logan JE, Collins RW, Gustafson NJ.** Food-containing hypocaloric diets are as effective as liquid-supplement diets for obese individuals with NIDDM. *Diabetes Care.* 1994;17:602–4.
32. **Anderson J, Brinkman-Kaplan V, Lee H, Wood C.** Relationship of weight loss to cardiovascular risk factors in morbidly obese individuals. *J Am Coll Nutr.* 1994;13:256–61.
33. **Wing RR, Blair E, Marcus M, Epstein LH, Harvey J.** Year-long weight loss treatment for obese patients with type II diabetes: does including an intermittent very-low-calorie diet improve outcome? *Am J Med.* 1994;97:354–62.
34. **Foster GD, Wadden TA, Feuer ID, et al.** Controlled trial of the metabolic effects of a very-low-calorie diet: short- and long-term effects. *Am J Clin Nutr.* 1990;51:167–72.
35. **Doherty JU, Wadden TA, Zuk L, Letizia KA, Foster GD, Day SC.** Long-term evaluation of cardiac function in obese patients treated with a very-low-calorie diet: a controlled clinical study of patients without underlying cardiac disease. *Am J Clin Nutr.* 1991;53:854–8.
36. **Foster GD, Wadden TA, Peterson FJ, Letizia KA, Bartlett SJ, Conill AM.** A controlled comparison of three very-low-calorie diets: effects on weight, body composition, and symptoms. *Am J Clin Nutr.* 1992;55:811–7.
37. **Sweeney ME, Hill JO, Heller PA, Baney R, DiGirolamo M.** Severe vs moderate energy restriction with and without exercise in the treatment of obesity: efficiency of weight loss. *Am J Clin Nutr.* 1993;57:127–34.
38. **Rossner S, Flaten H.** VLCD versus LCD in long-term treatment of obesity. *Int J Obes.* 1997;21:22–6.
39. **Rossner S.** Intermittent vs continuous VLCD therapy in obesity treatment. *Int J Obes.* 1998;22:190–2.
40. **Leslie WS, Lean ME, Baillie HM, Hankey CR.** Weight management: a comparison of existing dietary approaches in a work-site setting. *Int J Obes.* 2002;26:1469–75.
41. **Toubro S, Astrup A.** Randomised comparison of diets for maintaining obese subjects' weight after major weight loss: ad lib, low fat, high carbohydrate diet v fixed energy intake. *BMJ.* 1997;314:29–34.
42. **Wadden TA, Sternberg JA, Letizia KA, Stunkard AJ, Foster GD.** Treatment of obesity by very low calorie diet, behavior therapy, and their combination: a five-year perspective. *Int J Obes.* 1989;13:39–46.
43. **Ryttig KR, Flaten H, Rossner S.** Long-term effects of a very low calorie diet (Nutrilett) in obesity treatment: a prospective,

randomized, comparison between VLCD and a hypocaloric diet + behavior modification and their combination. *Int J Obes.* 1997;21:574–9.

44. **Wing RR, Marcus MD, Salata R, Epstein LH, Miaskiewicz S, Blair EH.** Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. *Arch Intern Med.* 1991;151:1334–40.
45. **Wadden TA, Foster GD, Letizia KA.** One-year behavioral treatment of obesity: comparison of moderate and severe caloric restriction and the effects of weight maintenance therapy. *J Consult Clin Psychol.* 1994;62:165–71.
46. **Torgerson JS, Lissner L, Lindroos AK, Kruijer H, Sjöström L.** VLCD plus dietary and behavioural support versus support alone in the treatment of severe obesity: a randomised two-year clinical trial. *Int J Obes.* 1997;21:987–94.
47. **Miura J, Arcu K, Tsukahara S, Ohno M, Ikeda Y.** The long-term effectiveness of combined therapy by behaviour modification and very-low-calorie diet: two year follow-up. *Int J Obes.* 1989;13:73–7S.
48. **Pekkarinen T, Mustajoki P.** Comparison of behavior therapy with and without very-low-energy diet in the treatment of morbid obesity: a 5-year outcome. *Arch Intern Med.* 1997; 157:1581–5.
49. **Deeks JJ, Altman DG, Bradburn MJ.** Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care: Meta-Analysis in Context.* 2nd ed. London, UK: BMJ Publishing Group; 2001, pp. 285–312.
50. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–88.
51. **Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, Leutenegger E.** Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am J Med.* 1999;106: 179–84.
52. **Mathus-Vliegen EM.** Long-term maintenance of weight loss with sibutramine in a GP setting following a specialist guided very-low-calorie diet: a double-blind, placebo-controlled, parallel group study. *Eur J Clin Nutr.* 2005;59:S31–8.
53. **Andersen T, Astrup A, Quaade F.** Dexfenfluramine as adjuvant to a low-calorie formula diet in the treatment of obesity: a randomized clinical trial. *Int J Obes.* 1992;16:35–40.
54. **Bowen R, Glicklich A, Kahn M, et al.** Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services Interim Public Health Recommendations, November 1997. *Morb Mortal Wkly Rep.* 1997;46:1061–6.
55. **Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S.** Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet.* 2005;365:1389–97.
56. **Wadden TA, Bartlett SJ, Foster GD, et al.** Sertraline and relapse prevention training following treatment by very-low-calorie diet: a controlled clinical trial. *Obes Res.* 1995;3:549–57.
57. **Agras WS, Berkowitz RI, Arnow BA, et al.** Maintenance following a very-low-calorie diet. *J Consult Clin Psychol.* 1996;64:610–3.
58. **Pavlou KN, Krey S, Steffee WP.** Exercise as an adjunct to weight loss and maintenance in moderately obese subjects. *Am J Clin Nutr.* 1989;49:1115–23.
59. **Sikand G, Kondo A, Foreyt JP, Jones PH, Gotto AM, Jr.** Two-year follow-up of patients treated with a very-low-calorie diet and exercise training. *J Am Diet Assoc.* 1988;88: 487–8.
60. **Smith DE, Wing RR.** Diminished weight loss and behavioral compliance during repeated diets in obese patients with type II diabetes. *Health Psychol.* 1991;10:378–83.
61. **Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL.** Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab.* 2002;87:2391–4.
62. **Schwartz MW, Woods SC, Porte D, Jr., Seeley RJ, Baskin DG.** Central nervous system control of food intake. *Nature.* 2000;404:661–71.
63. **Cummings DE, Weigle DS, Frayo RS, et al.** Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med.* 2002;346:1623–30.
64. **Maggard MA, Shugarman LR, Suttorp M, et al.** Meta-analysis: surgical treatment of obesity. *Ann Intern Med.* 2005; 142:547–59.
65. **Gregg EW, Williamson DF.** The relationship of intentional weight loss to disease incidence and mortality. In: Wadden TA, Stunkard AJ, eds. *Handbook of Obesity Treatment.* New York: Guilford Press; 2002, pp. 125–43.
66. **Jeffery RW, French SA.** Socioeconomic status and weight control practices among 20- to 45-year-old women. *Am J Public Health.* 1996;86:1005–10.
67. **Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM.** Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA.* 2004;291:2847–50.
68. **Ditschuneit HH, Flechtner-Mors M, Johnson TD, Adler G.** Metabolic and weight-loss effects of a long-term dietary intervention in obese patients. *Am J Clin Nutr.* 1999;69:198–204.
69. **Wadden TA, Foster GD, Sarwer DB, et al.** Dieting and the development of eating disorders in obese women: results of a randomized controlled trial. *Am J Clin Nutr.* 2004;80:560–8.
70. **Heymsfield SB, van Mierlo CA, van der Knaap HC, Heo M, Frier HI.** Weight management using a meal replacement strategy: meta and pooling analysis from six studies. *Int J Obes.* 2003;27:537–49.
71. **Flechtner-Mors M, Ditschuneit HH, Johnson TD, Suchard MA, Adler G.** Metabolic and weight loss effects of long-term dietary intervention in obese patients: four-year results. *Obes Res.* 2000;8:399–402.
72. **Rothacker DQ, Staniszewski BA, Ellis PK.** Liquid meal replacement vs traditional food: a potential model for women who cannot maintain eating habit change. *J Am Diet Assoc.* 2001;101:345–7.

73. **Yip I, Go VL, DeShields S, et al.** Liquid meal replacements and glycemic control in obese type 2 diabetes patients. *Obes Res.* 2001;9:341–7S.
74. **Ahrens R, Hower M.** Evaluation of the effectiveness of an OTC weight loss product versus traditional diet methods in a rural community pharmacy setting. *J Am Pharm Assoc.* 2000; 40:275.
75. **Ashley JM, St Jeor ST, Schrage JP, et al.** Weight control in the physician's office. *Arch Intern Med.* 2001;161:1599–604.
76. **Hensrud DD.** Dietary treatment and long-term weight loss and maintenance in type 2 diabetes. *Obes Res.* 2001;9:348–53S.
77. **Allison DB, Gadbury G, Schwartz LG, et al.** A novel soy-based meal replacement formula for weight loss among obese individuals: a randomized controlled clinical trial. *Eur J Clin Nutr.* 2003;57:514–22.
78. **Noakes M, Foster PR, Keogh JB, Clifton PM.** Meal replacements are as effective as structured weight-loss diets for treating obesity in adults with features of metabolic syndrome. *J Nutr.* 2004;134:1894–9.
79. **Lichtman SW, Pisarska K, Berman ER, et al.** Discrepancy between self-reported and actual caloric intake and exercise in obese subjects. *N Engl J Med.* 1992;327:1893–8.
80. **Jeffery RW, Wing RR, Thorson C, et al.** Strengthening behavioral interventions for weight loss: a randomized trial of food provision and monetary incentives. *J Consult Clin Psychol.* 1993;61:1038–45.
81. **Haynes RB, Kris-Etherton P, McCarron DA, et al.** Nutritionally complete prepared meal plan to reduce cardiovascular risk factors: a randomized clinical trial. *J Am Diet Assoc.* 1999;99:1077–83.
82. **Metz JA, Stern JS, Kris-Etherton P, et al.** A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients: impact on cardiovascular risk reduction. *Arch Intern Med.* 2000;160:2150–8.
83. **Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP.** Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann Intern Med.* 2005;142:403–11.
84. **Stern L, Iqbal N, Seshadri P, et al.** The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med.* 2004;140:778–85.
85. **Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO.** A descriptive study of individuals successful at long-term maintenance of substantial weight loss. *Am J Clin Nutr.* 1997;66: 239–46.
86. **Perri MG, McAdoo WG, McAllister DA, Lauer JB, Yancey DZ.** Enhancing the efficacy of behavior therapy for obesity: effects of aerobic exercise and a multicomponent maintenance program. *J Consult Clin Psychol.* 1986;54: 670–5.
87. **Perri MG, McAllister DA, Gange JJ, Jordan RC, McAdoo G, Nezu AM.** Effects of four maintenance programs on the long-term management of obesity. *J Consult Clin Psychol.* 1988;56:529–34.
88. **Perri MG, Nezu AM, McKelvey WF, Shermer RL, Renjilian DA, Viegener BJ.** Relapse prevention training and problem-solving therapy in the long-term management of obesity. *J Consult Clin Psychol.* 2001;69:722–6.
89. **James WP, Astrup A, Finer N, et al.** Effect of sibutramine on weight maintenance after weight loss: a randomised trial: STORM Study Group Sibutramine Trial of Obesity Reduction and Maintenance. *Lancet.* 2000;356:2119–25.
90. **Wadden TA, Berkowitz RI, Womble LG, et al.** Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med.* 2005;353:2111–220.
91. **Knowler WC, Barrett-Connor E, Fowler SE, et al.** Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393–403.
92. **Tuomilehto J, Lindstrom J, Eriksson J, et al.** G. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med.* 2001;344:1343–50.

Received: 3 April 2020 | Revised: 4 May 2020 | Accepted: 5 May 2020

DOI: 10.1111/obr.13053

OBESITY TREATMENT/DIET

OBESITY Reviews WILEY

Scientific evidence underlying contraindications to the ketogenic diet: An update

Mikiko Watanabe[1] | Dario Tuccinardi[2] | Ilaria Ernesti[1,3] | Sabrina Basciani[1] | Stefania Mariani[1] | Alfredo Genco[3] | Silvia Manfrini[2] | Carla Lubrano[1] | Lucio Gnessi[1]

[1]Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Sapienza University of Rome, Rome, Italy

[2]Department of Endocrinology and Diabetes, University Campus Bio-Medico of Rome, Rome, Italy

[3]Department of Surgical Sciences, Surgical Endoscopy Unit, Sapienza University of Rome, Rome, Italy

Correspondence
Mikiko Watanabe, MD, PhD, Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Sapienza University of Rome, Rome, Italy.
Email: mikiko.watanabe@uniroma1.it

Summary

First identified as a feasible treatment for intractable epilepsy, the ketogenic diet (KD) has recently gained popularity thanks to growing evidence on applications such as weight loss, most importantly, but also NAFLD, cancer, neurologic conditions and chronic pain. As with any treatment, whether pharmacologic or not, the KD might not be an appropriate intervention for every individual, and a number of contraindications have been proposed, now deeply rooted into clinical practice, excluding de facto many patients that could benefit from its use. However, many of these concerns were expressed due to the absence of clinical studies conducted on fragile populations, and an assessment of lately emerged evidence relative to KD safety is currently lacking and much needed. We herein provide a critical revision of the literature behind each safety alert, in order to guide through the treatment options in the case of subjects with an indication to the KD and a borderline safe situation. Based on available evidence, the possible use of this diet as a therapeutic intervention should be assessed on a patient-to-patient basis by adequately skilled medical doctors, keeping in mind current recommendations, but reading them through the knowledge of the current state of the art.

KEYWORDS

low-carbohydrate diet, safety, very low-calorie diet, VLCKD

1 | INTRODUCTION

The ketogenic diet (KD) is defined as a dietary manipulation characterized by a very low carbohydrate content (5%–10% of total daily calorie intake, or 20–50 g per day[1,2]), but the macronutrient composition may vary, defining different ways to reach nutritional ketosis. High-fat ketogenic diets (HFKD) are characterized by a restriction of carbohydrates <50 g/day, with ad libitum fat and calorie intake. Despite their initial introduction as a treatment for refractory epilepsy, they are currently the most widespread weight loss oriented KD. The very low-calorie KD (VLCKD) is a subtype of very low-calorie diet (VLCD), also referred as protein-sparing modified fast (PSMF), that usually relies on meal replacements based on protein derived from whey, soy, eggs and green peas. VLCDs are characterized by extreme energy restriction (400–800 kcal/daily), that, if not associated with major carbohydrate intake reduction, is not necessarily capable of inducing ketosis.[3] The European Food Safety Authority (EFSA) defined a VLCD to be ketogenic when carbohydrate content is below <30–50 g/day

and fats account for 15%–30% of total caloric intake.[3] However, it should be noted that the carbohydrate and calorie intake under which an individual enters ketosis is subjective, making the line between starvation and nutritional ketosis subtle.

Dietary manipulation does not usually recognize specific contraindications as pharmacological interventions do, hence the lack of a 'drug facts label' for the KD. However, ketone bodies are now proven to be signalling, drug-like, mediators.[4] Moreover, the VLCKD is a fairly extreme dietary manipulation possibly leading to serious adverse events when not medically supervised. A recent Italian consensus has therefore updated indications and contraindications to the VLCKD,[5] implementing those proposed initially,[6] similar to what reported by other authors in the United States.[7]

The applications of the KD are now diverse and ever increasing, the most validated being obesity and refractory epilepsy, but with an emerging role in the treatment of neurological disorders, cancer, NAFLD, type 2 diabetes and chronic pain among many others.[5] With the prevalence of obesity steadily growing, and the several newly proposed fields of application, it is more and more frequent to face situations where the patient could benefit from a KD and also suffers from co-morbidities or conditions contraindicating its use according to the current recommendations.[5–7]

We herein aimed at providing an updated and critical revision on the evidence underlying each current safety concern (Table 1). We report that most studies are low quality, sample size often very small, and duration usually quite short, making no definitive conclusion possibly be drawn. However, based on current evidence, it seems reasonable to recommend that a patient-to-patient tailoring be made by experienced physicians, possibly reconsidering many alerts proven questionable (Table 2).

2 | MATERIALS AND METHODS

An updated literature review was conducted to investigate the safety profile of the KD in specific fragile populations. The research was conducted on MEDLINE, EMBASE and Cochrane Database by using the keywords reported in Table S1. We initially selected relevant studies meeting the following criteria: (1) case-reports, case series, case-control studies, cohort studies, observational prospective and retrospective studies, randomized clinical trials; (2) reported safety outcomes following any kind of KD; (3) no age limitation; (4) sufficient detail about nutritional intervention reported; and (5) studies written in English or Japanese or Italian. Case reports and case series were then excluded if higher quality data was available. Preclinical studies were occasionally included if no clinical study was retrieved or when the findings were of particular interest according to the authors.

A total of 1034 manuscripts were identified through database search and reference lists of retrieved articles. After removal of 821 studies based on title and abstract or for being duplicates, 213 full text articles were assessed and 52 included in the present study (Figure 1).

3 | REPORTED CONTRAINDICATIONS TO THE KETOGENIC DIET

3.1 | Liver failure

Nonalcoholic fatty liver disease (NAFLD) is nowadays the second cause of liver transplant in the United States.[60] A relevant body of evidence suggests a protective role of KDs in its pathogenesis, possibly going beyond simple weight loss: virtually all studies assessing liver fat content report positive results after all kinds of KDs, including those with a high fat content.[9]

Noteworthy, malnutrition is a common issue in chronic liver disease.[61] The 2019 Guidelines of the European Association for the Study of the Liver therefore recommend consuming an adequate number of calories and protein. To avoid hepatic encephalopathy, it is suggested to privilege vegetable and dairy protein and decrease the amount of animal (meat) protein, with no reduction in total protein intake even when cirrhosis is present, unless directed by a health professional.[62] However, with the prevalence of obesity increasing all over the world, and NAFLD being now a common cause of cirrhosis, over 30% of liver transplant recipients are obese, and weight loss is strongly encouraged.[63] A case series reports that VLCKD treatment for obesity was well tolerated by two subjects with end stage liver disease (ESLD) effectively reducing weight with no adverse events, and possibly improving liver damage.[8]

Upon close medical monitoring, liver damage may not be exacerbated by the KD, that could conversely prove beneficial. An application might be retained up until ESLD, although further studies are needed to recommend it.

3.2 | Chronic kidney disease

Obesity is a well-established risk factor for chronic kidney disease (CKD),[64] and it is therefore common to encounter patients affected by both severe obesity and renal failure, whom the KD is not proposed due to its relative protein excess that could potentially harm the kidney. Guidelines are inconclusive on recommendations relative to protein intake in patients with CKD at early stages, with some suggesting .8 g/kg body weight,[65] and others recommending up to 1.4 g/kg body weight.[66] Renal function may be differentially affected by protein sources, with red meat proving potentially harmful in a dose dependent way, and other protein sources (fish, egg and dairies) being less noxious,[67] with vegetable derived protein possibly even playing a protective role.[68,69]

A systematic review assessing renal outcomes reports that the kidney seems scarcely affected by VLCDs, although the diets were heterogeneous in macronutrient composition, and the studies only included subjects with normal renal function, making the findings not applicable to those with baseline impaired function.[70] In our hands, kidney function is unaffected in obese individuals with normal glomerular filtration rate (GFR).[71] Moreover, we previously showed that kidney function is not altered by VLCKD in patients with mild chronic

TABLE 1 Summary of data available regarding each contraindication to the KD

Main contraindications	Summary of data
Liver failure	All KDs are beneficial towards NASH. Two patients with ESLD on a VLCKD lost weight with no adverse events.
Kidney disease	VLCDs seem not to affect the kidney in healthy patients. Mild CKD may be improved and is not worsened in obese patients undergoing a VLCKD. 10 patients with obesity and advanced nephropathy lost weight on a VLCKD with no major safety concern.
Type 1 diabetes	One retrospective and one prospective study report that 23 patients with T1D on an HFKD had an improvement in glycaemic variability with a small increase in the hypoglycaemia risk.
Concomitant use of SGLT-2 inhibitors	Several case reports are available regarding the onset of euglycaemic DKA in those consuming HFKDs while on SGLT-2 treatment.
Pregnancy	A teratogenic effect of HFKD is suggested by a case series, and preclinical data partially support the hypothesis.
Breastfeeding	Lactation ketoacidosis is rarely described to happen spontaneously, but a few case reports show an increased risk when KD is a precipitating factor.
Cardiac arrhythmias	Cardiomyopathy and arrhythmias were occasionally reported in epileptic children undergoing an HFKD due to selenium deficiency. VLCDs caused fatal cardiac arrhythmias in the 1970s due to inadequate supplementation. A recent prospective study suggests that a low carbohydrate, high fat diet is associated with increased risk of atrial fibrillation, further studies are needed to confirm the hypothesis.
Recent stroke or myocardial infarction	Preclinical evidence suggests ketone bodies to be protective on ischaemic brain and heart damage. No clinical data are available yet.
Heart failure	The human failing heart uses ketone bodies as a fuel source. One report shows that ketones infusion was harmless and increased cardiac output significantly in those at an NYHA II-III stage.
Respiratory failure	A study in lean subjects with COPD on LCD reports significant improvement and no adverse events. Unreplicated small studies from the 1980s showed that an HFKD was beneficial in patients with respiratory failure or on mechanical ventilation.
Active/severe infections	Clinical studies on KDs do not report a clear immunosuppressive effect. Preclinical data suggest a possible protection towards viral infections.
Frail elderly patients, history of mental disorders and substance abuse	No studies or reports are available.
Elective surgery or invasive procedures	Fasting related perioperative ketosis seems not to increase acidosis risk. Preoperative VLCD may induce hypovolaemia possibly increasing the risk of perioperative complications. Adverse events were not reported when a VLCKD was interrupted 24 h before surgery.
Malignancy	KD does not cause major adverse events around cancer treatment.
Increased serum uric acid and abnormal lipid profile	KDs might induce mild worsening short term, with following improvement or no change in patients with obesity. Sustained dyslipidaemia is observed in lean epileptic subjects on HFKD.
Rare disorders	No studies or reports are available.

Abbreviations: T1D, type 1 diabetes; DKA, diabetic ketoacidosis; ESLD, end stage liver disease; NASH, nonalcoholic steatohepatitis; CKD, chronic kidney disease; NYHA, New York heart association functional classification; COPD, chronic obstructive pulmonary disease; VLCKD, very low-calorie ketogenic diet; HFKD, high fat ketogenic diet; LCD, low carbohydrate diet.

kidney disease (GFR > 60), with almost one third even presenting GFR normalization after the dietary intervention.[10] Noteworthy, VLCKDs rely on meal replacements whose protein source is whey and plant derived, and, when gradual reintroduction of other protein sources occurs, fish, poultry and dairy are strongly recommended over red meat, with total protein intake being always equal to or lower than 1.5 g/kg/ideal body weight. Taken together, available evidence suggests that a VLCKD, with the profound weight loss usually obtained, might be an effective tool to manage patients with obesity and mild kidney failure.

Conversely, very little evidence is available relative to the safety profile in patients with more prominent kidney function impairment. A small 12-week study conducted on five patients with obesity and advanced diabetic nephropathy reported significant improvement in kidney function together with weight loss after a VLCKD intervention.[11] Pointing in the same direction, five patients on haemodialysis underwent a low-calorie, low carbohydrate diet for a median time of 364 days with no major safety concern and prominent weight loss.[12]

While considering the use of KD on patients with end stage CKD, it is crucial to keep in mind that this condition is characterized by limited capacity to handle acid loads and partial impairment of ketones urinary excretion. Moreover, in the initial phase of a KD, increased diuresis will require careful monitoring of goal dry weight if the patient is on haemodialysis treatment. Another possible side effect is

TABLE 2 Summary of reported contraindication to the KD with theoretical reason in support to each, population where safety outcome was evaluated, type of dietary intervention, and critical revision based on available evidence

Main contraindications	Main arguments in support of contraindications	Population	Diet	Critical revision of the contraindications
Liver failure	Exacerbation of liver damage	Obesity with ESLD[8] and NASH[9]	VLCKD,[8,9] HFKD[9]	Skilled hepatologist to evaluate in ESLD, safe and therapeutic in NASH
Chronic kidney disease	Exacerbation of kidney damage	Obesity with mild[10] and severe CKD[11,12]	VLCKD[10–12]	Safe in mild disease, skilled nephrologist to evaluate in end stage disease
T1D	Hypoglycaemia and DKA	Lean T1D[13,14]	HFKD[13,14]	Skilled diabetologist to evaluate, continuous glucose monitoring
Concomitant use of SGLT-2 inhibitors	Euglycaemic DKA	T2D[15–19]	HFKD[15–19]	Not recommended
Pregnancy and breastfeeding	Ketoacidosis	Epilepsy and pregnancy,[20] breastfeeding[21]	HFKD,[20,21] VLCKD[21]	Not recommended
Cardiac arrhythmias	Sudden death and cardiomyopathy	Obesity,[22–25] paediatric epilepsy,[26–28] general population[29]	VLCKD,[22–25] HFKD,[26–28] LCD[25,29]	Skilled cardiologist to evaluate
Recent stroke or myocardial infarction	Increased risk of arrhythmia	Preclinical[30–37]		Skilled cardiologist to evaluate
Heart failure	Increased risk of arrhythmia, hydroelectrolitic alterations	NYHA II-III[38]	bOHb infusion[38]	Avoid in NYHA IV, skilled cardiologist to evaluate in other cases
Respiratory failure	Acidosis	Lean COPD,[39] mechanical ventilation,[40,41] respiratory failure[42–44]	LCD,[39] HFKD,[40–42,44] VLCKD[43]	Skilled pneumologist to evaluate
Active/severe infections	Immunosuppression	Cancer,[45] general population,[46] paediatric epilepsy,[47] obesity,[48,49] preclinical[50]	HFKD,[45–47] VLCKD[48,49]	Generally not recommended
Frail elderly patients, history of mental disorders and substance abuse	Reduced compliance, increased risk of adverse events	n/a	n/a	Only consider if adequate support and monitoring available
Elective surgery or invasive procedures	Ketoacidosis	Obesity,[51,52] adult undergoing surgery[53]	VLCKD,[51,52] 12 h fasting[53]	Not recommended
Malignancy	Malnutrition, exacerbation of common side effects	Cancer,[54] preclinical[55]	HFKD[54]	Avoid in kidney cancer and melanoma, avoid VLCKD
Increased serum uric acid and abnormal lipid profile	Exacerbation of metabolic abnormality	Obesity,[56–58] lean paediatric epilepsy[59]	VLCKD,[56,57] HFKD[58,59]	Extra caution if lean subject with baseline abnormalities or when long term treatment is foreseen
Rare disorders	Impaired ketogenesis, increased risk of relapse	n/a	n/a	n/a

Abbreviations: T1D, type 1 diabetes; DKA, diabetic ketoacidosis; ESLD, end stage liver disease; NASH, nonalcoholic steatohepatitis; CKD, chronic kidney disease; T2D, type 2 diabetes; NYHA, New York heart association functional classification; COPD, chronic obstructive pulmonary disease; VLCKD, very low-calorie ketogenic diet; HFKD, high fat ketogenic diet; LCD, low carbohydrate diet; bOHb, beta hydroxy butyrate.

electrolyte imbalance, and most commonly hyperkalaemia; hence, repeat testing is warranted for an early diagnosis.

Given the scanty—although promising—evidence, with a total of only 10 patients being studied, it is of utmost importance to accurately assess pros and cons of such dietary intervention in advanced stage renal failure.

3.3 | Type 1 diabetes

Type 1 diabetes (T1D) is possibly the most well-described contraindication to the KD due to the increased risk of diabetic ketoacidosis and possible hypoglycaemia. However, it is more and more common to encounter patients affected by both T1D and weight excess, where a

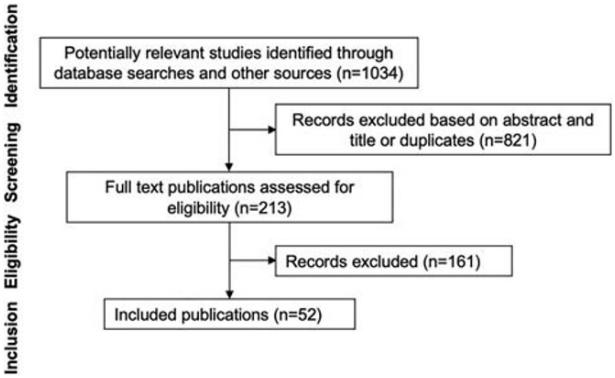


FIGURE 1 Flow chart of publications selection

change in dietary habits is necessary. The latest American Diabetes Association (ADA) guidelines do not support one eating plan over another, but education on carbohydrate counting is highly encouraged.[72]

In a retrospective study investigating the safety of an HFKD together with its efficacy in improving glucose control, 12 subjects with T1D followed an intense glucose monitoring (>4 times daily) and strictly titrated insulin regimen (<7 IU) while dieting. No severe hypoglycaemic events and a significant A1C reduction after 18 months of treatment were reported.[13] Pointing in the same direction, a recent report on 11 subjects with T1D on continuous glucose monitoring consuming an HFKD suggests glycaemic benefits in the form of decreased variability, a well-established cardiovascular risk factor.[73,74] However, in this case, it came at the cost of increased risk of hypoglycaemia.[14] Because of the heterogeneity of the studies and the lack of high-quality prospective trials, it is not possible to finally conclude whether KDs can be safely used in patients with T1D. Moreover, current evidence aimed at assessing a possible application of the KD to improve glucose control in T1D, rather than investigating its safety in those with T1D consuming it for other purposes such as weight loss. Overall, the scanty literature available suggests that its application might be considered in very selected cases, such as the concomitant presence of T1D and obesity or wide prandial excursions, always in the hands of experienced health professionals and with the aid of continuous glucose monitoring. It should be kept in mind that the cost-to-benefit ratio might be unfavourable in some individuals, and further testing is needed to better identify those possibly candidate to its use.

3.4 | Concomitant use of SGLT-2 inhibitors

Since the introduction of the glucose lowering class of drugs sodium–glucose cotransporter-2 inhibitors (SGLT2-i), several reports have been published regarding the risk of euglycaemic diabetic ketoacidosis (DKA) in those consuming HFKDs while on SGLT-2 treatment for type 2 diabetes.[15–19] SGLT2-i increase glucose urinary excretion by inhibiting the sodium and glucose reuptake in the kidney. In addition to the daily loss of ~60–70 g/day,[75] SGLT2-i also decrease insulin secretion and hyperglucagonaemia promoting lipolysis and ketogenesis.[76] As SGLT2-i facilitate ketosis, concomitant severe insulin impairment or significant dietary carbohydrate restriction might lead to DKA.

The reportedly normal glucose levels make such a diagnosis difficult to be formulated unless suspected. As this is a life-threatening condition, it seems advisable to strongly recommend against the concomitant use of this class of medications while on any kind of KD.

3.5 | Pregnancy and breastfeeding

Unsurprisingly, no clinical study is available relative to the use of KDs in pregnant women, with one case-series on two women suggesting a possible teratogenic effect of an HFKD as a treatment to refractory epilepsy.[20] Preclinical studies report a significant reduction in the cerebral blood flow, reduced glucose utilization similar to metabolic encephalopathies, and embryonic growth retardation,[77] but it should be noted that the KD given to rodent models is highly insufficient in protein and not comparable to a KD usually prescribed to human beings, making results scarcely translational.[78]

Lactation ketoacidosis is a well-described condition in cows, and it occurs as the high demand of glucose leads to fat mobilization, ketosis and ultimately acidosis under certain circumstances. Lactation ketoacidosis is rarely described to happen spontaneously in women, but a few case reports show an increased risk when KD is a precipitating factor.[21]

Given the potentially serious adverse events and the limited time that these conditions make KD not recommendable, it is reasonable to conclude that the KD should never be suggested in pregnant and breastfeeding women.

3.6 | Cardiac arrhythmias

VLCDs became very popular in the 1970s thanks to the rapid weight loss obtained, but soon, several fatal cardiac arrhythmias were reported in association with their use.[22] The absence of appropriate electrolyte supplementation and the use of low quality protein led to

such dramatic consequences, and nowadays, these complications are anecdotal.[79] However, the presence of baseline EKG abnormalities might potentially pose at increased risk of malignant arrhythmias upon KD consumption, although the little available evidence suggests it not being a common precipitating factor[23,26] unless accompanied by other concurring conditions.[24] Noteworthy, obesity is itself a risk factor for prolonged QT,[80] and it has been shown that weight loss in general, and both a low carbohydrate and a VLCD diet, in particular, are able to shorten the QT interval significantly.[25,80] Some cases of children undergoing an HFKD to treat refractory epilepsy and incurring in selenium deficiency are reported, causing cardiomyopathy and prolonged QT interval, with lethal outcomes on some occasions. It is therefore of particular importance to make sure that selenium supplementation is appropriate while following a ketogenic diet.[27,28] A recent prospective cohort study demonstrated that a low carbohydrate, high fat diet is associated with increased risk of incident atrial fibrillation. The authors suggest a possible link with reduced vegetables and fruit intake with subsequent increase in oxidative stress. Nevertheless, the association, proposed for the first time, seems to be controversial at the very least, and further studies are needed to confirm or reject the hypothesis.[29]

Overall, the cost-to-benefit ratio of KDs in patients with obesity might be favourable even in those with baseline prolonged QT interval, provided the patient is accurately monitored, and strict compliance with multivitamin, mineral and electrolyte supplementation is ensured. However, very low-calorie dietary manipulations are reasonably safer to be avoided, especially when protein quality and adequate supplementation cannot be guaranteed, with less calorie restricted options to be preferred, always in the hands of skilled cardiologists.

3.7 | Recent stroke or myocardial infarction

Obesity, diabetes, NAFLD and the metabolic syndrome are all strictly linked and represent major risk factors for cardio- and cerebrovascular accidents. It is therefore unsurprising to observe the concomitant presence of these conditions, possibly benefiting from KD treatment, in those with a recent history of stroke or myocardial infarction, absolute contraindications to such dietary intervention. Interestingly, preclinical evidence suggests a protective role played by nutritional ketosis and ketone body β hydroxy-butyrate (βOHb) infusion on ischaemia induced brain and heart damage.[30–36] The authors suggest that ketone bodies may inhibit excitotoxicity, oxidative stress and apoptosis, avoiding further cellular loss in the penumbra zone around the necrotic core.

It should be noted that some evidence, upon superficial evaluation, seems to suggest opposite effects. For example, Liu et al. report increased mortality and greater myocardial injury in rats undergoing ischaemia reperfusion injury and previously fed a normal protein, high fat, low carbohydrate diet similar in composition to the Atkins diet commonly consumed as a form of HFKD in human subjects.[37,81,82] If it has been proven that dietary protein has little contribution to endogenous glucose production in human subjects,[83] making the Atkins Diet a feasible option to induce nutritional ketosis, the physiology of rodents is different, and the same macronutrient ratio leads to obesity and insulin resistance.[84] In fact, nutritional ketosis and weight loss are only observed in rats and mice when both protein and carbohydrate intake are reduced to less than 10%.[78] Therefore, despite the low carbohydrate content, the dietary model applied by Liu et al. is not comparable to an HFKD for human purposes, and the results should not lead to the conclusion that ketone bodies are harmful to the ischaemic heart.

Current evidence on the effect of ketone bodies on ischaemia-reperfusion injury outcomes is promising overall but only present at a preclinical level. It is therefore still not possible to infer on the safety of a KD in those suffering from recent myocardial infarction or stroke, even when other co-morbidities could significantly improve following its use.

3.8 | Heart failure

Obesity is a strong predictor of cardiac insufficiency as seen for acute cardiovascular accidents.[85] However, it is currently recommended against the induction of nutritional ketosis in patients with heart failure NYHA III-IV. Noteworthy, it has been proven that the human failing heart shifts to ketone bodies as a significant fuel source,[86] and myocardial lipid analysis conducted on hearts of nondiabetic, lean, advanced heart failure patients undergoing cardiac transplant confirmed increased ketone utilization.[87] Infusion of βOHb was harmless, and even increased cardiac output significantly in 34 patients at an NYHA II-III stage,[38] suggesting that the present contraindication should be at least reduced to those with NYHA stage IV, for which no safety evidence is available to date.

Altogether, it seems reasonable to foresee that more studies will become available in the next years, possibly confirming a beneficial effect of ketone bodies on all stages of cardiac failure, thus shortening the list of contraindications to the KD.

3.9 | Respiratory failure

Excess fat is known to be associated with several respiratory conditions,[88] as obesity is characterized by low-grade systemic inflammation,[89] possibly playing a major role in the pathogenesis of pulmonary disease.[88] Furthermore, fat accumulates within the alveolar interstitium in obese diabetic rats,[90] and recent evidence confirms accumulation of adipose tissue within the lung of subjects with obesity, its presence correlating with inflammatory infiltrate.[91] Therefore, an intervention leading to weight loss might in theory ameliorate respiratory failure in subjects with obesity and respiratory failure.

Interestingly, a study conducted in 60 lean individuals with COPD consuming a low carbohydrate diet (75 g/die, an amount possibly leading to ketosis in lean individuals, although this was not confirmed in the study) reports significant improvements as measured by increase in Forced Expiratory Volume 1 (FEV1) levels and reduction of

airway resistance.[39] Studies from the 1980s showed that an HFKD was beneficial in 35 patients undergoing artificial ventilation, with a significant reduction of the time where ventilation was required.[40,41] In the same years, some authors suggested that a VLCKD was able to ameliorate respiratory failure in a total of 22 subjects.[42–44] However, extreme caution should be paid as the sample size was always very small, and the results were never replicated.

Current evidence is insufficient to determine whether patients with respiratory failure may safely consume a KD, but an unexpected, beneficial effect both in lean and obese patients has been suggested.

3.10 | Active/severe infections

Bovine peripartum ketosis can impair leukocyte localization to infections, increase the risk of mastitis and impair leukocyte function.[92,93] However, clinical studies investigating inflammation markers and/or white blood cell number or function report variable and contrasting results, overall pointing towards a neutral effect or even possible improvement in subjects with obesity undergoing weight loss while following a KD.[45–49] Interestingly, a recent preclinical report suggests that the KD could even protect against certain viral infections through activation of protective δ γ T lymphocytes.[50]

Further studies are needed to be conclusive on the role possibly played by the KD in active or severe infections, and a cost-to-benefit ratio should be assessed on a patient-to patient basis until clearer evidence is reported.

3.11 | Frail elderly patients, history of mental disorders and substance abuse

Elderly patients are frequently affected by sarcopenic obesity,[94] and those with mental disorders are often on medications known to prevent weight loss.[95] However, administration of a KD to frail and/or elderly subjects might not be advisable due to several reasons. First, the KD induces increased urination with possible hypotension and dehydration, leading to an increase in the risk of falls. Second, some KDs, such as VLCKDs, require the use of supplements. Elderly patients might find remembering these challenging, especially when impaired cognitive ability is present, possibly posing at risk of cardiac arrhythmias and vitamin deficiencies. Finally, elderly subjects with limited mobility are at increased risk of decubitus, and some evidence suggests that wound healing might be impaired during KD consumption.[96]

Severe mental illness, similar to impaired cognitive ability and aging, may lead to reduced compliance in adequate water consumption and constant use of prescribed electrolyte and vitamin supplement crucial to maintain a good safety profile especially during a VLCKD among all KDs, thus increasing the risk of side effects. Unless properly assisted and monitored, fragile subjects at increased risk of poor compliance should avoid the use of VLCKDs.

A separate chapter should be opened for eating disorders such as Bulimia and Anorexia Nervosa (AN). Carbohydrate counting typical of KDs may theoretically trigger eating disorders in predisposed subjects. However, it has been proposed that the KD might be a possible bridge treatment for those with AN in order to avoid starvation and increase patient compliance,[9] although no clinical evidence has been reported to support this hypothesis to date.

Finally, abuse of alcohol and some substances increase the risk of metabolic acidosis under certain circumstances.[97] The concomitant consumption of a KD exacerbates the risk, and it is therefore to be recommend against the prescription of a KD to those with a history of alcohol and substance abuse where relapse seems possible, especially in the absence of adequate support. Noteworthy, a ketogenic diet seems to be effective in suppressing alcohol cravings both at a preclinical level and in subjects with obesity,[98,99] although it should be kept in mind that the physiology underlying such association might be very different across species, as the link in rodent models seems to be an elevation in Fibroblast Growth Factor 21 levels,[78,100] whereas such elevation following a ketogenic diet is not observed in human beings.[101]

3.12 | Elective surgery or invasive procedures

The theoretical basis to the recommendation of avoiding ketosis within 48 h of elective surgery and in the immediate perioperative period is that acute stress is characterized by the use of large amounts of glucose, possibly posing at increased risk of ketoacidosis. However, fasting related perioperative ketosis seems not to pose at increased risk of acidosis.[53] A recent study reports a VLCKD to be interrupted the day before surgery in 44 prebariatric patients, but no safety outcomes are shown.[51] Of note, a recent case report showed that the concomitant use of SGLT-2 inhibitors and VLCKD consumption in a diabetic patient undergoing surgery led to recurrent intraoperative *torsade de pointes*.[24] Moreover, preoperative VLCD has been shown to induce hypovolaemia possibly increasing the risk of perioperative complications in a study including 28 prebariatric patients.[52] However, data relative to the treatment intervention and timing are insufficient to draw conclusions on such outcome.

Although there is not enough evidence to confirm reduced safety outcomes in this particular situation, it is reasonable to conclude that a KD should be interrupted for some time while foreseeing elective surgery or invasive procedures, and adequate fluid repletion has to be ensured.

3.13 | Malignancy

Obesity is a well-established risk factor for many cancer types,[102] and long-term survival following tumour resection/treatment is increasingly observed. However, a diagnosis of malignancy is listed as a contraindication to KDs according to some[7] but not all recommendations.[5] This is possibly due to the growing evidence emerged in

between suggesting a beneficial effect of nutritional ketosis during, before and after cancer treatment, without significant adverse events being reported.[54] Of note, the KD stands in line with current nutritional recommendations of the American Institute for cancer Research (AIRC) and the American Cancer Society regarding the avoidance of refined grains, alcohol, and sugary drinks, and not in line relative to the consumption of fresh fruits, whole grain and legumes.[103] It should be acknowledged that preclinical evidence suggests a possible detrimental effect of an HFKD on melanoma and kidney cancer outcomes.[55] Therefore, KD consumption should be discouraged in those affected by these solid tumours until further evidence emerges. For other cancer types, ad libitum KD rather than VLCKD is usually best, unless rapid weight loss is advisable for specific reasons.

3.14 | Increased serum uric acid and abnormal lipid profile

Hyperuricaemia and dyslipidaemia are co-morbidities commonly seen in subjects seeking a KD for weight loss purposes, but they may be exacerbated by it due to the relative increase in protein intake and the variable dietary fat depending on the approach to achieve nutritional ketosis, despite not being listed as absolute contraindications according to available recommendations. However, it has been reported that both HFKD and VLCKD might lead to mild worsening short term, progressing to significant improvement or no change in most patients, possibly due to subsequent weight loss and insulin resistance amelioration in those with overweight or obesity,[56–58] whereas sustained hypercholesterolaemia and hypertriglyceridaemia are observed in lean subjects undergoing an HFKD for the treatment of refractory epilepsy.[59] Overall, extra caution should be paid when considering this nutritional intervention not for weight loss purposes in those with baseline metabolic abnormalities and no weight excess, or in the case of refractory epilepsy, where treatment might be considered long-term and macronutrient ratio is strongly hyper lipidic.

3.15 | Rare disorders

Carnitine deficiency, carnitine palmitoyl-transferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders and pyruvate carboxylase deficiency are conditions characterized by defective ketogenesis. Where individuals with no such disorder, under frank reduction of carbohydrate intake would mobilize fat depots leading to ketogenesis, patients affected by these rare disorders would eventually experience hypoglycaemia, coma and ultimately death.[104–106]

Finally, subjects with acute intermittent porphyria should avoid the KD as the lack of carbohydrates in is a well-known precipitating factor causing relapse of the condition.[107]

4 | DISCUSSION

Nutritional ketosis, although long known to be an effective treatment for refractory epilepsy, has only recently gained broad attention thanks to the several emerging applications ranging from obesity to type 2 diabetes and neurologic disorders.[5] However, its absolute contraindications according to the currently available scientific societies consensus and position papers may make patients potentially receiving significant benefit from it not candidate to such dietary intervention[5–7] (Table 2).

Some of these, such as pregnancy, breastfeeding and perioperative timing, find no reason in not being followed, given the short non-applicable time and the potential major adverse events that could develop. The presence of co-morbidities such as liver, kidney and respiratory failure, together with type 1 diabetes, should be addressed by specialists of the relative discipline and the patient be accurately assessed and monitored, with eventual treatment tailored and characterized by favourable cost-to-benefit ratio. The KD might ultimately find an indication in the treatment of cardio- and cerebrovascular injury within a few years should current evidence be confirmed, despite these conditions being at present defined as absolute contraindications to the KD. Up until then, an adequately experienced cardiologist/neurologist should take the lead deciding on a patient-to-patient basis. The application to fragile subjects such as the elderly, those with a history of mental disorder, eating behaviour or substance abuse must benefit from an appropriate support in the daily routine for the KD to be potentially considered as a feasible treatment for concomitant conditions. Finally, further, specifically targeted studies are needed to assess whether KD consumption may influence wound healing, infections resolution or chronic organ damage, to better understand if its use might not be contraindicated in these frail patients.

Upon critical revision of the current state of the art, it emerges that most studies are low quality, sample size often very small, and duration usually quite short, making no definitive conclusion possibly be drawn. However, it seems reasonable to say that many alerts are cautionary in the attempt of protecting fragile populations, rather than being based on actual evidence supporting the risk of inducing serious adverse events, or recent evidence has proven them questionable. Overall, as the KD is comparable in efficacy to pharmacological interventions, and is similarly not devoid of adverse events if not coupled with proper care, it deserves very careful management, and its prescription should therefore be in the hands of adequately skilled medical doctors, who, while keeping in mind current recommendations, possess the necessary knowledge to putting them into the context of the single individual being evaluated.

ACKNOWLEDGEMENTS

Laboratoire Therascience s.a.m. made funding available for publication charges. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

CONFLICT OF INTEREST

The authors declare no competing interest.

ORCID

Mikiko Watanabe https://orcid.org/0000-0003-2225-8814
Dario Tuccinardi https://orcid.org/0000-0002-9139-7159
Ilaria Ernesti https://orcid.org/0000-0002-6711-5115
Alfredo Genco https://orcid.org/0000-0001-9702-8998
Lucio Gnessi https://orcid.org/0000-0001-8217-2372

REFERENCES

1. Phinney SD, Bistrian BR, Wolfe RR, Blackburn GL. The human metabolic response to chronic ketosis without caloric restriction: physical and biochemical adaptation. *Metabolism*. 1983;32(8):757-768.
2. Yancy WS Jr, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med*. 2004;140(10):769-777.
3. Terzikhan N, Doets EL, Vonk N-SM. Extensive literature search and review as preparatory work for the evaluation of the essential composition of total diet replacement products for weight control. *EFSA Supporting Publications*. 2015:EN-590.
4. Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metab*. 2017;25(2):262-284.
5. Caprio M, Infante M, Moriconi E, et al. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE). *J Endocrinol Invest*. 2019;42(11):1365-1386.
6. Pezzana A, Amerio ML, Fatati G, et al. La dieta chetogenica—fondazione ADI: position paper. *ADI*. 2014;6:38-43.
7. Chang J, Kashyap SR. The protein-sparing modified fast for obese patients with type 2 diabetes: what to expect. *Cleve Clin J Med*. 2014;81(9):557-565.
8. Temmerman JC, Friedman AN. Very low calorie ketogenic weight reduction diet in patients with cirrhosis: a case series. *Nutr Diabetes*. 2013;3(11):e95.
9. Watanabe M, Tozzi R, Risi R, et al. Beneficial effects of the ketogenic diet on nonalcoholic fatty liver disease: a comprehensive review of the literature. *Obes Rev*. 2020;21:e13024.
10. Bruci A, Tuccinardi D, Tozzi R, et al. Very low-calorie ketogenic diet: a safe and effective tool for weight loss in patients with obesity and mild kidney failure. *Nutrients*. 2020;12(2):E333
11. Friedman AN, Chambers M, Kamendulis LM, Temmerman J. Short-term changes after a weight reduction intervention in advanced diabetic nephropathy. *Clin J am Soc Nephrol*. 2013;8(11):1892-1898.
12. Lassemillante AM, Oliver V, Hickman I, Murray E, Campbell KL. Meal replacements as a strategy for weight loss in obese hemodialysis patients. *Hemodial Int*. 2016;20(4):E18-E23.
13. Vernon MC, Mavropoulos J, Transue M, Yancy WS, Westman EC. Clinical experience of a carbohydrate-restricted diet: effect on diabetes mellitus. *Metab Syndr Relat Disord*. 2003;1(3):233-237.
14. Leow ZZX, Guelfi KJ, Davis EA, Jones TW, Fournier PA. The glycaemic benefits of a very-low-carbohydrate ketogenic diet in adults with type 1 diabetes mellitus may be opposed by increased hypoglycaemia risk and dyslipidaemia. *Diabet Med*. 2018;35(9):1258-1263.
15. Bonikowska K, Magnusson P, Sjoholm A. Life-threatening ketoacidosis in patients with type 2 diabetes on LCHF diet. *Lakartidningen*. 2018;115:E4AD.
16. Tougaard NH, Faber J, Eldrup E. Very low carbohydrate diet and SGLT-2-inhibitor: double jeopardy in relation to ketoacidosis. *BMJ Case Rep*. 2019;12:e227516.
17. Yamamoto M, Ide N, Kitajima S, et al. Risk of euglycemic diabetic ketoacidosis due to low-carbohydrate diet while taking empagliflozin: a case report. *Yakugaku Zasshi*. 2019;139(11):1479-1483.
18. Dorcely B, Nitis J, Schwartzbard A, Newman J, Goldberg I, Sum M. A case report: euglycemic diabetic ketoacidosis presenting as chest pain in a patient on a low carbohydrate diet. *Curr Diabetes Rev*. 2020. [Epub ahead of print].
19. Thiruvenkatarajan V, Meyer EJ, Nanjappa N, Van Wijk RM, Jesudason D. Perioperative diabetic ketoacidosis associated with sodium-glucose co-transporter-2 inhibitors: a systematic review. *Br J Anaesth*. 2019;123(1):27-36.
20. van der Louw EJ, Williams TJ, Henry-Barron BJ, et al. Ketogenic diet therapy for epilepsy during pregnancy: a case series. *Seizure*. 2017;45:198-201.
21. Al Alawi AM, Falhammar H. Lactation ketoacidosis: case presentation and literature review. *BMJ Case Rep*. 2018;2018:bcr-2017.
22. Isner JM, Sours HE, Paris AL, Ferrans VJ, Roberts WC. Sudden, unexpected death in avid dieters using the liquid-protein-modified-fast diet. Observations in 17 patients and the role of the prolonged QT interval. *Circulation*. 1979;60(6):1401-1412.
23. Seim HC, Mitchell JE, Pomeroy C, de Zwaan M. Electrocardiographic findings associated with very low calorie dieting. *Int J Obes Relat Metab Disord*. 1995;19:817-819.
24. Crawford EJ, Cochran D. Recurrent torsades de pointes in association with a very low calorie diet. *Anaesthesia*. 2009;64(8):903-907.
25. Seshadri P, Samaha FF, Stern L, Chicano KL, Daily DA, Iqbal N. Free fatty acids, insulin resistance, and corrected qt intervals in morbid obesity: effect of weight loss during 6 months with differing dietary interventions. *Endocr Pract*. 2005;11(4):234-239.
26. Ozdemir R, Guzel O, Kucuk M, et al. The impact of 3:1 ketogenic diet on cardiac repolarization changes in children with refractory seizures: a prospective follow-up study. *Neuropediatrics*. 2016;47(3):157-161.
27. Bank IM, Shemie SD, Rosenblatt B, Bernard C, Mackie AS. Sudden cardiac death in association with the ketogenic diet. *Pediatr Neurol*. 2008;39(6):429-431.
28. Sirikonda NS, Patten WD, Phillips JR, Mullett CJ. Ketogenic diet: rapid onset of selenium deficiency-induced cardiac decompensation. *Pediatr Cardiol*. 2012;33(5):834-838.
29. Zhang S, Zhuang X, Lin X, et al. Low-carbohydrate diets and risk of incident atrial fibrillation: a prospective cohort study. *J am Heart Assoc*. 2019;8(9):e011955.
30. Shaafi S, Mahmoudi J, Pashapour A, et al. Ketogenic diet provides neuroprotective effects against ischemic stroke neuronal damages. *Adv Pharm Bull*. 2014;4:479-481.
31. Yang Q, Guo M, Wang X, et al. Ischemic preconditioning with a ketogenic diet improves brain ischemic tolerance through increased extracellular adenosine levels and hypoxia-inducible factors. *Brain Res*. 1667;2017:11-18.
32. Yu Y, Yu Y, Zhang Y, Zhang Z, An W, Zhao X. Treatment with D-beta-hydroxybutyrate protects heart from ischemia/reperfusion injury in mice. *Eur J Pharmacol*. 2018;829:121-128.
33. Takahashi S, Iizumi T, Mashima K, Abe T, Suzuki N. Roles and regulation of ketogenesis in cultured astroglia and neurons under hypoxia and hypoglycemia. *ASN Neuro*. 2014;6(5):175909141455099.
34. Xu K, Ye L, Sharma K, et al. Diet-induced ketosis protects against focal cerebral ischemia in mouse. *Adv Exp Med Biol*. 2017;977:205-213.
35. Shaafi S, Sharifi-Bonab M, Ghaemian N, Mokhtarkhani M, Akbari H. Early motor-behavioral outcome of ischemic stroke with ketogenic

diet preconditioning: interventional animal study. *J Stroke Cerebrovasc Dis*. 2019;28(4):1032-1039.
36. Tai KK, Nguyen N, Pham L, Truong DD. Ketogenic diet prevents cardiac arrest-induced cerebral ischemic neurodegeneration. *J Neural Transm (Vienna)*. 2008;115:1011-1017.
37. Liu J, Wang P, Zou L, et al. High-fat, low-carbohydrate diet promotes arrhythmic death and increases myocardial ischemia-reperfusion injury in rats. *Am J Physiol Heart Circ Physiol*. 2014;307(4):H598-H608.
38. Nielsen R, Moller N, Gormsen LC, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. *Circulation*. 2019;139(18):2129-2141.
39. Cai B, Zhu Y, Ma Y, et al. Effect of supplementing a high-fat, low-carbohydrate enteral formula in COPD patients. *Nutrition*. 2003;19(3):229-232.
40. Al-Saady NM, Blackmore CM, Bennett ED. High fat, low carbohydrate, enteral feeding lowers $PaCO_2$ and reduces the period of ventilation in artificially ventilated patients. *Intensive Care Med*. 1989;15:290-295.
41. van den Berg B, Bogaard JM, Hop WC. High fat, low carbohydrate, enteral feeding in patients weaning from the ventilator. *Intensive Care Med*. 1994;20(7):470-475.
42. Kwan RM, Thomas S, Mir MA. Effects of a low carbohydrate isoenergetic diet on sleep behavior and pulmonary functions in healthy female adult humans. *J Nutr*. 1986;116(12):2393-2402.
43. Tirlapur VG, Mir MA. Effect of low calorie intake on abnormal pulmonary physiology in patients with chronic hypercapneic respiratory failure. *Am J Med*. 1984;77(6):987-994.
44. Kwan R, Mir MA. Beneficial effects of dietary carbohydrate restriction in chronic cor pulmonale. *Am J Med*. 1987;82(4):751-758.
45. Schmidt M, Pfetzer N, Schwab M, Strauss I, Kammerer U. Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: a pilot trial. *Nutr Metab (Lond)*. 2011;8:54.
46. Urbain P, Strom L, Morawski L, et al. Impact of a 6-week non-energy-restricted ketogenic diet on physical fitness, body composition and biochemical parameters in healthy adults. *Nutr Metab (Lond)*. 2017;14:17.
47. Kossoff EH, McGrogan JR, Bluml RM, et al. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia*. 2006;47(2):421-424.
48. Pekkarinen T, Mustajoki P. Use of very low-calorie diet in preoperative weight loss: efficacy and safety. *Obes Res*. 1997;5(6):595-602.
49. Tanaka S, Isoda F, Ishihara Y, Kimura M, Yamakawa T. T lymphopaenia in relation to body mass index and TNF-alpha in human obesity: adequate weight reduction can be corrective. *Clin Endocrinol (Oxf)*. 2001;54(3):347-354.
50. Goldberg EL, Molony RD, Kudo E, et al. Ketogenic diet activates protective gammadelta T cell responses against influenza virus infection. *Sci Immunol*. 2019;4(41):eaav2026.
51. Sivakumar J, Chong L, Ward S, Sutherland TR, Read M, Hii MW. Body composition changes following a very-low-calorie preoperative diet in patients undergoing bariatric surgery. *Obes Surg*. 2020;30(1):119-126.
52. Poso T, Kesek D, Aroch R, Winso O. Rapid weight loss is associated with preoperative hypovolemia in morbidly obese patients. *Obes Surg*. 2013;23(3):306-313.
53. Ohkawa H, Iwakawa T, Ohtomo N, et al. Clinical study on intraoperative hyperketonemia in non-diabetic surgical patients under general anesthesia. *Masui*. 1993;42:1803-1807.
54. Klement RJ, Brehm N, Sweeney RA. Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes. *Med Oncol*. 2020;37(2):14.
55. Weber DD, Aminazdeh-Gohari S, Kofler B. Ketogenic diet in cancer therapy. *Aging (Albany NY)*. 2018;10(2):164-165.
56. Li Z, Tseng CH, Li Q, et al. Clinical efficacy of a medically supervised outpatient high-protein, low-calorie diet program is equivalent in prediabetic, diabetic and normoglycemic obese patients. *Nutr Diabetes*. 2014;4(2):e105.
57. Castellana M, Conte E, Cignarelli A, et al. Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: a systematic review and meta-analysis. *Rev Endocr Metab Disord*. 2019;21(1):5-16.
58. Hussain TA, Mathew TC, Dashti AA, Asfar S, al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition*. 2012;28(10):1016-1021.
59. Zamani GR, Mohammadi M, Ashrafi MR, et al. The effects of classic ketogenic diet on serum lipid profile in children with refractory seizures. *Acta Neurol Belg*. 2016;116(4):529-534.
60. Noureddin M, Vipani A, Bresee C, et al. NASH leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. *Am J Gastroenterol*. 2018;113(11):1649-1659.
61. Saunders J, Brian A, Wright M, Stroud M. Malnutrition and nutrition support in patients with liver disease. *Frontline Gastroenterol*. 2010;1(2):105-111.
62. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;70:172-193.
63. Spengler EK, O'Leary JG, Te HS, et al. Liver transplantation in the obese cirrhotic patient. *Transplantation*. 2017;101(10):2288-2296.
64. Fox CS, Larson MG, Leip EP, et al. Predictors of new-onset kidney disease in a community-based population. *JAMA*. 2004;291(7):844-850.
65. Ko GJ, Obi Y, Tortorici AR, Kalantar-Zadeh K. Dietary protein intake and chronic kidney disease. *Curr Opin Clin Nutr Metab Care*. 2017;20(1):77-85.
66. Kidney Disease Outcomes Quality I. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;43:S1-S290.
67. Lew QJ, Jafar TH, Koh HW, et al. Red meat intake and risk of ESRD. *J am Soc Nephrol*. 2017;28(1):304-312.
68. Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. *Eur J Clin Nutr*. 2003;57(10):1292-1294.
69. Jibani MM, Bloodworth LL, Foden E, Griffiths KD, Galpin OP. Predominantly vegetarian diet in patients with incipient and early clinical diabetic nephropathy: effects on albumin excretion rate and nutritional status. *Diabet Med*. 1991;8(10):949-953.
70. Rolland C, Mavroeidi A, Johnston KL, Broom J. The effect of very low-calorie diets on renal and hepatic outcomes: a systematic review. *Diabetes Metab Syndr Obes*. 2013;6:393-401.
71. Basciani S, Costantini D, Contini S, et al. Safety and efficacy of a multiphase dietetic protocol with meal replacements including a step with very low calorie diet. *Endocrine*. 2015;48(3):863-870.
72. American Diabetes A. 5. Lifestyle management: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Supplement 1):S46-S60.
73. Nusca A, Tuccinardi D, Albano M, et al. Glycemic variability in the development of cardiovascular complications in diabetes. *Diabetes Metab Res Rev*. 2018;34(8):e3047.
74. Nusca A, Tuccinardi D, Proscia C, et al. Incremental role of glycaemic variability over HbA1c in identifying type 2 diabetic patients with high platelet reactivity undergoing percutaneous coronary intervention. *Cardiovasc Diabetol*. 2019;18(1):147.
75. Kasichayanula S, Liu X, Lacreta F, Griffen SC, Boulton DW. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a

selective inhibitor of sodium-glucose co-transporter type 2. *Clin Pharmacokinet*. 2014;53(1):17-27.
76. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*. 2015;38(9):1638-1642.
77. Mahajan A, Donovan LE, Vallee R, Yamamoto JM. Evidenced-based nutrition for gestational diabetes mellitus. *Curr Diab Rep*. 2019;19 (10):94.
78. Watanabe M, Singhal G, Fisher FM, et al. Liver-derived FGF21 is essential for full adaptation to ketogenic diet but does not regulate glucose homeostasis. *Endocrine*. 2019;67(1):95-108.
79. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring)*. 2006;14(8):1283-1293.
80. Carella MJ, Mantz SL, Rovner DR, et al. Obesity, adiposity, and lengthening of the QT interval: improvement after weight loss. *Int J Obes Relat Metab Disord*. 1996;20(10):938-942.
81. Liu J, Wang P, Douglas SL, Tate JM, Sham S, Lloyd SG. Impact of high-fat, low-carbohydrate diet on myocardial substrate oxidation, insulin sensitivity, and cardiac function after ischemia-reperfusion. *Am J Physiol Heart Circ Physiol*. 2016;311(1):H1-H10.
82. Liu J, Lloyd SG. High-fat, low-carbohydrate diet alters myocardial oxidative stress and impairs recovery of cardiac function after ischemia and reperfusion in obese rats. *Nutr Res*. 2013;33(4):311-321.
83. Fromentin C, Tome D, Nau F, et al. Dietary proteins contribute little to glucose production, even under optimal gluconeogenic conditions in healthy humans. *Diabetes*. 2013;62(5):1435-1442.
84. Borghjid S, Feinman RD. Response of C57Bl/6 mice to a carbohydrate-free diet. *Nutr Metab (Lond)*. 2012;9(1):69.
85. Perrone-Filardi P, Paolillo S, Costanzo P, Savarese G, Trimarco B, Bonow RO. The role of metabolic syndrome in heart failure. *Eur Heart J*. 2015;36(39):2630-2634.
86. Aubert G, Martin OJ, Horton JL, et al. The failing heart relies on ketone bodies as a fuel. *Circulation*. 2016;133(8):698-705.
87. Bedi KC Jr, Snyder NW, Brandimarto J, et al. Evidence for Intramyocardial disruption of lipid metabolism and increased myocardial ketone utilization in advanced human heart failure. *Circulation*. 2016;133(8):706-716.
88. Mancuso P. Obesity and lung inflammation. *J Appl Physiol (1985)*. 2010;108:722-728.
89. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. *Nat Rev Endocrinol*. 2017;13(11):633-643.
90. Foster DJ, Ravikumar P, Bellotto DJ, Unger RH, Hsia CC. Fatty diabetic lung: altered alveolar structure and surfactant protein expression. *Am J Physiol Lung Cell Mol Physiol*. 2010;298(3):L392-L403.
91. Elliot JG, Donovan GM, Wang KCW, Green FHY, James AL, Noble PB. Fatty airways: implications for obstructive disease. *Eur Respir J*. 2019;54(6):1900857.
92. Grinberg N, Elazar S, Rosenshine I, Shpigel NY. Beta-hydroxybutyrate abrogates formation of bovine neutrophil extracellular traps and bactericidal activity against mammary pathogenic Escherichia coli. *Infect Immun*. 2008;76(6):2802-2807.
93. Zarrin M, Wellnitz O, van Dorland HA, Gross JJ, Bruckmaier RM. Hyperketonemia during lipopolysaccharide-induced mastitis affects systemic and local intramammary metabolism in dairy cows. *J Dairy Sci*. 2014;97(6):3531-3541.
94. Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. *Nat Rev Endocrinol*. 2018;14 (9):513-537.
95. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med*. 2011;17(2):97-107.
96. Chakravartty S, Vivian G, Mullholland N, et al. Preoperative liver shrinking diet for bariatric surgery may impact wound healing: a randomized controlled trial. *Surg Obes Relat Dis*. 2019;15(1):117-125.
97. Fulop M. Alcoholic ketoacidosis. *Endocrinol Metab Clin North am*. 1993;22(2):209-219.
98. Dencker D, Molander A, Thomsen M, et al. Ketogenic diet suppresses alcohol withdrawal syndrome in rats. *Alcohol Clin Exp Res*. 2018;42(2):270-277.
99. Castro AI, Gomez-Arbelaez D, Crujeiras AB, et al. Effect of a very low-calorie ketogenic diet on food and alcohol cravings, physical and sexual activity, sleep disturbances, and quality of life in obese patients. *Nutrients*. 2018;10(10):1348.
100. Desai BN, Singhal G, Watanabe M, et al. Fibroblast growth factor 21 (FGF21) is robustly induced by ethanol and has a protective role in ethanol associated liver injury. *Mol Metab*. 2017;6(11):1395-1406.
101. Dushay J, Chui PC, Gopalakrishnan GS, et al. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. *Gastroenterology*. 2010;139(2):456-463.
102. Eheman C, Henley SJ, Ballard-Barbash R, et al. Annual report to the nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer*. 2012;118(9):2338-2366.
103. Zick SM, Snyder D, Abrams DI. Pros and cons of dietary strategies popular among cancer patients. *Oncology (Williston Park)*. 2018;32 (11):542-547.
104. Fukao T, Mitchell G, Sass JO, Hori T, Orii K, Aoyama Y. Ketone body metabolism and its defects. *J Inherit Metab Dis*. 2014;37(4):541-551.
105. Olpin SE. Implications of impaired ketogenesis in fatty acid oxidation disorders. *Prostaglandins Leukot Essent Fatty Acids*. 2004;70(3): 293-308.
106. Stanley CA. Carnitine deficiency disorders in children. *Ann N Y Acad Sci*. 2004;1033(1):42-51.
107. Storjord E, Dahl JA, Landsem A, et al. Lifestyle factors including diet and biochemical biomarkers in acute intermittent porphyria: results from a case-control study in northern Norway. *Mol Genet Metab*. 2019;128(3):254-270.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Watanabe M, Tuccinardi D, Ernesti I, et al. Scientific evidence underlying contraindications to the ketogenic diet: An update. *Obesity Reviews*. 2020;21:e13053. https://doi.org/10.1111/obr.13053

Obesity Facts
The European Journal of Obesity

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721
Received: November 19, 2015
Accepted: November 24, 2015
Published online: December 5, 2015

1662–4033/15/0086–0402$39.50/0
www.karger.com/ofa

Karger Open access

Clinical Information

European Guidelines for Obesity Management in Adults

Volkan Yumuk[a] Constantine Tsigos[b] Martin Fried[c]
Karin Schindler[d] Luca Busetto[e] Dragan Micic[f]
Hermann Toplak[g] for the Obesity Management Task Force of the European Association for the Study of Obesity

[a]Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey; [b]Department of Nutrition and Dietetics, Harokopio University, Athens, Greece; [c]Clinical Center for Minimally Invasive and Bariatric Surgery, ISCARE Lighthouse, Prague and 1st Medical Faculty, Charles University, Prague, Czech Republic; [d]Department of Medicine III, Medical University of Vienna, Vienna, Austria; [e]Department of Medicine, Padova University Hospital – Bariatric Unit, University of Padova, Padova, Italy; [f]Centre for Metabolic Disorders in Endocrinology, Institute of Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade, Serbia; [g]Department of Medicine, Institute for Diabetes and Metabolism, Medical University, Graz, Austria

Key Words
European guidelines · Obesity management · Multidisciplinary · Primary care · OMTF · COMs

Abstract
Obesity is a chronic metabolic disease characterised by an increase of body fat stores. It is a gateway to ill health, and it has become one of the leading causes of disability and death, affecting not only adults but also children and adolescents worldwide. In clinical practice, the body fatness is estimated by BMI, and the accumulation of intra-abdominal fat (marker for higher metabolic and cardiovascular disease risk) can be assessed by waist circumference. Complex interactions between biological, behavioural, social and environmental factors are involved in regulation of energy balance and fat stores. A comprehensive history, physical examination and laboratory assessment relevant to the patient's obesity should be obtained. Appropriate goals of weight management emphasise realistic weight loss to achieve a reduction in health risks and should include promotion of weight loss, maintenance and prevention of weight regain. Management of co-morbidities and improving quality of life of obese patients are also included in treatment aims. Balanced hypocaloric diets result in clinically meaningful weight loss regardless of which macronutrients they emphasise. Aerobic training is the optimal mode of exercise for reducing fat mass while a programme including resistance train-

Prof. Dr. Volkan Yumuk
Division of Endocrinology, Metabolism and Diabetes
Department of Medicine, Istanbul University Cerrahpasa Medical Faculty
34098 Istanbul, Turkey
vdyumuk@istanbul.edu.tr

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

ing is needed for increasing lean mass in middle-aged and overweight/obese individuals. Cognitive behavioural therapy directly addresses behaviours that require change for successful weight loss and weight loss maintenance. Pharmacotherapy can help patients to maintain compliance and ameliorate obesity-related health risks. Surgery is the most effective treatment for morbid obesity in terms of long-term weight loss. A comprehensive obesity management can only be accomplished by a multidisciplinary obesity management team. We conclude that physicians have a responsibility to recognise obesity as a disease and help obese patients with appropriate prevention and treatment. Treatment should be based on good clinical care, and evidence-based interventions; should focus on realistic goals and lifelong multidisciplinary management.

Introduction

Obesity is a metabolic disease (ICD-10 code E66) that has reached epidemic proportions. The World Health Organization (WHO) has declared obesity as the largest global chronic health problem in adults which is increasingly turning into a more serious problem than malnutrition. Obesity is a gateway to ill health, and it has become one of the leading causes of disability and death, affecting not only adults but also children and adolescents worldwide [1]. In 2014, more than 1.9 billion adults (18 years and older) were overweight. Of these over 600 million were obese. 42 million children under the age of 5 were overweight or obese in 2013 [2]. The WHO world health statistics report in 2015 shows that in the European region the overall obesity rate among adults is 21.5% in males and 24.5% in females (fig. 1). The same report states that the prevalence for overweight among children under the age of 5 is 12.4% [3]. It has been further projected that 60% of the world's population, i.e. 3.3 billion people, could be overweight (2.2 billion) or obese (1.1 billion) by 2030 if recent trends continue [4]. Obesity has important consequences for morbidity, disability and quality of life and entails a higher risk of developing type 2 diabetes, cardiovascular diseases, several common forms of cancer, osteoarthritis and other health problems [5]. In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 4% of years of life lost, and 4% of disability-adjusted life years (DALYs) [6].

Definition and Classification

Obesity is a chronic disease characterised by an increase of body fat stores. In clinical practice, the body fatness is usually estimated by BMI. BMI is calculated as measured body weight (kg) divided by measured height squared (m^2). In adults (age over 18 years) obesity is defined by a BMI 30 kg/m^2 and overweight (also termed pre-obesity) by a BMI between 25 and 29.9 kg/m^2. Lower BMI cut-off points apply for some ethnic groups (e.g. Southeast Asians) [7, 8] (table 1) {level 1}. Accumulation of intra-abdominal fat is associated with higher metabolic and cardiovascular disease risk [7, 9] {level 1}. The amount of abdominal fat can be assessed by waist circumference (WC) which highly correlates with intra-abdominal fat content. The WC is measured in the horizontal plane midway in the distance of the superior iliac crest and the lower margin of the last rib. The most recent International Diabetes Federation (IDF) consensus defined central obesity (also known as visceral, android, apple-shaped or upper body obesity) in Europids as a WC of ≥94 cm in men and ≥80 cm in non-pregnant women. Lower cut-off points for central obesity are proposed for different ethnic groups [10] {level 4}.

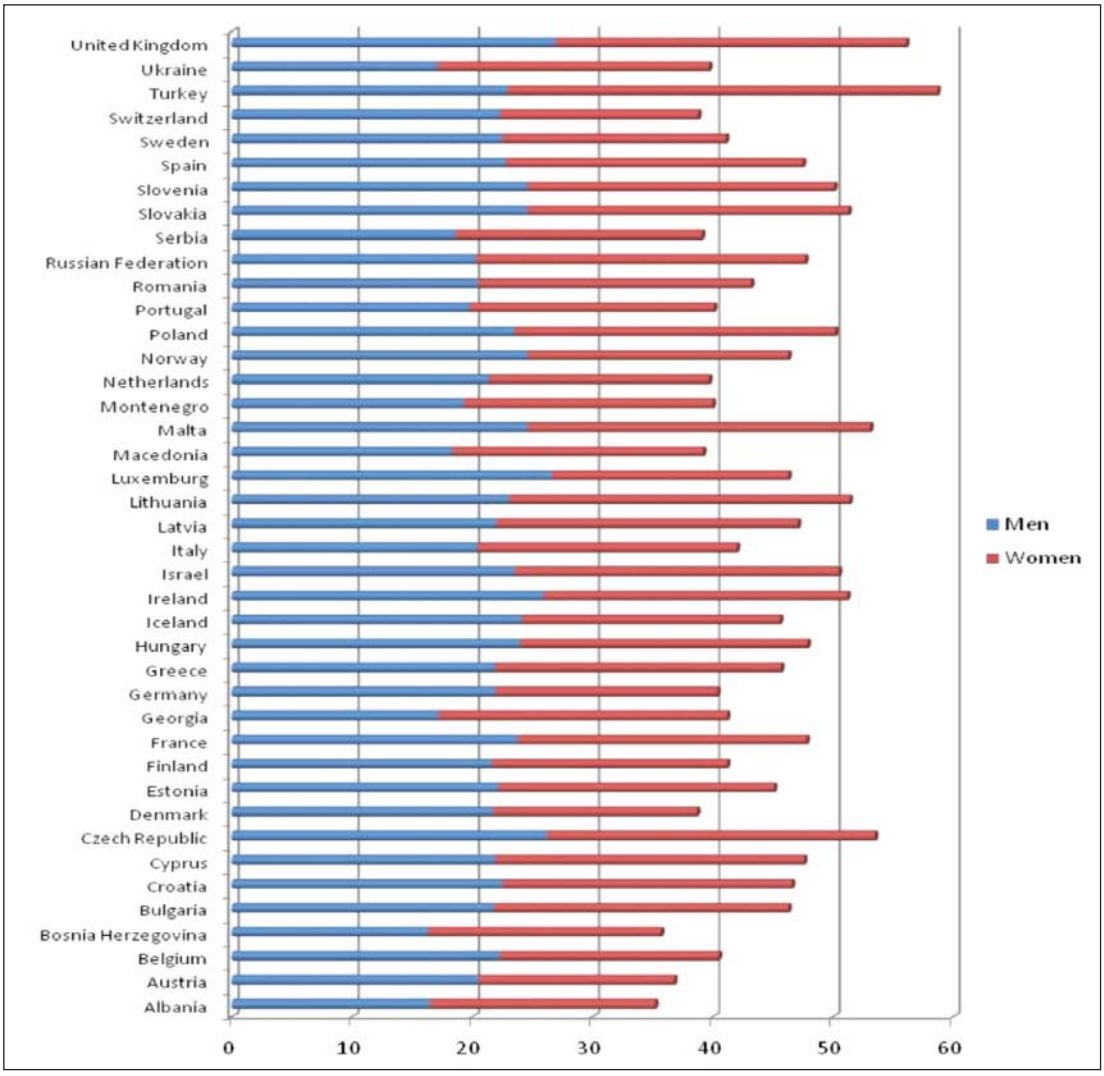


Fig. 1. Obesity prevalence in adults in Europe (Source: WHO 2014 data).

Table 1. BMI categories (WHO 1997)

Category	BMI, kg/m^2
Underweight	<18.5
Healthy weight	18.5–24.9
Pre-obese state	25.0–29.9
Obesity grade I	30.0–34.9
Obesity grade II	35.0–39.9
Obesity grade III	≥40

Pathogenesis of Obesity

The cause of obesity is complex and multifactorial [11, 12]. At the simplest level, obesity develops as a result of a period of chronic energy imbalance and is maintained by a continued elevated energy intake sufficient to maintain the acquired higher energy needs of the obese state. Complex interactions between biological (including genetic and epigenetic), behav-

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

ioural, social and environmental factors (including chronic stress) are involved in regulation of energy balance and fat stores [13, 14]. The rapid increase in the prevalence of obesity over the past 30 years is mainly a result of cultural and environmental influences. High energy density diet, increased portion size, low physical activity and adoption of a sedentary lifestyle as well as eating disorders are considered as important risk factors for the development of obesity [8, 15]. These behavioural and environmental factors lead to alterations in adipose tissue structure (hypertrophy and hyperplasia of adipocytes, inflammation) and secretion (e.g. adipokines) [16, 17]. Weight loss surgery has proven to be a convenient and proper research tool facilitating insights into the pathogenesis of obesity as well as regulation of hunger and satiation. Gut hormones communicate information from the gastrointestinal tract to the regulatory appetite centres within the CNS via the so-called 'gut-brain axis' [18, 19]. Obesity is associated with changes in the composition of the intestinal microbiota. Products of intestinal microbes may induce beneficial metabolic effects through enhancement of mitochondrial activity, prevention of metabolic endotoxaemia and activation of intestinal gluconeogenesis via different routes of gene expression and hormone regulation [20, 21]. The role of thermogenesis of brown adipose tissue and its contribution to energy expenditure is being investigated mainly to develop strategies to recruit and activate energy-dissipating brown adipose tissue as a preventive or remedial measure for weight control in obesity [22–24].

Clinical Evaluation of the Obese Patient

A comprehensive history, physical examination and laboratory assessment relevant to the patient's obesity should be obtained [25–27] {Recommended Best Practice (RBP)}.

History Taking

- Ethnicity
- Family history
- Dietary habits
- Physical activity frequency and nature
- Eating pattern and possible presence of an eating disorder (binge eating disorder, night eating syndrome, bulimia)
- Presence of depression and other mood disorders
- Other determinants, e.g., genetic, drugs, endocrine abnormalities, psychosocial factors, chronic stress, smoking cessation etc.
- Health consequences of obesity (table 2)
- Patient expectations and motivation for change
- Previous treatments for obesity.

Physical Examination

- Measure weight and height (from which BMI is calculated), WC, blood pressure (appropriate size cuff) {grade 3}
- Assess the presence and impact of obesity-related diseases (diabetes, hypertension, dyslipidaemia; cardiovascular, respiratory and joint diseases; non-alcoholic fatty liver disease (NAFLD), sleep disorders etc.) {RBP}
- Look for the presence of acanthosis nigricans as a sign of insulin resistance {RBP}.

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

Table 2. A guide to deciding the initial level of intervention to discuss with the patient

BMI, kg/m^2*	WC, cm*		Co-morbidities
	men < 94, women < 80	men ≥ 94, women ≥ 80	
25.0–29.9	L	L	L ± D
30.0–34.9	L	L ± D	L ± D±S**
35.0–39.9	L ± D	L ± D	L ± D ± S
≥40.0	L ± D ± S	L ± D ± S	L ± D ± S

L = Lifestyle intervention (diet and physical activity); D = consider drugs; S = consider surgery.

*BMI and waist circumference cut-off points are different for some ethnic groups.

**Patients with type 2 diabetes on individual basis.

Laboratory Examinations

The minimum data set required will include {RBP}:

- Fasting blood glucose
- Serum lipid profile (total, HDL and LDL cholesterol, triglycerides)
- Uric acid
- Thyroid function (thyroid-stimulating hormone (TSH) level)
- Liver function (hepatic enzymes)
- Cardiovascular assessment, if indicated {RBP}
- Endocrine evaluation if Cushing's syndrome or hypothalamic disease suspected
- Liver investigation (ultrasound, biopsy) if abnormal liver function tests suggest NAFLD or other liver pathology
- Sleep laboratory investigation for sleep apnoea.

Body Composition Analysis

WC can be used as a proxy for abdominal fat [9] {level 3; RBP}. With the development of devices and equipment to more accurately measure body fat, including dual energy X-ray absorptiometry (DEXA), air-displacement plethysmography (BodPod), bioimpedance analysis (BIA) and body scanning procedures – replacing the cumbersome underwater weighing –, it has become possible to more easily classify individuals according to the degree of body fat, independently of BMI. This approach has also drawn attention to the function of non-adipose tissue – that is, fat-free mass (FFM) or lean mass – and the contribution made by FFM to physiological functioning, pathology and well-being [28–30]. Assessment of body composition is not essential for the management of obesity in routine clinical practice, but may be a useful tool in measuring fat and FFM before and during treatment {RBP}.

Comprehensive Obesity Management

Appropriate goals of weight management emphasise realistic weight loss to achieve a reduction in health risks and should include promotion of weight loss, maintenance and prevention of weight regain (fig. 2) {RBP}. Patients should understand that, since obesity is a chronic disease, weight management will need to be continued lifelong.

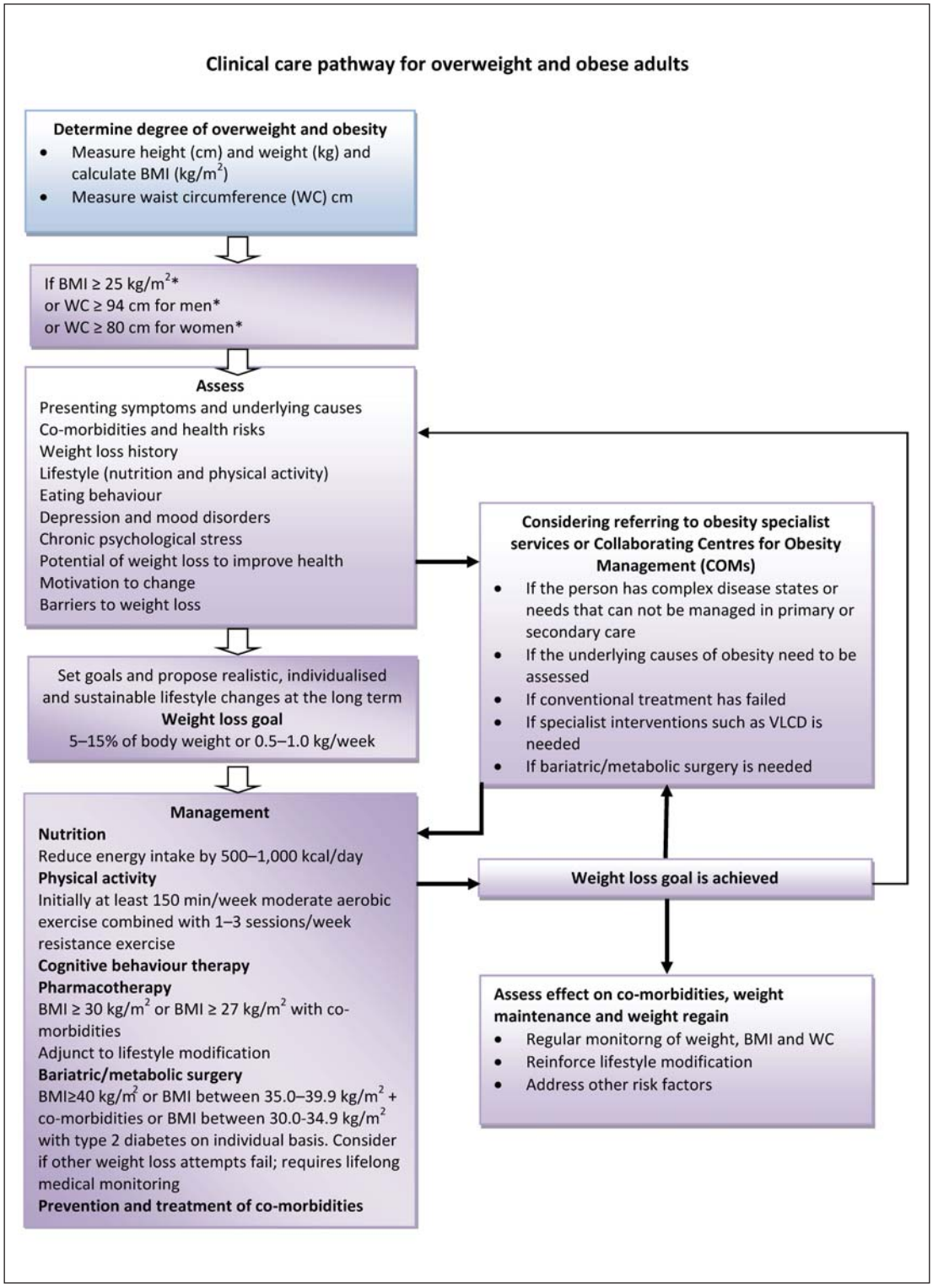


Fig. 2. Algorithm for the assessment and stepwise management of overweight and obese adults. *BMI and WC cut-off points are different for some ethnic groups (see text).

Aims of Treatment

The management and treatment of obesity (fig. 2) have wider objectives than weight loss alone and include risk reduction and health improvement. Significant clinical benefits may be achieved even by modest weight loss (i.e. 5–10% of initial body weight), and lifestyle modification (improved nutritional content of the diet and modest increases in physical activity and fitness) [31–34] {level 1}. Obesity management cannot focus only on weight (and BMI) reduction. More attention is to be paid to WC and the improvement in body composition which is focusing on ameliorating or maintaining FFM and decreasing fat mass [35].

Management of co-morbidities, improving quality of life and well-being of obese patients are also included in treatment aims. Appropriate management of obesity complications in addition to weight management should include management of dyslipidaemia, optimising glycaemic control in type 2 diabetic patients, normalising blood pressure in hypertension, management of pulmonary disorders such as sleep apnoea syndrome (SAS), attention to pain control and mobility needs in osteoarthritis, management of psychosocial disturbances including affective disorders, eating disorders, low self-esteem and body image disturbance. Obesity management may reduce the need to treat co-morbidities by drugs [36–38] {level 1; grade A}.

Prevention of Further Weight Gain

In overweight patients (BMI 25.0–29.9 kg/m^2) without overt co-morbidities, prevention of further weight gain (through dietary advice and increase in physical activity) rather than weight loss per se may be an appropriate target. Weight loss objectives should be realistic, individualised and aimed at the long term (table 3) {RBP}.

Practical Weight Loss Objectives

A 5–15% weight loss over a period of 6 months is realistic and of proven health benefit [39, 40] {level 1}. A greater (20% or more) weight loss may be considered for those with greater degrees of obesity (BMI ≥ 35 kg/m^2) {RBP}. Maintenance of weight loss and prevention and treatment of co-morbidities are the two main criteria for success.

Failure to Lose and Maintain Weight

Referral to an obesity specialist (or an obesity management team) should be considered if the patient fails to lose weight in response to the prescribed intervention (fig. 2). Weight cycling, defined by repeated loss and regain of body weight, is more frequent in women and may be linked to increased risk for hypertension, dyslipidaemia and gallbladder disease [41]. It has been associated with psychological distress and depression and may require appropriate psychological care and/or antidepressant therapy [42].

Patient Follow-Up

Obesity is a chronic disease. A follow-up and continued supervision is necessary [43] to prevent weight regain {level 2}, and to monitor disease risks and treat co-morbidities (e.g. type 2 diabetes mellitus, cardiovascular disease) {RBP}.

Table 3. Pharmacotherapy for obesity in Europe (November 2015) [71–74, 80]

Drugs	Status	Mechanism	Dosing	Response evaluation	Warnings	Contraindications	Side-effects
Orlistat	FDA & EMA approved	pancreatic, gastric lipase inhibitor	120 mg tid 60 mg tid (OTC)	2.9–3.4% 1 year	hepatitis, liver failure (rare), concomitant multivitamin advised	pregnancy, breast feeding, chronic malabsorption syndrome, cholestasis	decreased absorption of fat soluble vitamins, steatorrhoea, faecal urgency
Lorcaserin	FDA approved	5HT2c R agonist	10 bid	3.6% 1 year stop if <%5 weight loss at 12 weeks	serotonin syndrome, cognitive impairment, depression, valvulopathy hypoglycaemia, priapism	pregnancy, breast feeding, use with caution: MAOIs, SSRIs, SNRIs	headache, nausea dry mouth, dizziness fatigue, constipation
Phentermine/ topiramate	FDA approved	NE release (P) GABA modulation (T)	starting dose: 3.75/23 qd recommended dose: 7.5/46 qd *high dose: 15/92 qd	6.6% (recommended dose) 1 year 8.6% (high dose) 1 year stop if <%5 weight loss at 12 weeks	fetal toxicity, acute myopia, cognitive dysfunction, metabolic acidosis, hypoglycaemia	pregnancy, breast feeding, glaucoma, hyperthyroidism, use with caution: MAOIs	insomnia, dry mouth constipation, paresthesia, dizziness, dysgeusia
Bupropione/ naltrexone	FDA & EMA approved	DA/NE reuptake inhibitor(B) opioid antagonist (N)	8/90 mg tb 2 tb bid	4.8% 1 year stop if <%5 weight loss at 12 weeks	fetal toxicity, increased seizure risk, glaucoma, hepatoxicity	uncontrolled hypertension, seizure, anorexia nervosa / bulimia, drug or alcohol withdrawal, use with caution: MAO inhibitors	nausea, constipation, headache, vomiting, dizziness
Liraglutide	FDA & EMA approved	GLP-1 agonist	3 mg sc	5.8 kg 1 year stop if <%4 weight loss at 14 wks	acute pancreatitis, acute gall bladder disease	medullary thyroid cancer history, MEN type 2 history	nausea, vomiting, pancreatitis

FDA = Food & Drug Administration; EMA= European Medicinal Agency; OTC = over the counter; 5HT2c-R = 5 hydroxytryptamine 2c receptor; MAOI = monoamino oxidase ınhibitor; SSRI = selective serotonin reuptake ınhibitor; SNRI = serotonin norepinephrine reuptake ınhibitor; NE = norepinephrine; GABA = gamma amino butyric acid; DA = dopamine; GLP-1 = glucagon-like peptide-1; MEN = multiple endocrine neoplasia.

*Careful observation.

Obesity Facts
The European Journal of Obesity
Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

Specific Components of Treatment

Nutrition and Dieting

The use of self-recorded food diary allows a qualitative assessment of the diet. In addition, it can be used to help the patient identify meal frequency (night eating, snacking, meal skipping) perceptions and beliefs about emotional eating behaviour (cognition), eating habits (behaviour) and environmental challenges to following a healthy diet {RBP}.

Before giving dietary advice it might be useful to address motivation for change: How important is weight loss for the patients, and how confident the individual patient is to successfully and sustainably achieve body weight reduction [44, 45]? Dietary advice should encourage healthy eating and emphasise the need to increase consumption of vegetables, beans, legumes, lentils, grain, unsweetened cereals and fibre, and to substitute low-fat dairy products and meats for high-fat alternatives. It should also emphasise increased intake of seafood. It is recommended to avoid foods containing added sugars and solid fats, as well as consumption of sugary drinks and alcohol-containing beverages [37, 46–48] {level 1, 2}. An appropriate dietary regimen can be achieved in a number of ways:

General Advice {level 3, 4}

- Decrease energy density of foods and drinks
- Decrease the size of food portions
- Avoid snacking between meals
- Do not skip breakfast and avoid eating in the night time
- Manage and reduce episodes of loss of control or binge eating.

Specific Advice

Energy (calorie) restriction should be individualised and take account of nutritional habits, physical activity, co-morbidities and previous dieting attempts. Prescribing an energy-restricted diet may require the intervention of a nutritionist (dietitian) {RBP}. Balanced hypocaloric diets result in clinically meaningful weight loss regardless of which macronutrients they emphasise. An emphasis put on the macronutrient proportion in the various diets (low fat, low carbohydrate or high protein etc.) has not proved better than a balanced hypocaloric diet, except for low-glycaemic load diets (carbohydrate content of the diet × glycaemic index) in the short term [49–51] {level 1}. Despite various ranges of macronutrient composition, these diets have beneficial effects on reducing risk factors for cardiovascular disease and type 2 diabetes as well as on promoting adherence, diet acceptability and sustainability, satiety and satisfaction. Balanced hypocaloric diets can be tailored to individual patients on the basis of their personal and cultural preferences and may therefore have the best chance for long-term success (e.g. Mediterranean diet) [52, 53].

A 15–30% decrease in energy (calorie) intake from habitual intake in a weight-stable individual is sufficient and appropriate. However, underreporting of energy intake by obese patients is common. There is a great variation in energy requirements between the individuals which is dependent on the individual's gender, age, BMI and physical activity level. Tables predicting energy requirements taking into account gender, age, BMI and physical activity ratio can be used. An easy rule of thumb is a daily energy requirement of 25 kcal/kg for either gender but, for the same body weight, this creates a greater energy deficit in men. The recommended weight-reducing dietary regimen tailored to an individual's need usually provides an energy deficit of 600 kcal/day {grade A, B}. A 600 kcal (2,600 kJ) daily deficit will predict a weight loss of about 0.5 kg weekly. Thus for an obese sedentary woman with a BMI

of 32 kg/m^2 and with an estimated daily intake of 2,100 kcal (8,800 kJ), a diet prescribing 1,400–1,600 kcal (6,000–7,000 kJ) would be appropriate [50, 54] {level 2}.

Diets providing 1,200 kcal/day or more are classified as hypocaloric balanced diets (HBD) or balanced deficit diets [51]. Diets providing less than 1,200 kcal/day might yield micronutrient deficiencies, which could exert untoward effects not only on nutritional status but also on the weight management outcome. However in clinical practice a further reduction in caloric intake might be required. In this case the appropriate use of dietary supplements may prevent such nutritional deficits. In clinical practice low-calorie diets (LCDs) and very-low-calorie diets (VLCDs) are used. LCDs, consisting of normal meals and partial meal replacements, have an energy content between 800 and 1,200 kcal/day. VLCDs usually provide less than 800 kcal/day and may be used only as part of a comprehensive programme under the supervision of an obesity specialist or another physician trained in nutrition and dietetics. Their administration should be limited for specific patients and for short periods of time. VLCDs are unsuitable as a sole source of nutrition for children and adolescents, pregnant or lactating women and the elderly. Meal replacement diets (substitution of one or two daily meal portions by VLCD) may contribute to nutritionally well-balanced diet and weight loss maintenance [55–59] {level 2}.

Physical Activity

Exercise is considered an important component of a weight reduction programme in conjunction with caloric reduction. Several studies report additive benefits of combining exercise with caloric restriction on reducing body weight and body fat and preservation of FFM as compared to diet alone. In balancing time commitments against health benefits, it appears that aerobic training is the optimal mode of exercise for reducing fat mass and body mass while a programme including resistance training is needed for increasing lean mass in middle-aged and overweight/obese individuals [60, 61] {level 1; grade B}. However, if we limit the discussion to the outcome 'weight loss' or 'fat mass loss', only aerobic exercise has solid evidence supporting its efficacy in the literature. There is enough evidence which suggests that aerobic and resistance exercises are beneficial for patients with obesity and related morbidities. For this reason, all scientific guidelines recommend that at least 150 min/week of moderate aerobic exercise (such as brisk walking) should be combined with three weekly sessions of resistance exercise to increase muscle strength [60–62] {level 2; grade B}.

Increasing physical activity reduces intra-abdominal fat and increases lean (muscle and bone) mass {level 2}, while it attenuates the weight loss-induced decline of resting energy expenditure {level 2}, reduces blood pressure, improves glucose tolerance, insulin sensitivity, lipid profile and physical fitness {level 1}, ameliorates compliance to the dietary regimen, has a positive influence on the long-term weight maintenance {level 2}, improves feeling of well-being and self-esteem {level 2}, and reduces anxiety and depression {level 2} [63–65]. Further objectives should be to reduce sedentary behaviour (e.g. television viewing and computer use) and increase daily activities (e.g. walking or cycling instead of using a car, climbing stairs instead of using elevators). Patients should be advised and helped in undertaking (or increasing) physical activity [66, 67] {level 2; grade B}. Exercise advice must be tailored to the patient's ability and health and focus on a gradual increase to levels that are safe {RBP}.

Cognitive Behavioural Therapy

Cognitive Behavioural Therapy (CBT) is a blend of cognitive therapy and behavioural therapy and aims to help a patient modify his/her insight and understanding of thoughts and

beliefs concerning weight regulation, obesity and its consequences; it also directly addresses behaviours that require change for successful weight loss and weight loss maintenance. CBT includes several components such as self-monitoring (e.g. dietary record), techniques controlling the process of eating, stimulus control and re-enforcement as well as cognitive and relaxation techniques. CBT elements should form part of routine dietary management or, as a structured programme, form the basis of specialist intervention {grade B}. This care can be in part delivered in a group setting or using self-help manuals [68–70]. CBT can be provided not only by registered psychologists but also by other trained health professionals such as physicians, dieticians, exercise physiologists or psychiatrists {RBP}.

Psychological Support

Physicians should recognise where psychological or psychiatric issues interfere with successful obesity management, e.g. depression. Psychological support and/or treatment will then form an integral part of management; in special cases (anxiety, depression and stress), referral to a specialist may be indicated. Self-help lay groups and the support of the obesity treatment group may all be useful in this setting {RBP}.

Pharmacological Treatment

Pharmacological treatment should be considered as part of a comprehensive strategy of disease management [37, 71] {grade A}. Pharmacotherapy can help patients to maintain compliance, ameliorate obesity-related health risks and improve quality of life. It can also help to prevent the development of obesity co-morbidities (e.g. type 2 diabetes mellitus). Current drug therapy is recommended for patients with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with an obesity-related disease (e.g. hypertension, type 2 diabetes mellitus, sleep apnoea) [37] (table 2) {RBP}. Drugs should be used according to their licensed indications and restrictions {RBP}. The efficacy of pharmacotherapy should be evaluated after the first 3 months. If weight loss achieved is satisfactory (>5% weight loss in non-diabetic and >3% in diabetic patients), treatment should be continued [37, 71–74] {grade A}. Treatment should be discontinued in non-responders (table 3) {RBP}.

Orlistat

Orlistat is a potent and selective inhibitor of pancreatic lipase that reduces intestinal digestion of fat. The drug is available over the counter at a dose of 60 mg and a prescription dosage of 120 mg. Both forms are given before each meal and produce a moderate absolute and placebo-subtracted weight loss [71–74]. The efficacy and safety of the drug were assessed in the following RCTs: XENDOS [75] and X-PERT [76]. Faecal fat loss and related gastrointestinal symptoms are common. It may causes small decreases in fat-soluble vitamins; thus a multivitamin can be prescribed [77].

Lorcaserin

Lorcaserin is a serotonin type 2C receptor agonist with hypophagic effects [78]. Lorcaserin has been available in the USA since June 2013. The recommended dose is 10 mg twice daily. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74, 79, 80]. The efficacy and safety of the drug were assessed in the following RCTs: BLOOM [81], BLOOM-DM [82] and BLOSSOM [83]. In the BLOOM-DM trial, both fasting blood glucose and haemoglobin A1C

(HbA1c) levels were improved. No statistically significant differences in the incidence of cardiac valvulopathy between the placebo and lorcaserin groups were found [82, 84]. The most common adverse events associated with lorcaserin included blurred vision, dizziness, somnolence, headache, gastrointestinal disturbance and nausea. The results of the ongoing cardiovascular outcomes trial CAMELLIA TIMI 61 will determine the role of lorcaserin in primary prevention of diabetes in overweight/obese individuals and its use in the high-risk population of patients with established cardiovascular disease or multiple cardiovascular risk factors [85, 86].

Phentermine/Topiramate

Phentermine and extended-release topiramate (PHEN/TPM-ER) is based on the principle of a synergistic combination of two drugs at a lower dose to obtain efficacy with less toxicity. Phentermine is an atypical amphetamine analogue that suppresses appetite by norepinephrine agonism in the CNS. Topiramate is an atypical anticonvulsant drug previously evaluated as a potential anti-obesity drug after reports of weight loss occurring in epileptic patients taking this drug. The mechanisms by which topiramate induces a weight loss are unknown and may include carbonic anhydrase inhibition of taste or influences on GABA transmission, thus reducing appetite [87]. After approval by the Food and Drug Administration (FDA), the drug was launched in the USA in September 2012. The recommended dosage is 7.5 mg phentermine / 46 mg topiramate once a day. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74]. The efficacy and safety of the drug were assessed in the following RCTs: EQUIP [88], CONQUER [89], SEQUEL [90] and EQUATE [91]. Adverse events associated with PHEN/TPM-ER treatment were dry mouth, constipation, insomnia, palpitations, dizziness, paraesthesia, disturbances in attention, metabolic acidosis and renal calculi, headache, dysgeusia (distortion of sense of taste), alopecia and hypokalaemia [71–74, 92]. The combination is contraindicated during pregnancy due to its teratogenic potential. The FORTRESS (Fetal Outcome RetrospectiveTopiRamate Exposure Study) has estimated that women taking this combination had a two times increased risk of giving birth to children with oral clefts when compared to non-users. Owing to this risk, the drug has been approved with a risk evaluation and mitigation strategy recommendation by the FDA [93].

Bupropion/Naltrexone

Bupropion/naltrexone combines two centrally acting medications that had already been approved. Bupropion is used for treating depression and to aid smoking cessation. It is a non-selective inhibitor of the dopamine and norepinephrine transporters. Naltrexone is an opioid receptor antagonist widely used to treat alcohol and opiate dependence syndromes. The anorectic effect of the bupropion/naltrexone combination is believed to result from activation of POMC neurons in the arcuate nucleus. POMC neurons release a melanocyte stimulating hormone (α-MSH), which is a potent anorectic feeding neuropeptide, and these neurons project to other hypothalamic areas involved in feeding and body weight control. After approval by the FDA and the European Medicinal Agency (EMA), the drug is available in the USA since September 2012 and will be launched in Europe in approximately mid-2016. The recommended dosage is 16 mg naltrexone / 180 mg bupropion twice a day. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74, 94]. The efficacy and safety of the drug were assessed in the following RCTs: COR-I [95], COR-II [96], COR-BMOD [97] and COR-DM [98]. The most common reported adverse event was nausea, which in most cases was transient for the first few weeks of treatment. Along with nausea, headache, dizziness, insomnia and

vomiting were the most common adverse events that led to discontinuation [94]. The Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects with Cardiovascular Risk Factors (The Light Study) is still ongoing [99].

Liraglutide

Liraglutide is an injectable long-acting GLP-1R agonist designed to resist rapid metabolism by dipeptidyl peptidase-IV. While glucose-induced insulin release is stimulated, the glucagon response is reduced and appetite suppressed with additional effects on gastric emptying [100]. It has already successfully been introduced in type 2 diabetic patients (1.2–1.8 mg) once daily. After approval by the FDA and EMA, the drug (in a dosage of 3 mg once daily) was launched for obesity treatment in the USA in November 2014 and in Europe in March 2015. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74, 101–104]. The efficacy and safety of the drug were assessed in the following RCTs: SCALE-Maintenance [105], SCALE-Obesity [106] and LEADER [107–109]. Liraglutide is generally well tolerated. Nausea and vomiting are the main, usually transient, side-effects, but they may actively contribute to weight loss [110].

Bariatric and Metabolic Surgery

Surgery is the most effective treatment for morbid obesity in terms of long-term weight loss, improvements of co-morbidities and quality of life and decreases of overall mortality [111–115]. A comprehensive overview of surgical treatment options for obesity and obesity-related co-morbidities is provided in the Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery, published in 2013 by joint effort of the European Association for the Study of Obesity (EASO), and the International Federation for the Surgery of Obesity and Metabolic Disorders – European Chapter (IFSO-EC) [116]. Surgery should be considered for patients aged 18–60 years with a BMI ≥40.0 kg/m^2 or with BMI between 35.0 and 39.9 kg/m^2 and co-morbidities, in whom surgically induced weight loss is expected to improve the disorder (such as type 2 diabetes and other metabolic disorders, cardiorespiratory disease, severe joint disease and obesity-related severe psychological problems). BMI criterion may be the current BMI or a documented previous BMI of this severity [117].

Bariatric surgery is clearly confirmed to be beneficial in type 2 diabetes remission – at least in the short and medium term. Thus, patients with BMI >30 and <35 kg/m^2 with type 2 diabetes may also be considered for bariatric surgery on an individual basis, as there is evidence-based data supporting bariatric surgery benefits in regards to type 2 diabetes mellitus remission or improvement in this group [118–120] {level 1}.

Multidisciplinary skills are needed to support surgical interventions. Patients should only be referred to units able to assess patients prior to surgery, to offer a comprehensive approach to diagnosis, assessment and treatment, and to provide long-term follow-up. A decision to offer surgery should follow a comprehensive interdisciplinary assessment. The core team providing such assessment should optimally consist of the following specialists experienced in obesity management and bariatric surgery [121–123] {level 2}:

- Physician
- Surgeon
- Anaesthetist (anaesthesiologist)
- Psychologist or psychiatrist
- Nutritionist and/or dietitian, and
- Nurse practitioner/social worker.

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

Table 4. Obesity-related health risks and complications

I. Metabolic complications
Diabetes
insulin resistance
Dyslipidaemia
Metabolic syndrome
Hyperuricaemia
Gout
Low-grade inflammation
II. Cardiovascular disorders
Hypertension
Coronary heart disease
Congestive heart failure
Stroke
Venous thromboembolism
III. Respiratory disease
Asthma
Hypoxemia
Sleep apnoea syndrome
Obesity hypoventilation syndrome
IV. Cancers
Oesophagus, small intestine, colon, rectum, liver, gallbladder, pancreas, kidney, leukaemia, multiple myeloma, and lymphoma
In women: endometrial, cervix uteri, ovary, breast cancer after menopause
In men: prostate
V. Osteoarthritis
Knee and an increase in pain in the weight bearing joints
VI. Gastrointestinal
Gallbladder disease
Non-alcoholic fatty liver disease
Non-alcoholic steatohepatitis
Gastro-esophageal reflux
Hernia

Table 4 continued on next page

A laparoscopic technique should be considered as the first treatment choice in bariatric surgery. In all situations the bariatric surgeon's experience is a key issue for an immediate successful outcome. It is not advisable to perform bariatric techniques on an occasional basis [124] {level 1}. Morbid obesity is a lifelong disease. The treating physician and surgeon are responsible for the treatment of co-morbidities before the operation and for the follow-up after the operation. However, the patient takes lifelong responsibility for adhering to the follow-up rules {RBP}.

In the past several years, better understanding of substantial metabolic changes induced by different surgical interventions to the alimentary tract was achieved. Therefore, the former classification of operations according to their influence on food ingestion, defined as limiting stomach capacity (restrictive), limiting absorption of nutrients (malabsorptive) or combined procedures does not appropriately reflect the current level of knowledge about early and weight-independent metabolic effects of these operations. Nowadays, most of the standard surgical interventions are being mostly referred to as metabolic operations. The focus when treating obese patients is gradually shifting from the primary goal of weight loss outcomes to the metabolic effects of the operations [125–137] {levels 1, 2}.

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

Table 4 (continued)

VII. Genitourinary system /reproductive health
Urinary incontinence
Menstrual irregularity
İnfertility
Hirsutism
Polycystic ovary disease
Miscarriage
Gestational diabetes
Hypertension
Preeclampsia
Macrosomia
Foetal distress
Malformation (i.e. neural tube defect)
Dystocia and primary caesarean section
VIII. Psychological and social consequences
Low self-esteem
Anxiety and depression
Stigmatisation
Discrimination in employment, college acceptance, job earning etc.
IX. Miscellaneous
Idiopathic intracranial hypertension
Proteinuria
Nephrotic syndrome
Skin infection
Lymphoedema
Complications from anaesthesia
Periodontal disease

Treatment of Co-Morbidities

Active treatment of obesity-related co-morbidities (table 4) should be integral part of the comprehensive management of the obese patients. Appropriate management of obesity complications in addition to weight management should include [37, 138] {level 1, 2}:

- Management of dyslipidaemia
- Optimising glycaemic control in type 2 diabetics
- Normalising blood pressure in hypertension
- Management of pulmonary disorders, such as SAS
- Attention to pain control and mobility needs in osteoarthritis
- Management of psychosocial disturbances, including affective disorders, eating disorders, low self-esteem and body image disturbance.

The presence of obesity and the effects that treatments have on body weight, body composition or metabolic status should be taken into account in the selection of the drugs used to treat obesity-related co-morbidities or even non-obesity-related diseases occurring in a patient with obesity. Drugs increasing body weight and/or with negative metabolic effects should be possibly avoided or substituted. Weight-losing and weight-neutral medications should be preferred [73]. Specific guidelines for the management of hypertension in obese patients [139] have been released by the EASO in conjunction with the European Society of Hypertension.

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

Alternative Therapies

Obesity treatment has often been unsuccessful. As a result, unorthodox and unproven treatments flourish and are often offered. There is insufficient evidence to recommend in favour of herbal medicines, dietary supplements or homoeopathy for obesity management in the obese person. Physicians should advise patients to follow evidence-based treatments and recommend treatments only where evidence of safety and efficacy has been established {RBP}.

Collaborating Centre for Obesity Management

A comprehensive obesity management can only be accomplished by an appropriate obesity management team which is multidisciplinary and comprises different professionals who are able to tackle the different aspects of obesity and its related disorders. In accordance with this vision the EASO has developed a network of Collaborating Centres for Obesity Management. This European networking comprises education and training, research initiatives and contemporary obesity care [140].

Conclusion

Physicians have a responsibility to recognise obesity as a gateway disease and help patients with appropriate prevention and treatment schemes for obesity and its co-morbidities. Along with physicians all care givers have the same responsibility. Obesity care needs to be delivered by certified obesity experts in specialised and accredited obesity centres. Treatment should be based on good clinical care and evidence-based interventions and it should be individualised and multidisciplinary, focus on realistic goals, weight maintenance and prevention of weight regain. Everybody in the field, including the patients, should understand that, since obesity is a chronic disease, weight management will need to be lifelong.

Appendix

Levels of Evidence and Grades of Recommendation

The evidence for the guidance given is drawn from a number of systematic reviews listed in the references. The grading system is based upon the Scottish Intercollegiate Guidelines Network (SIGN), but has been simplified by amalgamating sub-categories of each level into a single criterion. No health-care system can provide treatment for all who are obese and overweight. Support groups, commercial and lay organisations, books and other media can provide useful help and support; the advice they give should conform to the principles of these guidelines (table 5) [141] {RBP}.

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

Table 5. Levels of evidence, grades of recommendation and good practice points

Levels of evidence		
1	1++	high-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
	1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2	2++	high-quality systematic reviews of case-control or cohort or studies
	2+	high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is casual
	2–	well-conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is casual
3	non-analytic studies, e.g. case reports, case series	
4	expert opinion	
Grades of recommendation		
A	at least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results	
B	a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++, or 1+	
C	a body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++	
D	evidence level 3 or 4; or extrapolated evidence from studies rated as 2+	
Good practice points		
RBP	recommended best practice based on the clinical experience of the guideline development group	

References

1 Frühbeck G, Toplak H, Woodward E, Yumuk V, Maislos M, Oppert JM: Obesity: the gateway to ill health – an EASO position statement on a rising public health, clinical and scientific challenge in Europe. Obes Facts 2013; 6:117–120.
2 World Health Organization: Obesity and Overweight. WHO fact sheet Nº 311, Geneva, WHO, 2015. *www.who.int/mediacentre/factsheets/fs311/en/* (last accessed November 30, 2015).
3 World Health Organization: World Health Statistics 2015. Geneva, WHO, 2015, pp 101–111. *www.who.int/gho/publications/world_health_statistics/2015/en/* (last accessed November 30, 2015).
4 Kelly T, Yang W, Chen CS, Reynolds K, He J: Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 2008;32:1431–1437.
5 Finer N: Medical consequences of obesity. Medicine 2015;43:88–93.
6 Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E: Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766–781.

7 WHO: Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. Geneva, WHO Technical Report Series 894, 2000.
8 James WP: The epidemiology of obesity: the size of the problem. J Intern Med 2008;263:336–352.
9 Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB: Waist circumference and Obesity associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. Am J Clin Nutr 2002;76:743–749.
10 Alberti KG, Zimmet PZ, Shaw J: The metabolic syndrome – a new worldwide definition. Lancet 2005;366: 1059–1062.
11 Yanovski SZ, Yanovski JA: Obesity. N Engl J Med 2002;346:591–602.
12 Haslam DW, James WP: Obesity. Lancet 2005;366:1197–1209.
13 Farooqi S, O'Rahilly S: Genetics of obesity in humans. Endocr Rev 2006;27:710–718.
14 Kyrou I, Chrousos GP, Tsigos C: Stress, visceral obesity, and metabolic complications. Ann N Y Acad Sci 2006; 1083:77–110.
15 Branca F, Nikogosian H, Lobstein T (eds): The challenge of Obesity in the WHO European Region and the Strategies for Response: Summary. Copenhagen, WHO Regional Office for Europe, 2007.
16 Ailhaud G: Adipose tissue as a secretory organ: from adipogenesis to the metabolic syndrome. C R Biol 2006; 329:570–577.
17 Tilg H, Moschen AR: Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772–783.
18 Buhmann H, le Roux CW, Bueter M: The gut brain axis in obesity. Best Pract Res Clin Gastroenterol 2014;28: 559–571.
19 Holtmann G, Talley NJ: The stomach brain axis. Best Pract Res Clin Gastroenterol 2014;28:967–979.
20 Gerard P: Gut microbiota and obesity. Cell Mol Life Sci 2015. DOI 10.1007/s00018–015–2061–5.
21 Tilg H, Adolph TE: Influence of the human intestinal microbiome on obesity and metabolic dysfunction. Curr Opin Pediatr 2015:27:496–501.
22 Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng Y-H, Doria A, Kolodny GM, Kahn R: Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360:1509–1517.
23 Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto N-J, Enerback S, Nuutila P: Functional brown adipose tissue in healthy adults. N Engl J Med 2009;360:1518–1525.
24 Butler PW, Mentuccia D, Celi FS: Stimulating brown fat: a potential future therapeutic approach for obesity and insulin resistance? Heart Metab 2010;48:19–22.
25 National Institutes of Health: The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, NIH, 2000. *www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf* (last accessed November 30, 2015).
26 National Institute for Health and care Excellence: Obesity: Identification, Assessment and Management of Overweight and Obesity in Children, Young People and Adults. London, NICE, 2014. *www.nice.org.uk/guidance/cg189* (last accessed November 30, 2015).
27 Kushner RF: Clinical assessment and management of adult obesity. Circulation 2012;126:2870–2877.
28 Silver HJ, Welch EB, Avison MJ, Niswender KD: Imaging body composition in obesity and weight loss: challenges and opportunities. Diabetes Metab Syndr Obes 2010;3:337–347.
29 Bolanowski M, Nilsson BE: Assessment of human body composition using dual-energy x-ray absorptiometry and bioelectrical impedance analysis. Med Sci Monit 2001;7:1029–1033.
30 Cornier M-A, Després J-P, Davis N, Grossniklaus DA, Klein S, Lamarche B, Lopez-Jimenez F, Rao G, St-Onge M-P, Towfighi A, Poirier P; on behalf of the American Heart Association Obesity Committee of the Council on Nutrition, Physical Activity and Metabolism, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Stroke Council: Assessing adiposity: a scientific statement from the American Heart Association. Circulation 2011;124:1996–2019.
31 Yumuk V, Frühbeck G, Oppert JM, Woodward E, Toplak H, for the Executive Committee of the European Association for the Study of Obesity: An EASO position statement on multidisciplinary obesity management in adults. Obes Facts 2014;7:96–101.
32 Slentz CA, Duscha BD, Johnson JL, Ketchum K,Aiken LB, Samsa GP, Houmard JA, Bales CW, Kraus WE: Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE – a randomized controlled study. Arch Intern Med 2004;164:31–39.
33 Pietrobelli A, Heymsfield SB: Establishing body composition in obesity. J Endocrinol Invest 2002;25:884–892.
34 Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.
35 Blundell JE, Dulloo AG, Salvador J, Frühbeck G, on behalf of the EASO SAB Working Group on BMI: Beyond BMI – phenotyping the obesities. Obes Facts 2014;7:322–328.

▶36 Schwarz PE, Lindström J, Kissimova-Scarbeck K,Szybinski Z, Barengo NC, Peltonen M, Tuomilehto J: The European perspective of type 2 diabetes prevention: diabetes in Europe – prevention using lifestyle, physical activity and nutritional intervention (DE-PLAN) project. Exp Clin Endocrinol Diabetes 2008;116:167–172.
▶37 Hainer V, Toplak H, Mitrakou A: Treatment modalities of obesity: What fits whom? Diabetes Care 2008; 31(suppl 2):S269–S277.
▶38 Sampsel S, May J: Assessment and management of obesity and comorbid conditions. Dis Manag 2007;1:252–265.
▶39 Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, Jordan HS, Kendall KA, Lux LJ, Mentor-Marcel R, Morgan LC, Trisolini MG, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society: 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2014;129(suppl 2): S102–S138. Erratum in Circulation 2014;129(suppl 2):S139–140.
40 World Health Organization: Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation (WHO Technical Report Series 894). Geneva, WHO, 1998. *www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/* (last accessed November 30, 2015).
▶41 Lahti-Koski M, Männistö S, Pietinen P, Vartiainen E: Prevalence of weight cycling and its relation to health indicators in Finland. Obes Res 2005;13:333–341.
▶42 Marchesini G, Cuzzolaro M, Mannucci E, DalleGrave R, Gennaro M, Tomasi F, Barantani EG, Melchionda N; QUOVADIS Study Group: Weight cycling in treatment-seeking obese persons: data from the QUOVADIS study. Int J Obes Relat Metab Disord 2004;28:1456–1462.
▶43 Anderson JW, Konz EC, Frederich RC, Wood CL: Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr 2001;74:579–584..
▶44 Christie D, Channon S: The potential for motivational interviewing to improve outcomes in the management of diabetes and obesity in paediatric and adult populations: a clinical review. Diabetes, Obes Metab 2014;16: 381–387.
▶45 Armstrong MJ, Mottershead TA, Ronksley PE, Sigal RJ, Campbell TS, Hemmelgarn BR: Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2011;12:709–723.
▶46 Dansinger ML, Tatsioni A, Wong JB, Chung M, Balk EM: Meta-analysis: the effect of dietary counseling for weight loss. Ann Intern Med 2007;147:41–50.
▶47 Astrup A, Grunwald GK, Melanson EL, Saris WH, Hill JO: The role of low-fat diets in body weight control: a meta-analysis of ad libitum dietary intervention studies. Int J Obes Relat Metab Disord 2000;24:1545–1552.
▶48 Pirozzo S, Summerbell C, Cameron C, Glasziou P: Advice on low-fat diets for obesity. Cochrane Database Syst Rev 2002;2:CD003640.
▶49 Sacks FM, Bray GA, Carey VJ, Smith SR, Ryan DH, Anton SD, McManus K, Champagne CM, Bishop LM, Laranjo N, Leboff MS, Rood JC, de Jonge L, Greenway FL, Loria CM, Obarzanek E, Williamson DA: Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859–873.
▶50 Larsen TM, Dalskov S-M, van Baak M, Jebb SA, Papadaki A, Pfeiffer AFH, Martinez JA, Handjieva-Darlenska T, Kunešová M, Pihlsgård M, Stender S, Holst C, Saris WHM, Astrup A, for the Diet, Obesity, and Genes (Diogenes) Project: Diets with high or low protein content and glycemic index for weight-loss maintenance. N Engl J Med 2010;363:2102–2113.
▶51 Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Bluher M, Stumvoll M, Stampfer MJ, for the Dietary Intervention Randomized Controlled Trial (DIRECT) Group: Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359: 229–241.
▶52 Dernini S, Berry EM: Mediterranean diet: from a healthy diet to a sustainable dietary pattern. Front Nutr 2015; 2:1–6.
▶53 Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA, for the PREDIMED Study Investigators: Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279–1290.
▶54 Ayyad C, Andersen T: Long-term efficacy of dietary treatment of obesity: a systematic review of studies published between 1931 and 1999. Obes Rev 2000;1:113–119.
▶55 Rössner S: Treatment: Diet; in Bjorntorp P(ed): International Textbook of Obesity. Sussex, Wiley & Sons, 2001, pp 441–449.
▶56 Dubnov-Raz G, Berry EM. The dietary treatment of obesity. Endocrinol Metab Clin N Am 2008;37:873–886.
▶57 Tsai AG, Wadden TA: The evolution of very-low-calorie diets: an update and meta-analysis. Obesity (Silver Spring) 2006;14:1283–1293.
▶58 Heymsfield SB, van Mierlo CA, van der Knaap HC,Heo M, Frier HI: Weight management using a meal replacement strategy: meta and pooling analysis from six studies. Int J Obes Relat Metab Disord 2003;27:537–549.

59 Greenwald A: Current nutritional treatments of obesity. Adv Psychosom Med 2006;27:24–41.
60 Willis LH, Slentz CA, Bateman LA, Shields AT, Piner LW, Bales CW, Houmard JA, Kraus WE: Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults. J Appl Physiol 2012;113:1831–1837.
61 Geliebter A, Christopher N, Ochner CN, Dambkowski CL, Hashim SA: Obesity-related hormones and metabolic risk factors: a randomized trial of diet plus either strength or aerobic training versus diet alone in overweight participants. J Diabetes Obes 2015;1:1–7.
62 Poirier P, Després JP: Exercise in weight management of obesity. Cardiol Clin 2001;19:459–470.
63 Kay SJ, Fiatarone Singh MA: The influence of physical activity on abdominal fat: a systematic review of the literature. Obes Rev 2006;7:183–200.
64 Lee S, Kuk JL, Davidson LE, Hudson R, Kilpatrick K, Graham TE, Ross R: Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without type 2 diabetes. J Appl Physiol 2005;99:1220–1225.
65 Ross R, Janssen I, Dawson J, Kungl AM, Kuk JL, Wong SL, Nguyen-Duy TB, Lee S, Kilpatrick K, Hudson R: Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. Obes Res 2004;12:789–798.
66 Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Church TS: The role of exercise and physical activity in weight loss and maintenance. Prog Cardiovasc Dis 2014;56:441–447.
67 Jakicic JM, Otto AD: Physical activity considerations for the treatment and prevention of obesity. Am J Clin Nutr 2005;82(suppl 1): 226S–229S.
68 Sharma M: Behavioural interventions for preventing and treating obesity in adults. Obes Rev 2007;8:441–449.
69 Lang A, Froelicher ES: Management of overweight and obesity in adults: behavioral intervention for long-term weight loss and maintenance. Eur J Cardiovasc Nurs 2006;5:102–114.
70 Moffitt R, Haynes A, Mohr P: Treatment beliefs and preferences for psychological therapies for weight management. J Clin Psychol 2015;71:584–596.
71 Toplak H, Woodward E, Yumuk V, Oppert JM, Halford JCG, Frühbeck G: 2014 EASO position statement on the use of anti-obesity drugs. Obes Facts 2015;8:166–174.
72 Pucci A, Finer N: New medications for treatment of obesity: metabolic and cardiovascular effects. Can J Cardiol 2015;31:142–152.
73 Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD: Pharmacological management of obesity: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342–362.
74 Bray GA: Medical treatment of obesity: the past, the present and the future. Best Pract Res Clin Gastroenterol 2014;28:665–684.
75 Torgerson JS, Hauptman J, Boldrin MN, Sjöström L: Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27:155–161.
76 Toplak H, Ziegler O, Keller U, Hamann A, Godin C, Wittert G, Zanella MT, Zúñiga-Guajardo S, Van Gaal L: X-PERT: weight reduction with orlistat in obese subjects receiving a mildly or moderately reduced-energy diet: early response to treatment predicts weight maintenance. Diabetes Obes Metab 2005;7:699–708.
77 Ballinger A, Peikin SR: Orlistat: its current status as an anti-obesity drug. Eur J Pharmacol 2002;440:109–117.
78 Thomsen WJ, Grottick AJ, Menzaghi F, Reyes-Saldana H, Espitia S, Yuskin D, Whelan K, Martin M, Morgan M, Chen W, Al-Shamma H, Smith B, Chalmers D, Behan D: Lorcaserin: a novel selective human 5-hydroxytryptamine 2C agonist: in vitro and in vivo pharmacological characterization. J Pharmacol Exp Ther 2008;325:577–587.
79 Chan EW, He Y, Chui CS, Wong AY, Lau WC, Wong IC: Efficacy and safety of lorcaserin in obese adults: a meta-analysis of 1-year randomized controlled trials (RCTs) and narrative review on short-term RCTs. Obes Rev 2013;14:383–392.
80 Fujioka K: Safety and tolerability of medications approved for chronic weight management. Obesity (Silver Spring) 2015;23(suppl 1):S7–S11.
81 Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, Bays H, Shanahan WR; Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group: Multicenter, placebo controlled trial of lorcaserin for weight management. N Engl J Med 2010;363:245–256.
82 O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, Raether B, Anderson CM, Shanahan WR: Randomized placebo controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012;20:1426–1436.
83 Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, Anderson CM; BLOSSOM Clinical Trial Group: A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab 2011;96:3067–3077.
84 Weissman NJ, Sanchez M, Koch GG, Smith SR, Shanahan WR, Anderson CM: Echocardiographic assessment of cardiac valvular regurgitation with lorcaserin from analysis of 3 phase 3 clinical trials. Circ Cardiovasc Imaging 2013;6:560–567
85 Shukla AP, Kumar RB, Aronne LJ: Lorcaserin HCl for the treatment of obesity. Expert Opin Pharmacother 2015;15:1–8.

86 ClinicalTrials.gov: A study to evaluate the effect of long-term treatment with BELVIQ (lorcaserin HCl) on the incidence of major adverse cardiovascular events and conversion to type 2 diabetes mellitus in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors (CAMELLIA-TIMI). *https://clinicaltrials.gov/ct2/show/NCT02019264* (last accessed November 30, 2015).
87 Singh J, Kumar R: Phentermine-topiramate: First combination drug for obesity. Int J Appl Basic Med Res 2015; 5:157–158.
88 Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, Tam PY, Troupin B, Day WW: Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity (Silver Spring) 2012;20:330–342.
89 Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, Day WW: Effects of low-dose, controlled release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:1341–1352.
90 Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH: Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo controlled, phase 3 extension study. Am J Clin Nutr 2012; 95:297–308.
91 Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM: Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. Obesity (Silver Spring) 2013;21:2163–2171.
92 Jordan J, Astrup A, Engeli S, Narkiewicz K, Day WW, Finer N: Cardiovascular effects of phentermine and topiramate: a new drug combination for the treatment of obesity. J Hypertens 2014;32:1178–1188.
93 VIVUS Reports Topline Findings from FORTRESS. (media release on the internet). 21 December, 2011. *http://ir.vivus.com/releasedetail.cfm?ReleaseID=634920* (last accessed November 30, 2015).
94 Fujioka K: Sustained-release naltrexone/bupropion: a novel pharmacologic approach to obesity and food craving. US Endocrinology 2014;10:53–58.
95 Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, Kim DD, Dunayevich E; COR-I Study Group: Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010;376:595–605.
96 Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, Kim D, Dunayevich E COR-II Study Group: A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity (Silver Spring) 2013;21:935–943.
97 Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, Perri MG, Pi-Sunyer FX, Rock CL, Erickson JS, Maier HN, Kim DD, Dunayevich E: Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. Obesity (Silver Spring) 2011;19:110–120.
98 Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, Klassen P, Fujioka K; for The COR-Diabetes Study Group: Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care 2013;36:4022–4029.
99 ClinicalTrials.gov: Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects with Cardiovascular Risk Factors (The Light Study). *https://clinicaltrials.gov/ct2/show/record/NCT01601704* (last accessed November 30, 2015).
100 Holst JJ: Incretin hormones and the satiation signal. Int J Obes (Lond) 2013;37:1161–1168.
101 Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean ME, Niskanen L, Rasmussen MF, Rissanen A, Rössner S, Savolainen MJ, Van Gaal L; NN8022–1807 Investigators: Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes (Lond) 2012;36:843–854.
102 Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL: Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012;344:d7771.
103 Astrup A, Rossner S, Van Gaal L Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, Lean ME; NN8022–1807 Study Group: Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009;374:1606–1616.
104 Kim SH, Abbasi F, Lamendola C, Liu A, Ariel D, Schaaf P, Grove K, Tomasso V, Ochoa H, Liu YV, Chen YD, Reaven G: Benefits of liraglutide treatment in overweight and obese older individuals with prediabetes. Diabetes Care 2013;36:3276–3282.
105 Wadden TA, Hollander P, Klein S Niswender K, Woo V, Hale PM, Aronne L; NN8022–1923 Investigators: Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. Int J Obes (Lond) 2013;37:1443–1451.
106 Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DCW, le Roux CW, Ortiz RV, Bjorn-Jensen C, Wilding JPH for the SCALE Obesity and Prediabetes NN8022–1839 Study Group: A randomized controlled trial of 3.0 mg liraglutide in weight management. N Engl J Med 2015;373:11–22.
107 ClinicalTrials.gov: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation (LEADER®). *https://clinicaltrials.gov/ct2/show/NCT01179048* (last accessed November 30, 2015).
108 Marso SP, Poulter NR, Nissen SE, Nauck MA, Zinman B, Daniels GH, Pocock S, Steinberg WM, Bergenstal RM, Mann JF, Ravn LS, Frandsen KB, Moses AC, Buse JB: Design of the liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results (LEADER) trial. Am Heart J 2013;166:823–830.

109 Daniels GH, Hegedüs L, Marso SP, Nauck MA, Zinman B, Bergenstal RM, Mann JFE, Karsbøl JD, Moses AC, Buse JB, Tuttle RM on behalf of the LEADER trial investigators: LEADER 2: baseline calcitonin in 9340 people with type 2 diabetes enrolled in the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial: preliminary observations. Diabetes Obes Metab 2015;17:477–486.
110 Lean ME, Carraro R, Finer N, Hartvig H, Lindegaard ML, Rössner S, Van Gaal L, Astrup A; NN8022–1807 Investigators: Tolerability of nausea and vomiting, and associations with weight loss, in a randomized trial of liraglutide in obese, non-diabetic adults. Int J Obes (Lond) 2013;38:689–697.
111 Pories WJ: Bariatric surgery: risks and rewards. J Clin Endocrinol Metab 2008;93(suppl 1):S89–S96.
112 Sjöström L: Review of the key results from the Swedish Obese Subjects (SOS) trial – a prospective controlled intervention study of bariatric surgery. J Intern Med 2013;273:219–234.
113 Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N,Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ: Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211–2219.
114 Flegal KM, Kit BK, Orpana H, Graubard BI: Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309:71–82.
115 Neovius M, Narbro K, Keating C, Peltonen M, Sjöholm K, Agren G, Sjöström L, Carlsson L: Health care use during 20 years following bariatric surgery. JAMA 2012;308:1132–1141.
116 Fried M, Yumuk Y, Oppert JM, Scopinaro N, Torres AJ, Weiner R, Yashkov Y, Frühbeck G: Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Facts 2013;6:449–468.
117 Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I: Weight and type 2 diabetes after bariatric surgery: systemic review and meta-analysis. Am J Med 2009;122:248–256.
118 Hofsø D, Nordstrand N, Johnson LK, Karlsen TI, Hager H, Jenssen T, Bollerslev J, Godang K, Sandbu R, Røislien J, Hjelmesaeth J: Obesity-related cardiovascular risk factors after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. Eur J Endocrinol 2010;163; 735–745.
119 Hofsø D, Jenssen T, Bollerslev J Ueland T, Godang K, Stumvoll M, Sandbu R, Røislien J, Hjelmesæth J: Beta cell function after weight loss: a clinical trial comparing gastric bypass surgery and intensive lifestyle intervention. Eur J Endocrinol 2011;164:231–238.
120 Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ESH, Nissen SE, Kashyap SR for the STAMPEDE Investigators: Bariatric surgery versus intensive medical therapy for diabetes – 3-year outcomes. N Engl J Med 2014;370:2002–2013.
121 DeMaria EJ: Bariatric surgery for morbid obesity. N Engl J Med 2007;356:2176–2183.
122 Sauerland S, Angrisani L, Belachew M, Chevallier JM, Favretti F, Finer, N Fingerhut A, Garcia Caballero M, Guisado Macias JA, Mittermair R, Morino M, Msika S, Rubino F, Tacchino R, Weiner R, Neugebauer EA; European Association for Endoscopic Surgery: Obesity surgery: evidence based guidelines of the EAES. Surg Endosc 2005;19:200–221.
123 Ferraro DR: Preparing patients for bariatric surgery – the clinical considerations. Clin Rev 2004;14:57–63.
124 Reoch J, Mottillo S, Shimony A, Filion KB, Christou NV, Joseph L, Poirier P, Eisenberg MJ: Safety of laparoscopic vs open bariatric surgery: a systematic review and meta-analysis. Arch Surg 2011;146:1314–1322.
125 Korner J, Inabnet W, Febres G, Conwell IM, McMahon DJ, Salas R, Taveras C, Schrope B, Bessler M: Prospective study of gut hormone and metabolic changes after adjustable gastric banding and Roux-en-Y gastric bypass. Int J Obes (Lond) 2009;33:786–795.
126 Laferrere B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, Kovack B, Bawa B, Koshy N, Lee H, Yapp K, Olivan B: Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab 2008;93:2479–2485.
127 Bose M, Teixeira J, Olivan B, Bawa B, Arias S, Machineni S, Pi-Sunyer FX, Scherer PE, Laferrère B: Weight loss and incretin responsiveness improve glucose control independently after gastric bypass surgery. J Diabetes 2010;2:47–55.
128 Vidal J, Ibarzabal A, Romero F, Delgado S, Momblán D, Flores L, Lacy A: Type 2 diabetes mellitus and the metabolic syndrome following sleeve gastrectomy in severely obese subjects. Obes Surg 2008;18:1077–1082.
129 Leslie DB, Dorman RB, Serrot FJ, Swan TW, Kellogg TA, Torres-Villalobos G, Buchwald H, Slusarek BM, Sampson BK, Bantle JP, Ikramuddin S: Efficacy of the Roux-en-Y gastric bypass compared to medically managed controls in meeting the American Diabetes Association composite end point goals for management of type 2 diabetes mellitus. Obes Surg 2012;22:367–374.
130 Carlsson LM, Peltonen M, Ahlin S, Anveden Å, Bouchard C, Carlsson B, Jacobson P, Lönroth H, Maglio C, Näslund I, Pirazzi C, Romeo S, Sjöholm K, Sjöström E, Wedel H, Svensson PA, Sjöström L: Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. N Engl J Med 2012;367:695–704.
131 Arterburn DE, Bogart A, Sherwood NE, Sidney S, Coleman KJ, Haneuse S, O'Connor PJ, Theis MK, Campos GM, McCulloch D, Selby J: A multisite study of long-term remission and relapse of type 2 diabetes mellitus following gastric bypass. Obes Surg 2013;23:93–102.
132 Laferrere B: Effect of gastric bypass surgery on the incretins. Diabetes Metab 2009;35:513–517.
133 Kashyap SR, Daud S, Kelly KR, Gastaldelli A, Win H, Brethauer S, Kirwan JP, Schauer PR: Acute effects of gastric bypass versus gastric restrictive surgery on beta cell function and insulinotropic hormones in severely obese patients with type 2 diabetes. Int J Obes (Lond) 2010;34:462–471.

Obes Facts 2015;8:402–424
DOI: 10.1159/000442721

134 Peterli R, Wolnerhanssen B, Peters T, Devaux N, Kern B, Christoffel-Courtin C, Drewe J, von Flüe M, Beglinger C: Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann Surg 2009;250:234–241.
135 Mingrone G, Castagneto-Gissey L: Mechanisms of early improvement/resolution of type 2 diabetes after bariatric surgery. Diabetes Metab 2009;35:518–523.
136 Briatore L, Salani B, Andraghetti G, Maggi D, Adami GF, Scopinaro N, Cordera R: Beta-cell function improvement after biliopancreatic diversion in subjects with type 2 diabetes and morbid obesity. Obesity (Silver Spring) 2010;18:932–936.
137 Briatore L, Salani B, Andraghetti G, Danovaro C, Sferrazzo E, Scopinaro N, Adami GF, Maggi D, Cordera R: Restoration of acute insulin response in T2DM subjects 1 month after biliopancreatic diversion. Obesity (Silver Spring) 2008;16:77–81.
138 Sampsel S, May J: Assessment and management of obesity and comorbid conditions. Dis Manag 2007;1:252–265.
139 Jordan J, Yumuk V, Schlaich M, Nilsson PM, Zahorska-Markiewicz B, Grassi G, Schmieder RE, Engeli S, Finer N: Joint statement of the European Association for the Study of Obesity and the European Society of Hypertension: obesity and difficult to treat arterial hypertension. J Hypertens 2012;30:1047–1055.
140 Tsigos C, Hainer V, Basdevant A, Finer N, Mathus-Vliegen E, Micic D, Maislos M, Roman G, Schutz Y, Toplak H, Yumuk V, Zahorska-Markiewicz B; for the Obesity Management Task Force of the European Association for the Study of Obesity: Criteria for EASO-collaborating centres for obesity management. Obes Facts 2011;4:329–333.
141 Scottish Intercollegiate Guidelines Network: Obesity in Scotland. Integrating Prevention with Weight Management. A National Clinical Guideline Recommended for Use in Scotland. Edinburgh, Scottish Intercollegiate Guidelines Network, 1996.

Erratum

In the article by Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, Toplak H, for the Obesity Management Task Force of the European Association for the Study of Obesity , entitled 'European Guidelines for Obesity Management in Adults' [Obes Facts 2015;8:402–424, DOI:10.1159/000442721], figure 2 was not correctly given.

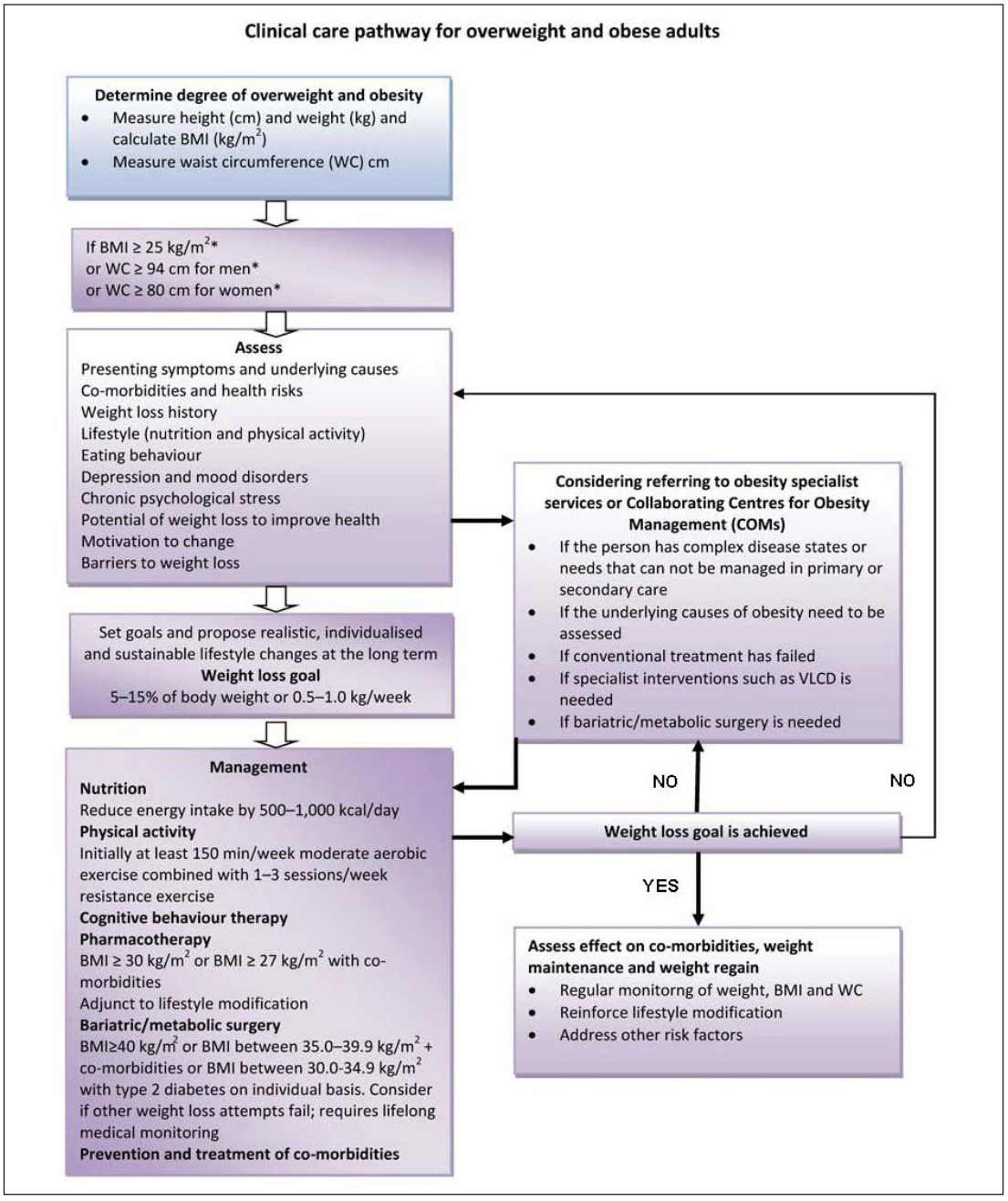


Fig. 2. Algorithm for the assessment and stepwise management of overweight and obese adults. *BMI and WC cut-off points are different for some ethnic groups (see text).

Obesity Facts

Guidelines

Obes Facts 2021;14:222–245
DOI: 10.1159/000515381

Received: January 19, 2021
Accepted: February 18, 2021
Published online: April 21, 2021

European Guidelines for Obesity Management in Adults with a Very Low-Calorie Ketogenic Diet: A Systematic Review and Meta-Analysis

Giovanna Muscogiuri[a, b] Marwan El Ghoch[c] Annamaria Colao[a, b] Maria Hassapidou[d] Volkan Yumuk[e] Luca Busetto[f] Obesity Management Task Force (OMTF) of the European Association for the Study of Obesity (EASO)

[a]Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università Federico II di Napoli, Naples, Italy; [b]Cattedra Unesco – Educazione alla salute e allo sviluppo sostenibile, Università Federico II, Naples, Italy; [c]Department of Nutrition and Dietetics, Faculty of Health Sciences, Beirut Arab University, Beirut, Lebanon; [d]Department of Nutritional Sciences and Dietetics, International Hellenic University, Thessaloniki, Greece; [e]Division of Endocrinology, Metabolism, and Diabetes, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey; [f]Dipartimento di Medicina, Università degli Studi di Padova, Padova, Italy

Keywords
Body weight · Body composition · Clinical outcomes · Glycemic profile · Lipid profile · Obesity · Weight loss · Very low-calorie ketogenic diet · Guidelines · Body mass index

Abstract

Background: The very low-calorie ketogenic diet (VLCKD) has been recently proposed as an appealing nutritional strategy for obesity management. The VLCKD is characterized by a low carbohydrate content (<50 g/day), 1–1.5 g of protein/kg of ideal body weight, 15–30 g of fat/day, and a daily intake of about 500–800 calories. ***Objectives:*** The aim of the current document is to suggest a common protocol for VLCKD and to summarize the existing literature on its efficacy in weight management and weight-related comorbidities, as well as the possible side effects. ***Methods:*** This document has been prepared in adherence with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. Literature searches, study selection, methodology development, and quality appraisal were performed independently by 2 authors and the data were collated by means of a meta-analysis and narrative synthesis. ***Results:*** Of the 645 articles retrieved, 15 studies met the inclusion criteria and were reviewed, revealing 4 main findings. First, the VLCKD was shown to result in a significant weight loss in the short, intermediate, and long terms and improvement in body composition parameters as well as glycemic and lipid profiles. Second, when compared with other weight loss interventions of the same duration, the VLCKD showed a major effect on reduction of body weight, fat mass, waist circumference, total cholesterol and triglyceridemia as well as improved insulin resistance. Third, although the VLCKD also resulted in a significant reduction of glycemia, HbA1c, and LDL cholesterol, these changes were similar to those obtained with other weight loss interventions. Finally, the VLCKD can be considered a safe nutritional approach under a health professional's supervision since the most common side effects are usually clinically mild and easily to manage and recovery is often spontaneous. ***Conclusions:*** The VLCKD can be recommended as an effective dietary treatment for individuals with obesity after considering potential contra-indications and keeping in mind that

G.M. and M.E.G. contributed equally to the preparation and writing of this document.

karger@karger.com
www.karger.com/ofa

Correspondence to:
Giovanna Muscogiuri, giovanna.muscogiuri@gmail.com

any dietary treatment has to be personalized. ***Prospero Registry:*** The assessment of the efficacy of VLCKD on body weight, body composition, glycemic and lipid parameters in overweight and obese subjects: a meta-analysis (CRD42020205189).

Introduction

Obesity is becoming a plague in countries all around the world, affecting over 200 million men and nearly 300 million women [1]. Beyond the body weight excess, obesity has been defined as "the silent killer"; indeed, it significantly increases the risk and contributes to the development of several diseases such as cardiovascular diseases, type 2 diabetes, dyslipidemia, arthropathy, some neoplasms, and infertility [2, 3].

Several strategies are currently used for weight management in obesity, with the first attempt to lose weight being focused on lifestyle changes based on physical activity and dietary recommendations. Usually, the most recommended nutritional pattern is characterized by an increase in complex/raw carbohydrates along with a reduction in fat intake aiming to reduce energy intake and increase energy expenditure through physical activity [4]. Lifestyle modification programs are not always successful, especially in patients with severe obesity. On the other hand, the use of antiobesity drugs is currently limited by nontrivial costs, potential side effects, and contraindications that cannot make them suitable for all subjects with obesity [5, 6]. Finally, bariatric surgery is another tool used for weight loss, mostly indicated for individuals with severe obesity (i.e., BMI = 40 or 35 with obesity-associated comorbidities). Despite its effectiveness for remission of type 2 diabetes, bariatric surgery can lead to several irreversible complications related to surgical procedures [7] and its availability is limited.

Recently, very low-carbohydrate ketogenic diets (VLCKD) have been proposed as an appealing nutritional strategy for obesity management [8]. VLCKD are characterized by a low carbohydrate content (< 50 g/day), 1–1.5 g of protein/kg of ideal body weight, 15–30 g of fat/day, and about 500–800 kcal/day [8]. The reduction of carbohydrate intake under the above reported threshold leads to ketone synthesis [9]. Ketone bodies are then utilized as fuel by several extrahepatic tissues such as the central nervous system, skeletal muscle, and the heart. To favor the patients' compliance, VLCKD are often delivered through meal replacements mimicking a natural diet. Among the beneficial effects, VLCKD have been reported to induce more weight loss than a standard low-calorie diet after 1 and 2 years of follow-up [10], to preserve muscle mass, muscle strength, and resting metabolic rate [11].

In view of these considerations, the 3 main aims of the current document were to: (1) describe a typical VLCKD protocol highlighting its indications and contraindications; (2) conduct a systematic review and meta-analysis on the efficacy of this protocol in terms of clinical outcomes (i.e., in the short and long term), i.e., weight loss and maintenance, and changes in body composition parameters and glycemic and lipid profiles; and finally (3) summarize the side effects (i.e., common and rare) of this dietary treatment as well as its medical management. A practical recommendation for the application of VLCKD in obesity management is therefore formulated.

VLCKD Protocol

The VLCKD is a nutritional protocol characterized by a reduction of daily carbohydrate intake, usually lower than 30 g/day (≃13% of the total energy intake), a relative increase in fat (~44%) and protein (~43%) percentages, and a total daily energy intake < 800 kcal [12]. The VLCKD protocol includes high-biological-value protein (coming from milk, peas, whey, and soy) artificial meals, and natural foods. Each artificial meal typically includes 18 g of protein, 4 g of carbohydrate, and 3 g of fat (mainly high-oleic vegetable oils) and provides approximately 100–150 kcal. This protocol is characterized by the following 3 stages: active, reeducation, and maintenance (Fig. 1).

Active Stage

The active stage is a very low-calorie diet (600–800 kcal/day) characterized by low amounts of carbohydrates (< 50 g daily from vegetables) and lipids (only 10 g of olive oil per day). The amount of high-biological-value proteins ranged between 0.8 and 1.2 g/kg of ideal body weight to preserve lean mass and meet the minimal daily body requirements. This stage is further divided in 3 ketogenic phases; in phase 1, the patients eat high-biological-value protein meals with vegetables with a low glycemic index 4–5 times a day. In phase 2, one of the protein artificial servings is replaced by a natural protein meal such as meat/egg/fish either at lunch or at dinner. In phase 3, a second serving of the natural protein low in fat can replace the second artificial protein serving. Supplementations with micronutrients (vitamins and minerals, such as K,

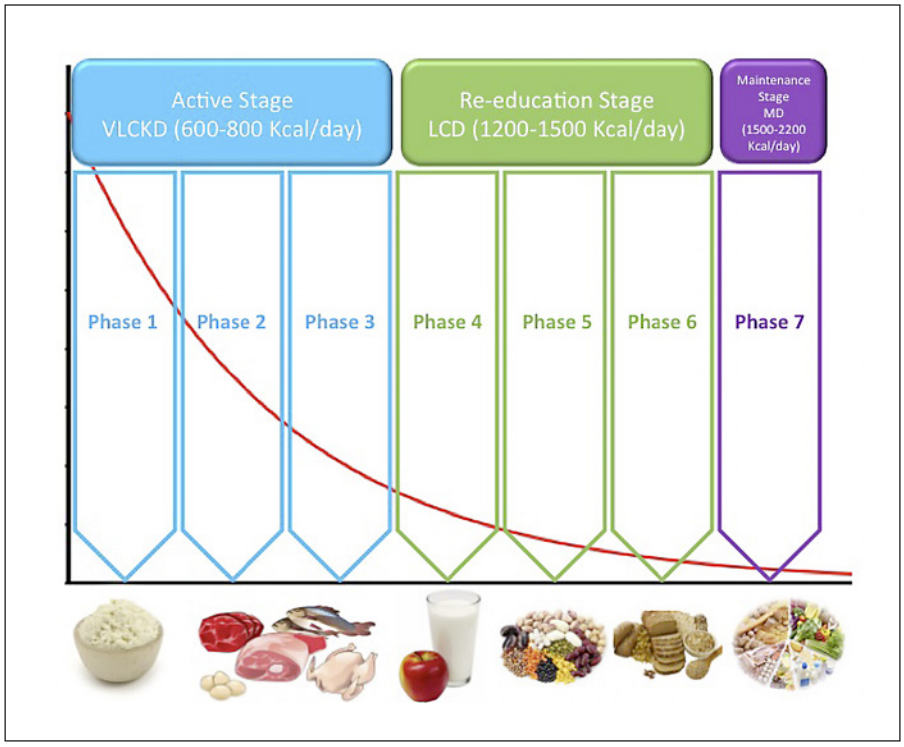


Fig. 1. Scheme of the stages of VLCKD protocol.

Na, Mg, Ca, and omega-3 fatty acids) are suggested at this stage. The active stage usually lasts 8–12 weeks, until the subjects lose most of the weight loss target (about 80%).

In the literature, it has also been reported that the active stage protocol could be reached providing half of the amount of daily protein using synthetic amino acid supplementation containing whey protein (13.42/bag), carbohydrate (0.03/bag), fat (0.15/bag), isoleucine (0.31/bag), ornithine α-ketoglutarate (0.25/bag), L-citrulline (0.25/bag), taurine, (0.25/bag), L-tryptophan (0.05/bag), and potassium citrate (0.45/bag), for a total of 64 kcal (268 KJ) which are dissolved in water. This drink is taken at breakfast and lunch or dinner [13].

Reeducation Stage

After the active stage, the patients will progressively reintroduce different food groups and in the meantime take part in a program of nutritional reeducation to keep long-term weight loss. Carbohydrates are gradually reintroduced according to the following order: foods with the lowest glycemic index (fruit and dairy products – phase 4), followed by foods with moderate (legumes – phase 5), and a high glycemic index (bread, pasta, and cereals – phase 6). The daily calorie intake in the reintroduction stage (phases 4–6) varies between 800 and 1,500 kcal/day.

Maintenance Stage

After the reintroduction stage, there is a maintenance stage which includes a nutritional program that ranges from 1500 to 2000 kcal/day, depending on the individual, and that is balanced by macronutrients and micronutrients viewpoints. The main purpose of this stage is the maintenance of long-term weight loss and to promote a healthy lifestyle.

Efficacy of VLCKD in Terms of Weight Loss, and Changes in Body Composition Parameters and Glycemic and Lipid Profiles: Systematic Review and Meta-Analysis

PICO Statements

We set out to conduct a systematic review on the topic in accordance with the PICO process [14], as detailed below:

P (population): adult participants (age ≥18 years) in the overweight or obesity categories however defined (i.e., BMI, body fat, waist circumference [WC], etc.) with or without comorbidities.

I (intervention): short- or long-term weight loss followed or not by a period of weight maintenance.

C (comparison): weight loss programs involving a VLCKD as a treatment for obesity/overweight, compared to any other diet as defined by the authors (whenever available).

O (outcome): changes in the following outcomes: body weight status, body composition, and glycemic and lipid profiles.

Body weight status (primary outcome) comprises: mean weight loss expressed as weight (kg) and BMI before and after VLCKD at 1, 2, 4–6, 12 and 24 months of follow-up, and comparison of mean weight loss between VLCKD and any other intervention in terms of weight (kg) and BMI changes.

Body composition (secondary outcome) comprises: WC (mean difference in cm between baseline and the last available follow-up in the VLCKD group), and comparison of changes in WC in cm between VLCKD and any other intervention.

Fat mass (FM) comprises: the mean difference (in kg) between baseline and the last available follow-up in the VLCKD group, and comparison of changes in FM (in kg) between VLCKD and any other intervention.

Fat-free mass (FFM) comprises: the mean difference (in kg) between baseline and the last available follow-up in the VLCKD group, and comparison of changes in FFM (in kg) between VLCKD and any other intervention.

Biochemical assessment comprises the glycemic profile, which includes: fasting blood glucose (FBG) (mean difference expressed in mg/dL between baseline and the last available follow-up in the VLCKD group, and comparison of changes in FBG in mg/dL between VLCKD and any other intervention), the Homeostatic Model Assessment for Insulin Resistance (HOMA index) (mean difference in HOMA index between baseline and the last available follow-up in the VLCKD group, and comparison of changes in HOMA index between VLCKD and any other intervention), and glycated hemoglobin (HbA1c) (mean difference in HbA1c expressed in % between baseline and the last available follow-up in the VLCKD group, and comparison of changes in HbA1c between VLCKD and any other intervention).

Biochemical assessment also comprises the lipid profile, which includes: total cholesterol (mean difference in total cholesterol expressed in mg/dL between baseline and the last available follow-up in the VLCKD group, and comparison of changes in total cholesterol between VLCKD and any other intervention), low-density lipoprotein (LDL) cholesterol (mean difference in LDL expressed in mg/dL between baseline and the last available follow-up in the VLCKD group, and comparison of changes in LDL between VLCKD and any other intervention), high-density lipoprotein (HDL) cholesterol (mean difference in HDL expressed in mg/dL between baseline and the last available follow-up in the VLCKD group, and comparison of changes in LDL between VLCKD and any other intervention), and triglycerides (TG) (mean difference in TG expressed in mg/dL between baseline and the last available follow-up in the VLCKD group, and comparison of changes in TG between VLCKD and any other intervention).

Methods

The meta-analysis was presented in adherence with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for completion of this review [15]. PROSPERO registry (September 20, 2020): "The Assessment of the Efficacy of VLCKD on Body Weight, Body Composition, Glycaemic and Lipid Parameters in Overweight and Obese Subjects: A Meta-Analysis" (CRD42020205189).

Inclusion and Exclusion Criteria

We includes all studies dealing with VLCKD and evaluating changes in weight status (expressed in any way) and changes in any weight-related clinical outcome before and after VLCKD, provided that they met the following criteria: (1) studies written in English; (2) original articles or studies with a longitudinal design; and (3) prospective or retrospective observational (analytical or descriptive), experimental, or quasi-experimental controlled studies. No reviews, cross-sectional, noncontrolled, or nonoriginal articles (i.e., case reports, editorials, letters to the editor, and book chapters) were included.

Considering that there is no complete agreement or set definition among clinicians and researchers regarding the macronutrients in VLCKD (i.e., carbohydrate, protein, and fat thresholds), for the purposes of this review we adopted the following [8]: total daily calories, ≤800 kcal; carbohydrates, 30–50 g/day (13–25% of the total calories); protein, 0.8–1.2 g/day for an ideal body weight (~40–45% of the total calories); and fat (~40–45% of the total calories).

Information Source and Search Strategy

The literature search was performed independently and in duplicate by 2 authors. Databases were systematically screened using the following MeSH terms combinations as follows: 1 obesity, 2 overweight, 3 very low-calorie ketogenic diet, 4 VLCKD, 5 VLKD, 6 weight loss, 7 weight reduction, 8 weight maintenance, 9 clinical outcomes, 10 body composition, 11 fat mass, 12 body fat, 13 fat-free mass, 14 lean body mass, 15 glycemic profile, 16 glycemia, 17 fasting blood glucose, 18 HbA1c, 19 HOMA-IR index, 20 lipid profile cholesterol, 21 LDL cholesterol, 22 HDL cholesterol, and 23 TG. The following combinations were also applied as search parameters: (1 OR 2) AND (3) AND (4 OR 5 OR 6) AND (7 OR 8 OR 9 OR 10 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23).

In addition, a manual search was carried out to retrieve other articles that were not identified via the initial search strategy. Publication date was not considered an exclusion criterion for the purposes of this review.

Study Selection and Quality Assessment

Two authors (G.M. and M.E.G.) independently screened the resulting articles for their methodology and appropriateness for inclusion. Noncontrolled observational studies were selected according to the National Institute for Health and Clinical Excellence (NICE) guideline checklist for quality appraisal [16]. For controlled observational studies, the appraisal was conducted according to the Newcastle-Ottawa Scale (NOS) [17], which relies on a 9-point system in which scores of 0–6 and 7–9 are considered poor and moderate to good quality, respectively. Scores of 4, 2, and 3, respectively, were assigned to the following criteria: selection of study groups, comparability of study groups, and assessment of outcomes and adequacy of follow-up criteria [18]. In randomized controlled trials, quality appraisal was conducted according to the Jadad scale [19], which relies on the following 3 items: randomization (2 points), blinding (2 points), and description of withdrawals or dropout (1 point), for a total of 5 possible points; ≥3 points indicates a good-quality trial [20]. Moreover, randomized controlled trials were assessed using risk-of-bias criteria, although 10 criteria (i.e., randomization method, allocation sequence concealment, participant blinding, outcome assessor blinding, outcome measurement, interventionist training, withdrawal, intent-to-treat analyses, clustering, and baseline characteristics) are generally used to assess the sufficiency of reporting. Studies were assigned a "yes" for each applicable criterion they fulfilled and a "no" for each criterion they did not fulfill. Studies containing insufficient information for judgement were indicated as "not reported," and any disagreement was documented and resolved by discussion [21]. Consensus discussion was used to resolve disagreements between reviewers.

Data Collection Process and Data Items

First, both the title and the abstract of each paper were assessed by 2 independent authors for language suitability and subject matter relevance, and then the selected studies were assessed for their appropriateness for inclusion and the quality of the methods. The following characteristics are reported in Table 1 for each study that passed these 2 rounds of screening: first author, year of publication, country of conduction, design, sample age, baseline weight, duration of follow-up, and outcome.

Data Synthesis

The studies that met the inclusion criteria are presented as a narrative synthesis. The effect size of interest was the raw mean difference in weight, BMI, WC, glycemic indicators, and blood lipid profile, reflecting a change from baseline and different intervals of VLCKD or differences from the control group. The mean difference was calculated as the difference between the reported means (equation 1):

$$D = \overline{X_2} - \overline{X_1}$$

The SD of the difference between means was calculated using the SEM for each reported mean (equation 2):

$$SD = \sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}$$

For reported means with a missing SD, the SD was imputed from other studies [22]. A meta-analysis was performed to calculate a weighted average of the overall mean differences from different studies included in the model. Assessment of heterogeneity was done using I^2 statistics as a measure of inconsistency to test that variation in effect estimates is only due to chance. Acceptable heterogeneity was determined at $I^2 < 60\%$. In studies with acceptable heterogeneity, analysis of pooled effects was done using a fixed-effects model. In studies with heterogeneity above 60%, a random-effects model was used [22]. A forest plot was used plotted to compare the change in outcomes of interest in response to VLCKD. Revman 5.3 was used to perform the meta-analysis and draw the forest plots [23]. For all statistical tests, $p < 0.05$ was considered statistically significant.

Results

The initial search retrieved 645 papers, and 321 were immediately eliminated because they were considered duplicates; thus 324 screened reports remained. In the first round of screening (titles and abstracts), 252 papers were excluded on the following grounds: language other than English, no bearing on overweight and obesity, and dealing with overweight and obesity but not clearly considering VLCKD. In the second round of screening of the remaining 72 articles, full-text papers were assessed for eligibility. A further 57 articles were excluded for: (1) being review articles (i.e., systematic or narrative) or consensus protocol studies; (2) dealing with diets similar to but not the same as VLCKD, such as very low-calorie diets (VLCD) and very low-carbohydrate diets (but not well identified in the abstract); and (3) VLCKD that did not satisfy our VLCKD protocol (Fig. 2).

In the end, 15 articles (7 noncontrolled, 2 controlled, and 6 randomized controlled studies) were available for systematic review, narrative, and meta-analysis. According to the NICE guidelines checklist, the noncontrolled studies ($n = 7$) were of a fair quality (mean score: 6.42 points; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000515381), while the NOS checklist indicated that the controlled studies ($n = 2$) were of a moderate quality (mean score: 5.50 points; online suppl. Table 2). Finally, the Jadad scale checklist indicated that the randomized controlled studies ($n = 6$) were of a high quality (mean score: 3.16 points; online suppl. Table 3), and the risk of bias was acceptable (online suppl. Table 4). Finally, the PRISMA checklist reported, item by item, the adherence to PRISMA guidelines for completion of this review (online suppl. Table 5).

Table 1. Studies included in the systematic review

First author	Year	Country	Design	Sample	Mean age (±SD), years	Baseline weight status	Follow-up duration	Other outcomes
Albanese [24]	2019	Italy	Retrospective controlled	*n* = 178 (M = 39; F = 139; 72 VLCKD and 106 VLCD)	VLCKD: 43.4±12.1 VLCD: 43.5±11.8	BW: 125.5±19.5 kg BMI: 46.0±6.3 BW: 120.9±22.6 kg BMI: 43.6±6.9	3 weeks	–
Bruci [25]	2020	Italy	Prospective observational noncontrolled	*n* = 93 (M = 23; F = 69)	51.3±12.2	BW: 92.40±18.31 kg BMI: 33.85±5.84	2–3 months	FM, FFM, glycemia, HbA1c, cholesterol (total, LDL, and HDL), and TG
Colica [26]	2017	Italy	RCT* including more than a VLCKD arm but not controlled vs. other diets	*n* = 40 (20 VLCKD and 20 VLCKD + amino acids of 50% proteins), and then they were crossed over	45.40±14.20	BW: 77.43±7.12 kg BMI: 29.42±2.24 BW: 82.23±14.60 kg BMI: 29.85±3.98	3 weeks	Glycemia and HOMA-IR index
de Luis [27]	2016	Spain	RCT* including more than VLCKD arm but not controlled vs. other diets	*n* = 29 (M = 12; F = 17; 15 VLCKD and 14 VLCKD + DHA)	44.3±11.7 47.4±9.1	BW: 92.2±13.1 kg BMI: 32.95±1.9 BW: 92.05±8.7 kg BMI: 33.4±1.4	6 months	WC, FM, glycemia, HOMA-IR index, cholesterol (total, LDL, and HDL), and TG
Goday [28]	2016	Spain	RCT	*n* = 89 (M = 31; F = 58; 45 VLCKD and 44 LCD)	54.89±8.81 54.17±7.97	BW: 91.47±11.43 kg BMI: 33.3±1.5 BW: 90.0±11.3 kg BMI: 32.9±1.6	4 months	WC, glycemia, HbA1c, HOMA-IR index, cholesterol (total, LDL, and HDL), and TG
Gomez-Arbelaez [29]	2017	Spain	Prospective interventional noncontrolled	*n* = 20 (M = 8; F = 12)	47.2±10.2	BW: 95.9±16.3 kg BMI: 35.5±4.4	4 months	WC, FM, and FFM
Gutiérrez-Repiso [30]	2019	Spain	RCT* including more than a VLCKD arm but not controlled vs. other diets	*n* = 33 (M = 13; F = 20)	48.67±9.16 47.00±8.97 38.22±11.27	BW: 92.74±15.86 kg BMI: 32.82±1.76 BW: 95.71±9.46 kg BMI: 32.96±1.47 BW: 90.58±10.83 kg BMI: 33.14±1.47	4 months	WC, FM, FFM, glycemia, HOMA-IR index, cholesterol (total, LDL, and HDL), and TG
Leonetti [31]	2015	Italy	Prospective noncontrolled	*n* = 50 (M = 19; F = 31)	47.4±11.2	BW: 150±26.3 kg BMI: 53.5±8.4	1 month	WC, cholesterol (total, LDL, and HDL), and TG
Merra [13]	2016	Italy	RCT	*n* = 18 (M = 5; F = 13; 9 VLCKD and 9 VLCD)	45.40±16.36 49.33±13.78	BW: 99.78±4.57 kg BMI: 33.69±3.51 BW: 74.77±5.04 kg BMI: 29.21±1.07	3 weeks	WC, FM, and FFM
Moreno [32]	2014	Spain	RCT	*n* = 53 (M = 6; F = 48; 27 VLCKD and 26 LCD)	44.4±8.6 46.3±9.3	BW: 97.9±18.9 kg BMI: 35.1±4.5 BW: 92.1±17.7 kg BMI: 35.1±5.3	12 months	WC, FM, FFM, glycemia, HbA1c, cholesterol (total, LDL, and HDL), and TG
Moreno [10]	2016	Spain	RCT	*n* = 45 (22 VLCKD and 23 LCD)	44.6±7.8 45.6±9.6	BW: 99.1±19.7 kg BMI: 35.2±4.8 BW: 90.6±17.8 kg BMI: 34.5±5.0	24 months	WC, FM, and VFM
Perticone [33]	2019	Italy	RCT	*n* = 56 (M = 32; F = 24; 28 VLCKD and 28 LCD)	42.6±6.6 50.9±13.3	BW: 113.9±31.0 kg BMI: 40.5±10.8 BW: 107.5±18.5 kg BMI 38.8±4.5	12 months	WC, FM, FFM, glycemia, HbA1c, HOMA-IR index, cholesterol (total, LDL, and HDL), and TG
Rubini [34]	2015	Italy	RCT	*n* = 32 (16 VLCKD and 16 MD)	51.4±12.4 44.7±13.9	BW: 82.0±12.4 kg BMI: 29.3±2.8 BW: 77.2±9.8 kg BMI: 27.5±2.8.4	3.5 months	–
Sajoux [35]	2019	Spain	Cohort controlled	*n* = 79 (M = 20; F = 59; 20 VLCKD, 20 LCD and 39 bariatric surgery)	47.1±10.2 49.9±9.3 40.8±10.4	BW: 96.0±16.3 kg BMI: 35.5±4.4 BW: 93.0±13.2 kg BMI: 35.8±4.5 BW: 121.3±21.5 kg BMI: 45.6±6.2	4–6 months	FM, FFM, and HOMA-IR index
Valenzano [36]	2019	Italy	Prospective noncontrolled	*n* = 20 (M = 10; F = 10)	48±8.2	BW: 91.33±17.11 kg BMI: 32.19±4.78	8 weeks	FM, FFM, HbA1c, cholesterol (total, LDL, and HDL), and TG

M, male; F, female; VFM, visceral fat mass; RCT, randomized controlled trial.

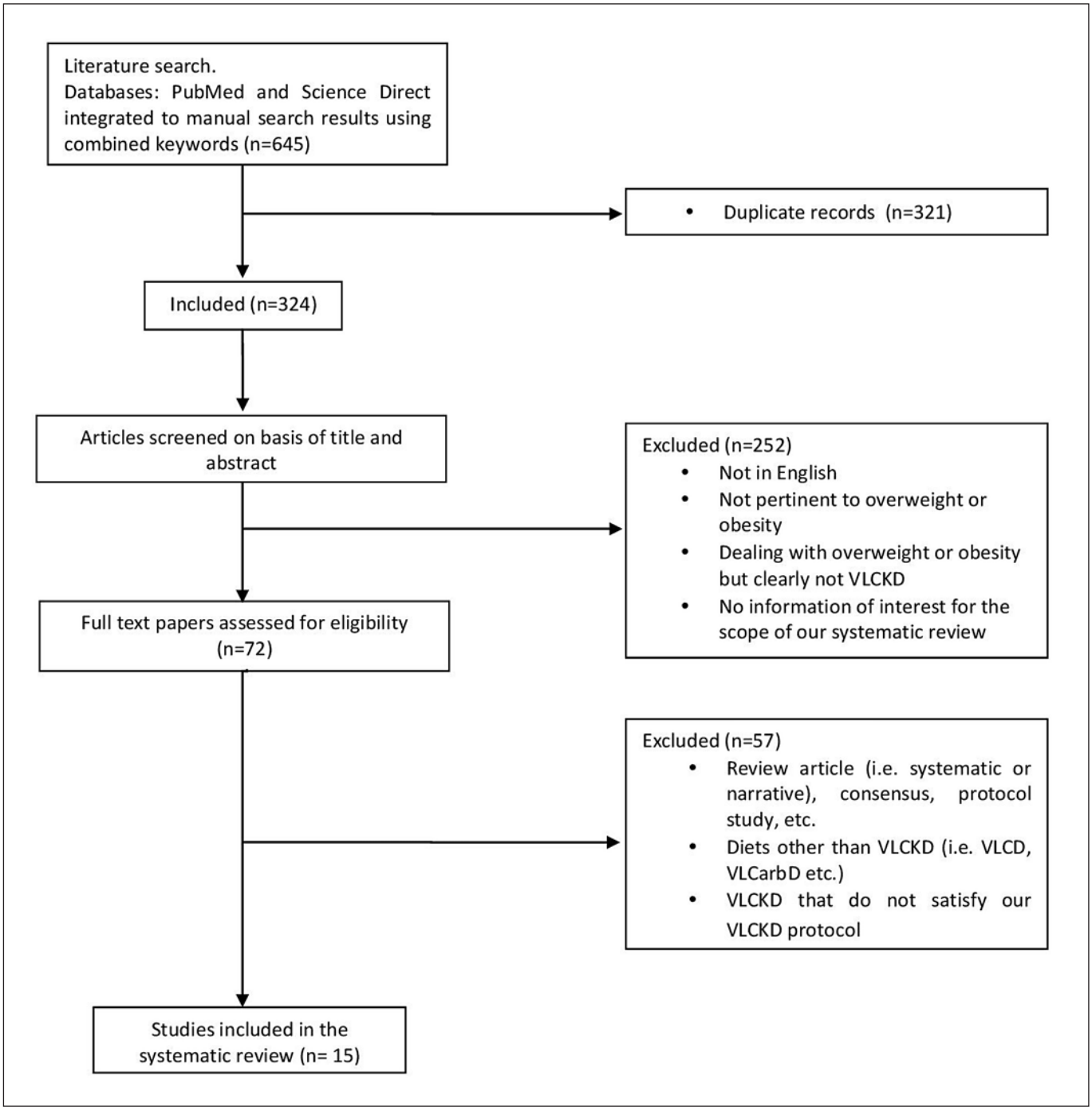


Fig. 2. Flow chart summarizing the study selection procedure.

Narrative Synthesis

Albanese et al. [24] included in a retrospective controlled study 178 patients (139 females and 39 males) with a mean age of 43 years and who were candidates for laparoscopic bariatric surgery. Seventy-two of those patients underwent a cycle of VLCKD in the 3 weeks before the bariatric procedure, and the other 106 followed VLCD for the same duration. The prediet mean BMI was 46.3 ± 6.3 for the VLCKD group and 43.1 ± 6.9 for VLCD, while immediately after diet and immediately prebariatric surgery

the BMI values were 43.9 ± 5.9 and 41.9 ± 6.8. The absolute weight loss was significantly better in the VLCKD group than in the VLCD group (5.8 ± 2.4 vs. 4.8 ± 2.5 kg; $p = 0.008$).

Bruci et al. [25] conducted a prospective observational noncontrolled real-life study including 92 patients (mean age = 51.3 ± 12.2 years; BMI 33.85 ± 5.84) with obesity and mild kidney failure and who underwent nearly 3 months of VLCKD. Anthropometric, body composition, and biochemical data were obtained before and after the dietary intervention. A significant reduction in body weight (92.40 ± 18.31 vs. 76.82 ± 14.95 kg; $p < 0.0001$), FM (35.63 ± 9.93 vs. 24.40 ± 9.00 kg; $p < 0.0001$), and FFM (56.77 ± 13.40 vs. 52.42 ± 10.89 kg; $p < 0.0001$) was observed, accompanied by improvements in glycemia (95.32 ± 13.26 vs. 88.25 ± 10.24 mg/dL; $p = 0.002$) and HbA1c (5.65 ± 0.81 vs. 5.33 ± 0.39%; $p < 0.0001$) and a reduction in total cholesterol (206.91 ± 45.65 vs. 184.46 ± 41.17 mg/dL; $p = 0.004$) and TG (156.44 ± 90.87 vs. 102.62 ± 35.71 mg/dL; $p = 0.003$).

Colica et al. [26] carried out a randomized crossover trial including 42 patients (mean age: 45.40 ± 14.20 years) with a BMI ≥25 and a FM ≥25% in males and ≥30 in females. Patients were allocated to the following 2 arms over 3 weeks of follow-up: VLCKD-1 ($n = 20$; mean BMI 29.85 ± 3.98) in which 50% of the protein intake was replaced with synthetic amino acids and a regular VLCKD-2 ($n = 20$; mean BMI 29.42 ± 2.24). At baseline, at the start and end of each arm, the health and nutritional status of all of the subjects were assessed by anthropometric analysis and a biochemical evaluation. A significant weight loss was observed in both arms of dietary treatment (VLCKD-1: 82.23 ± 14.60 vs. 77.62 ± 12.37 kg; $p = 0.00$; VLCKD-2: 77.43 ± 7.12 vs. 71.30 ± 6.91 kg; $p = 0.00$), as was improvement in the HOMA-IR index (VLCKD-1: 3.80 ± 2.85 vs. 1.44 ± 0.75; $p = 0.01$; VLCKD-2: 3.35 ± 1.45 vs. 1.36 ± 0.86; $p = 0.02$). On the other hand, a significant decrease in glycemia was only found in VLCKD-2 (4.91 ± 0.43 vs. 4.20 ± 0.89 mmol/L; $p = 0.03$), while no change in the lipid profile was noticed in both arms.

de Luis et al. [27] conducted a 6-months randomized controlled trial including 29 patients with obesity allocated to a VLCKD ($n = 15$; mean age = 44.3 ± 11.7 years and BMI 32.95 ± 1.9) or a VLCKD + DHA supplementation ($n = 14$; mean age = 47.4 ± 9.1 years and BMI 33.4 ± 1.4). The VLCKD group showed a significant reduction in body weight (92.2 ± 13.1 vs. 71.8 ± 11.4 kg; $p < 0.05$), FM (30.3 ± 6.1 vs. 16.8 ± 4.2; $p < 0.05$), WC (109.2 ± 7.8 vs. 87.4 ± 7.4 cm; $p < 0.05$), glycemia (101.6 ± 11.3 vs. 88.9 ± 7.6 mg/dL; $p < 0.05$), the HOMA-IR index (3.1 ± 2.2 vs. 1.0 ± 0.6; $p < 0.05$), total cholesterol (212.4 ± 37.8 vs. 183.4 ± 31.2 mg/dL), LDL cholesterol (139.4 ± 33.0 vs. 119.2 ± 28.9 mg/dL; $p < 0.05$), and TG (135.0 ± 50.6 vs. 78.5 ± 27.7 mg/dL). Similarly, in the VLCKD + DHA group reductions in body weight (92.1 ± 8.7 vs. 72.3 ± 7.1 kg; $p < 0.05$), FM (34.4 ± 5.3 vs. 26.3 ± 5.3 kg; $p < 0.05$), WC (109.1 ± 8.0 vs. 89.1 ± 5.2 cm; $p < 0.05$), glycemia (105.0 ± 17.5 vs. 89.0 ± 7.7 mg/dL; $p < 0.05$), the HOMA-IR index (3.8 ± 1.9 vs. 1.2 ± 0.4; $p < 0.05$), total cholesterol (195.8 ± 41.9 vs. 177.1 ± 43.2 mg/dL; $p < 0.05$), and TG (150.6 ± 71.2 vs. 83.9 ± 31.4 mg/dL) were observed.

Goday et al. [28] conducted a controlled trial including 89 adult patients with obesity and type 2 diabetes randomly allocated to either VLCKD ($n = 45$; mean age = 54.89 ± 8.81 years and BMI 33.25 ± 1.52) or standard LCD based on American Diabetes Association (ADA) guidelines ($n = 45$; mean age = 54.17 ± 7.97 years and BMI 32.88 ± 1.60). Clinical outcomes were assessed at baseline and at the 4-month follow-up. A significant reduction in body weight (91.5 ± 11.4 vs. 76.8 ± 9.1 kg; $p < 0.0001$), WC (108.1 ± 8.6 vs. 96.1 ± 7.6 cm; $p < 0.0001$), fasting glycemia (136.9 ± 34.4 vs. 108.9 ± 20.4 mg/dL; $p < 0.0001$), HbA1c (6.9 ± 1.1 vs. 6.0 ± 0.7% total Hb; $p < 0.0001$), the HOMA-IR index (6.9 ± 4.4 vs. 3.5 ± 1.9; $p < 0.0001$), and TG (150.5 ± 54.4 vs. 114.6 ± 57.2 mg/dL; $p = 0.004$) was observed with a VLCKD. On the other hand, a reduction only in WC (105.8 ± 8.5 vs. 100.4 ± 9.2 cm; $p = 0.048$) and the HOMA-IR index (5.8 ± 2.9 vs. 4.6 ± 2.5; $p = 0.001$) was observed in the LCD group.

Gomez-Arbelaez et al. [29] conducted a prospective interventional noncontrolled study in 20 adult patients with obesity (mean age 47.2 ± 10.2 years and BMI 35.5 ± 4.4) and who underwent a nutritional intervention based on a VLCKD. Anthropometric and body composition assessments were conducted at baseline and at a mean of 40, 90, and 120 days. At the 6-month follow-up, significant weight loss (95.9 ± 16.3 vs. 75.1 ± 11.8 kg; $p < 0.05$) and a reduction in WC (109.4 ± 12.8 vs. 88.6 ± 10.1 cm; $p < 0.05$), FM (42.2 ± 9.1 vs. 25.7 ± 5.8 kg; $p < 0.05$), and FFM (52.8 ± 10.2 vs. 49.0 ± 9.7 kg; $p < 0.05$) were observed.

Gutiérrez-Repiso et al. [30] conducted a randomized controlled study recruiting 33 patients with obesity (BMI ≥30) treated with a weight loss program VLCKD followed by an LCD over a period of 4 months of follow-up. Participants were allocated randomly to the following 3 arms: those supplemented with synbiotics during the VLCKD and the LCD ($n = 15$; mean age 48.67 ± 9.16 years and BMI 32.82 ± 1.76), those supplemented with a placebo during the VLCKD and synbiotics during the LCD phase ($n = 9$; mean age = 47.00 ± 8.97 years and BMI

32.96 ± 1.47), and a control group receiving a placebo during the VLCKD and the LCD (n = 9; mean age = 38.22 ± 11.27 years and BMI 33.14 ± 1.47). In all 3 treatment arms, calorie restriction induced significant changes in body weight (arm 1: 92.74 ± 15.86 vs. 79.78 ± 13.92 kg, $p < 0.01$; arm 2: 95.71 ± 9.46 vs. 76.63 ± 12.83 kg, $p < 0.01$; and arm 3: 90.58 ± 10.83 vs. 77.62 ± 8.22 kg, $p < 0.01$), WC (arm 1: 110.40 ± 10.88 vs. 97.53 ± 9.13 cm, $p < 0.01$; arm 2: 111.22 ± 7.12 vs. 95.67 ± 7.09 cm, $p < 0.01$, and arm 3: 109.67 ± 6.30 vs. 93.67 ± 5.74 cm, $p < 0.01$), FM (arm 1: 38.99 ± 8.35 vs. 26.97 ± 3.36 kg, $p < 0.01$; arm 2: 36.04 ± 5.89 vs. 23.63 ± 5.39 kg, $p < 0.01$; and arm 3: 34.20 ± 4.35 vs. 24.33 ± 5.33 kg, $p < 0.01$), and FFM (arm 2: 59.67 ± 11.31 vs. 55.98 ± 9.80 kg, $p < 0.01$; and arm 3: 56.40 ± 11.69 vs. 53.29 ± 10.45 kg, $p < 0.01$). Significant improvements were also observed in biochemical variables such as glycemia (arm 1: 93.13 ± 10.80 vs. 87.93 ± 10.24 mg/dL, $p < 0.05$; and arm 3: 88.77 ± 11.37 vs. 78.44 ± 4.30 mg/dL, $p < 0.01$), HDL cholesterol (arm 1: 57.07 ± 10.56 vs. 63.57 ± 11.02 mg/dL, $p < 0.05$; arm 2: 56.62 ± 11.68 vs. 67.11 ± 15.96 mg/dL, $p < 0.05$; and arm 3: 50.77 ± 14.43 vs. 62.00 ± 15.81 mg/dL, $p < 0.01$), and TG (arm 1: 133.33 ± 84.02 vs. 89.53 ± 31.37 mg/dL, $p < 0.05$; and arm 2: 146.11 ± 77.85 vs. 75.55 ± 28.71 mg/dL, $p < 0.05$).

Leonetti et al. [31] conducted a prospective noncontrolled study in which they evaluated the effectiveness of a sequential diet composed of a VLCKD (10 days), followed by a VLCD (10 days) and finally a LCD (10 days), in 50 patients affected by obesity (mean age = 47.4 ± 11.2 years and BMI 53.5 ± 8.4) who were scheduled for laparoscopic bariatric surgery. Body weight (150.4 ± 26.3 vs. 137.6 ± 22.5 kg; $p < 0.0001$), BMI (53.5 ± 8.4 vs. 49.2 ± 8.7; $p < 0.0001$), and WC (145.0 ± 15.6 vs. 126.4 ± 16.5 cm; $p < 0.003$) were significantly lower after 1 month of a sequential diet regime. However, the lipid profile did not show significant changes from baseline to 1 month.

Merra et al. [13] conducted a double-blind study in 18 adult participants with a BMI ≥25 and a FM ≥25% in males and ≥30 in females and who were randomized to a VLCKD integrated with amino acids (n = 9; mean age = 45.50 ± 16.39 years and BMI 33.69 ± 3.51) or a VLCD (n = 9; mean age = 49.33 ± 13.78 years and BMI 29.21 ± 1.07). Anthropometric data and body composition were assessed at baseline and after 3 weeks. Significant weight loss was noticed in the VLCKD (99.78 ± 4.57 vs. 92.80 ± 4.78 kg; $p = 0.00$) and VLCD (74.77 ± 5.04 vs. 68.80 ± 4.24 kg; $p = 0.00$) groups, accompanied by a reduction in FM (VLCKD: 37.24 ± 9.31 vs. 34.79 ± 9.38 kg; $p = 0.02$; VLCD: 33.06 ± 3.60 vs. 30.59 ± 3.65 kg; $p = 0.00$). Interestingly, the VLCKD group showed a reduction in WC (103.90 ± 5.98 vs. 98.40 ± 5.91 cm; $p = 0.00$) and conservation of the FFM (53.01 ± 12.86 vs. 54.93 ± 8.96; $p = 0.75$), while the VLCD group showed no change in WC (84.72 ± 2.73 vs. 83.75 ± 7.05 cm; $p = 0.34$) and a significant decrease in FFM (39.00 ± 3.03 vs. 35.70 ± 3.09 kg; $p = 0.00$).

Moreno et al. [32] conducted a controlled trial including a total of 79 patients with obesity randomized to a VLCKD (n = 27; mean age 44.4 ± 8.6 years, body weight 97.9 ± 18.9 kg, and BMI 35.1 ± 4.5) or a standard LCD (n = 26; mean age 46.3 ± 9.3 years, body weight: 92.1 ± 17.7 kg, and BMI 35.1 ± 5.3) over a 1-year follow-up. Both arms received external support counselling to perform physical activity and adhered to the diet. Body weight, WC, and BMI were the primary outcome measures. The main secondary outcomes were cardiovascular risk factors, adherence, body composition (i.e., FM and FFM), and other metabolic parameters (i.e., FBG, HbA1c, HDL and LDL cholesterol, TG, and others). Briefly, the weight reduction in the VLCKD and LCD groups was 13.6 ± 3.9 and 4.8 ± 2.7 kg ($p < 0.0001$), respectively, at 2 months, and this significant difference was maintained at the end of the follow-up (19.9 ± 12.3 vs. 7.0 ± 5.6 kg: $p < 0.0001$). Moreover, at the 1-year follow-up most of the patients in the VLCKD group had lost > 10% of their initial body weight and their lean mass was well preserved. The same authors later published their data on a longer follow-up that reached 24 months [10], apparently in a subgroup of their previous study, with potential samples overlapping; their aim was to evaluate the long-term effect of VLCKD (n = 22) versus LCD (n = 23) in terms of body weight, W and FM in a randomized trial. At 24 months, the VLCKD, when compared to the LCD, induced a significantly major reduction in body weight (–12.5 vs. –4.4 kg; $p < 0.001$), WC (–11.6 vs. 4.1 cm; $p < 0.001$), FM (–8.8 vs. 3.8 kg; $p < 0.001$), and visceral fat (–600 g vs. –202 g; $p < 0.001$).

Perticone et al. [33] conducted a randomized controlled trial enrolling 56 outpatients with obesity who went on either a traditional standard hypocaloric Mediterranean diet (n = 28; mean age = 50.9 ± 13.3 years, and BMI 38.8 ± 4.5) or a VLCKD (n = 28; mean age = 42.6 ± 6.6 years, and BMI 40.5 ± 10.8). After a 1-year follow-up, the standard hypocaloric Mediterranean diet group showed significant improvement in the glycemic profile represented by FBG (115.3 ± 32.6 vs. 99.7 ± 11.4 mg/dL; $p = 0.048$), HbA1c (6.5 ± 1.5 vs. 5.4 ± 0.18% Hb total; $p = 0.034$), and the HOMA-IR index (7.4 ± 0.9 vs. 3.5 ± 0.4; $p = 0.001$), as well as a reduction in TG (158.5 ± 62.3 vs. 113.0 ± 21.5 mg/dL; $p = 0.039$). On the other hand, reductions in WC (119.1 ± 22.9 vs. 95.0 ± 17.4 cm; $p = 0.044$),

HbA1c (6.1 ± 1.4 vs. 5.2 ± 0.15% Hb total; $p = 0.022$), the HOMA-IR index (7.3 ± 0.7 vs. 2.6 ± 0.2; $p < 0.0001$), and TG (151.3 ± 50.0 vs. 72.3 ± 29.6 mg/dL; $p = 0.004$) were observed in the VLCKD group.

Rubini et al. [34] conducted a 2-arm randomized controlled trial including 32 healthy subjects with overweight (BMI from 25 to 30). The first arm ($n = 16$; mean age 51.4 ± 12.4 years, body weight 82.0 ± 12.4 kg, and BMI 29.3 ± 2.8) followed a VLCKD for 20 days, switching to a low-carbohydrate nonketogenic diet for 20 days more, and finally to a Mediterranean diet for 2 more months. The mean body weight at 20 days, 40 days, and 2 months was 77.8 ± 12.0, 74.8 ± 11.7, and 73.5 ± 12.6 kg, respectively. The second arm ($n = 16$; mean age 44.7 ± 13.9 years, body weight 77.2 ± 9.8 kg, and BMI 27.5 ± 2.8.4) followed a Mediterranean diet over the same duration, with a mean body weight at 20 days, 40 days, and 2 months of 74.4 ± 10.0, 72.5 ± 9.6, and 72.1 ± 10.7 kg, respectively. Briefly, the average weight loss was 8.4 kg for the VLCKD group and 5.1 kg for the Mediterranean diet group at 3.5 months of follow-up. Both groups showed a reduction in FM, which was more significant for the VLCKD group.

Sajoux et al. [35] published a controlled study that included 79 patients with obesity; one group went on a VLCKD ($n = 20$; mean age 47.1 ± 10.2 years and BMI 35.5 ± 4.4), another group underwent a nutritional intervention based on a LCD ($n = 20$; mean age 49.9 ± 9.3 years and BMI 35.8 ± 4.5), and a third group comprised of those with morbid obesity underwent bariatric surgery (i.e., Roux-en-Y gastric bypass, biliopancreatic diversion, and sleeve gastrectomy; $n = 39$; mean age 40.8 ± 10.4 years, and BMI 45.6 ± 6.2). All of the patients included in this study achieved a statistically significant weight loss. At 4–6 months of follow-up, the VLCKD diet induced a ~20-kg reduction of body weight (96.0 ± 16.3 vs. 76.6 ± 11.1 kg; $p < 0.05$) compared to the ~38-kg reduction induced by bariatric surgery (121.3 ± 21.5 vs. 81.7 ± 14.3 kg; $p < 0.05$) and the ~9 kg reduction after the LCD (93.0 ± 13.2 vs. 87.6 ± 12.3 kg; $p < 0.05$). This was accompanied by a loss of ~16 kg of FM (42.2 ± 9.2 vs. 25.7 ± 5.8 kg; $p < 0.05$) and ~4 kg of FFM (52.8 ± 10.3 vs. 49.1 ± 9.7 kg; $p < 0.05$) in the VLCKD group. Patients who underwent bariatric surgery showed a ~31-kg reduction of FM (62.57 ± 14.9 vs. 31.7 ± 8.2 kg; $p < 0.05$) and a ~7-kg reduction of FFM (56.7 ± 9.9 vs. 49.6 ± 8.5 kg; $p < 0.05$), and the LCD induced a ~7-kg reduction of FM (34.6 ± 8.3 vs. 30.7 ± 7.6 kg; $p < 0.05$) and a ~2-kg reduction of FFM (57.6 ± 11.6 vs. 56.9 ± 11.2 kg; $p < 0.05$). Finally, the 3 weight loss approaches induced a significant improvement in the HOMA-IR index, with the larger improvement induced by the VLCKD.

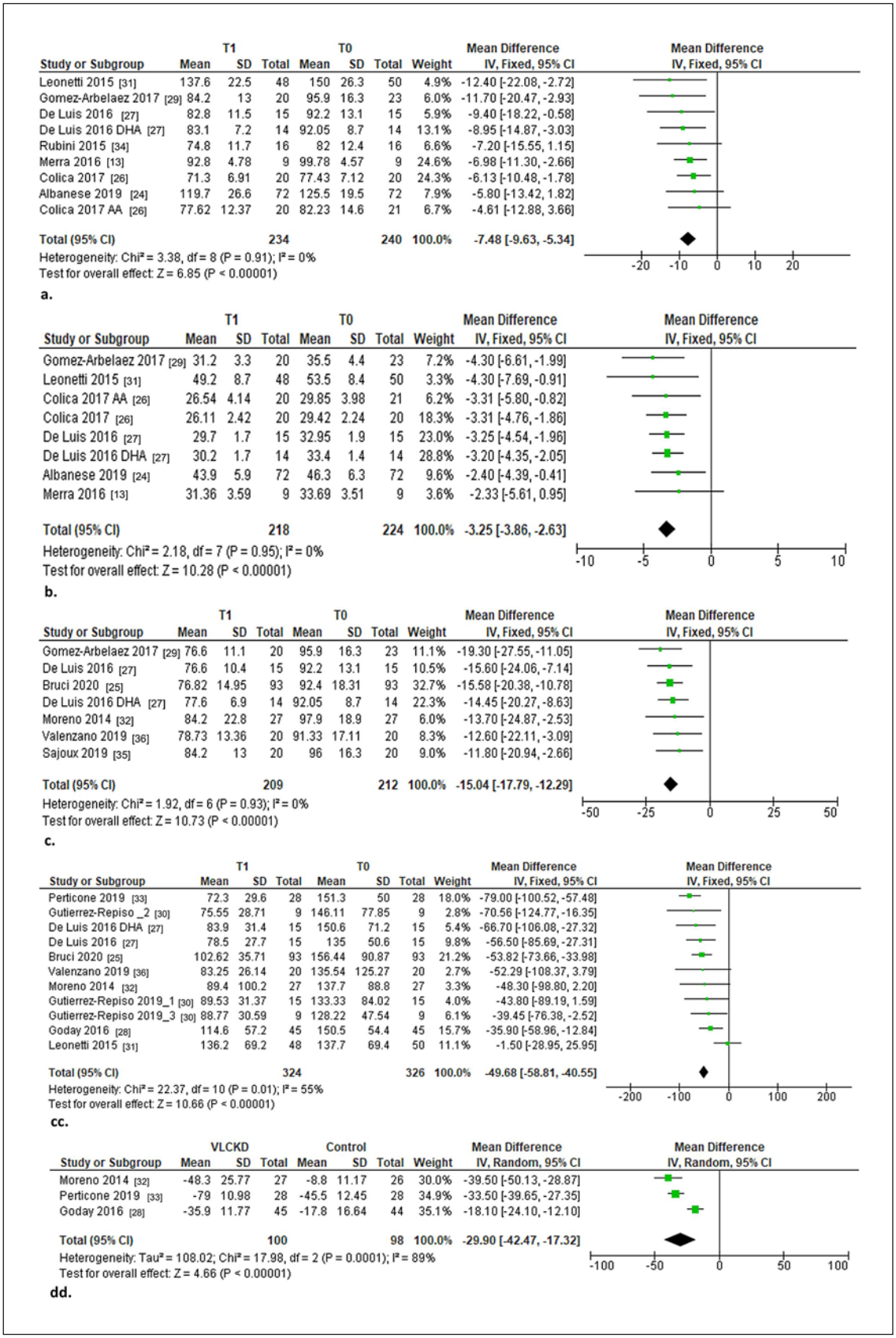
Finally, Valenzano et al. [36] conducted small prospective noncontrolled study including 20 patients with obesity (mean age 48 ± 8.2 years and BMI 32.19 ± 4.78) who underwent an 8-week nutritional intervention based on a VLCKD. The VLCKD resulted in significant weight loss (91.33 ± 17.11 vs. 78.73 ± 13.36 kg; $p < 0.001$) and a reduction of total (220.13 ± 50.77 vs. 173.91 ± 32.93 mg/dL; $p < 0.05$) and LDL cholesterol (141.83 ± 36.48 vs. 107.57 ± 27.72 mg/dL; $p < 0.05$), as well as TG (135.54 ± 125.27 vs. 83.25 ± 26.14 mg/dL; $p < 0.05$). Finally, a significant decrease in total FM (39,208.77 ± 1,432.55 vs. 27,377.0 ± 1,217.48 g; $p < 0.001$) and visceral adipose tissue (1,541.55 ± 141.63 vs. 927.79 ± 104.92 g; $p < 0.001$) was observed.

Meta-Analysis

Fourteen of the 15 included studies underwent meta-analysis, and only 1 study was excluded [10] because of potential sample overlapping. The primary outcome was the change in body weight and BMI from baseline to fol-

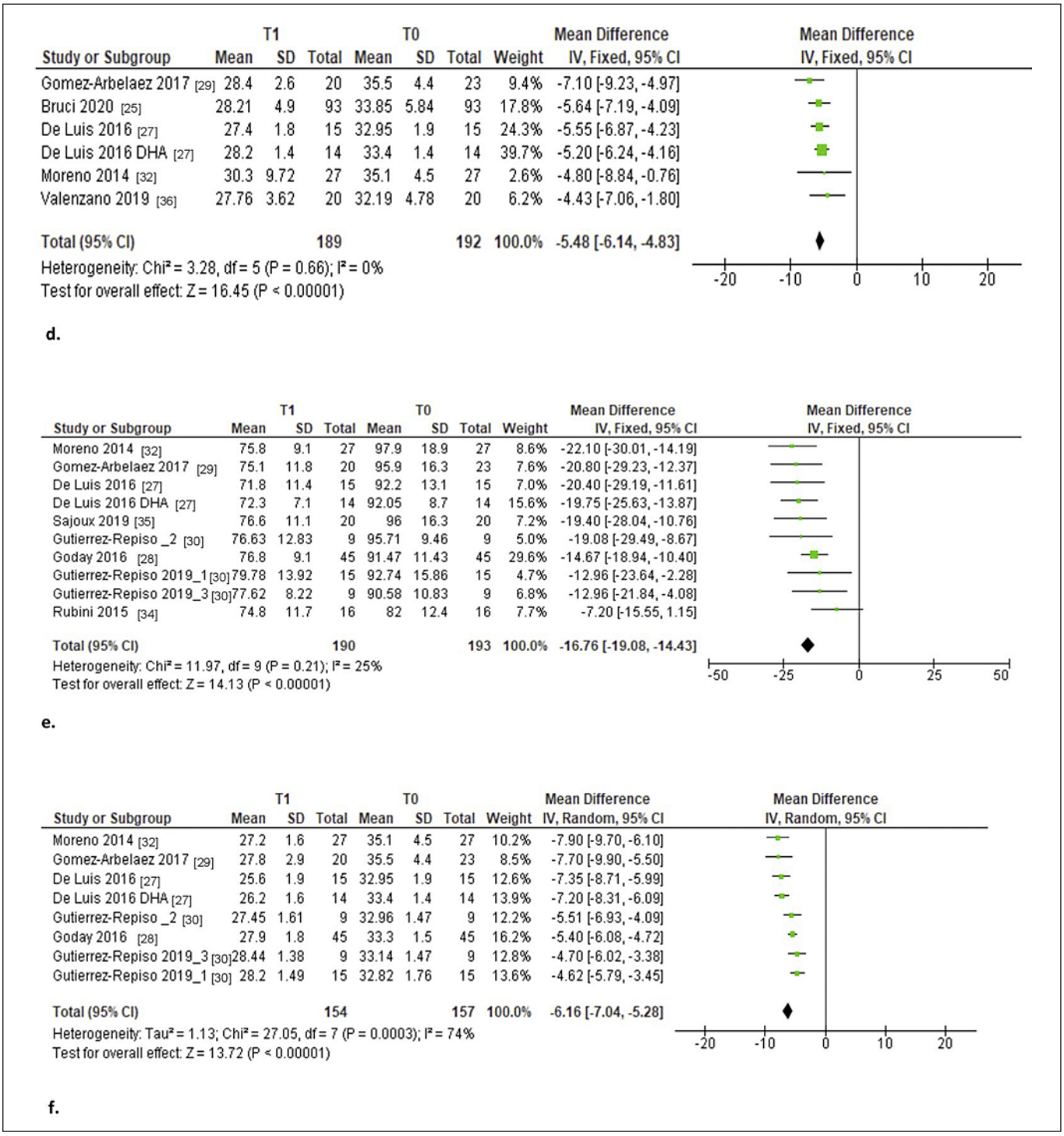
Fig. 3. Forest plots of the changes in clinical outcomes. **a** Weight loss (kg) after 1 month of VLCKD. **b** Weight loss as BMI after 1 month of VLCKD. **c** Weight loss (kg) after 2 months of VLCKD. **d** Weight loss as BMI after 2 months of VLCKD. **e** Weight loss (kg) after 4–6 months of VLCKD. **f** Weight loss as BMI after 4–6 months of VLCKD. **g** Weight loss (kg) after 12 months of VLCKD. **h** Weight loss as BMI after 12 months of VLCKD. **i** Comparison of mean weight loss (kg) between VLCKD and controls. **j** Comparison of mean weight loss as BMI between VLCKD and controls. **k** Reduction of WC (cm) after VLCKD. **l** Comparison of mean difference in WC (cm) between VLCKD and controls. **m** Reduction of FM (kg) after VLCKD. **n** Comparison of the mean difference in FM (kg) between VLCKD and controls. **o** Reduction of FFM (kg) after VLCKD. **p** Comparison of the mean difference in FFM (kg) between VLCKD and controls. **q** Reduction of glycemia (mg/dL) after VLCKD. **r** Comparison of the mean change in glycemia (mg/dL) between VLCKD and controls. **s** Change in HbA1c after VLCKD. **t** Comparison of the mean change in HbA1c between VLCKD and controls. **u** Change in HOMA-IR after VLCKD. **v** Comparison of the mean change in HOMA-IR between VLCKD and controls. **w** Change in serum total cholesterol (mg/dL) after VLCKD. **x** Comparison of the mean change in serum total cholesterol (mg/dL) between VLCKD and controls. **y** Change in serum LDL cholesterol (mg/dL) after VLCKD. **z** Comparison of the mean change in serum LDL cholesterol (mg/dL) between VLCKD and controls. **aa** Change in serum HDL cholesterol (mg/dL) after VLCKD. **bb** Comparison of the mean change in serum HDL cholesterol (mg/dL) between VLCKD and controls. **cc** Change in serum TG (mg/dL) after VLCKD. **dd** Comparison of the mean change in serum TG (mg/dL) between VLCKD and controls.

(For figure see next pages.)



3

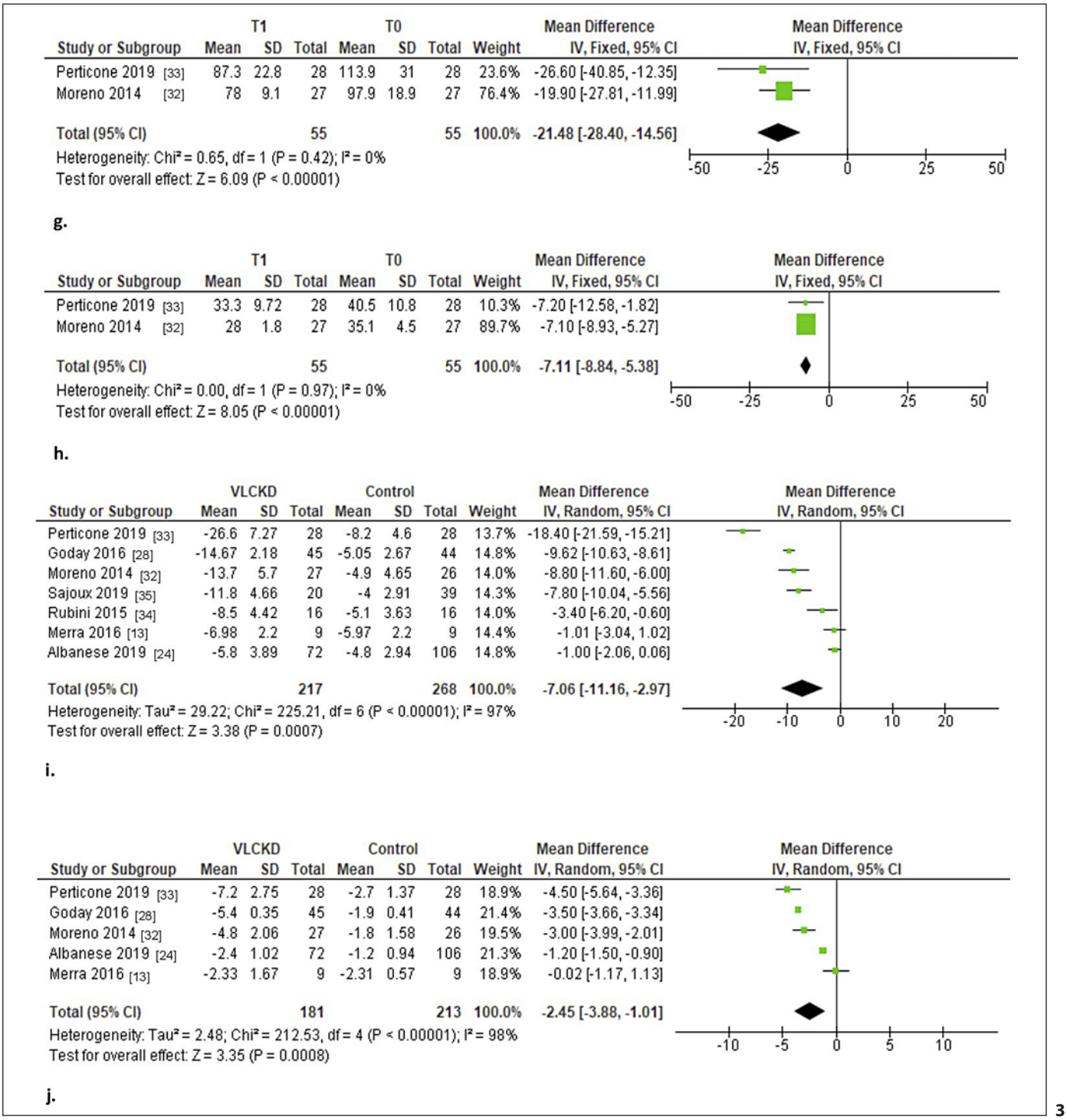
(Figure continued on next pages.)



3

(Figure continued on next pages.)

low-up with a VLCKD. Secondary outcomes were changes in body composition (expressed as WC in cm, FM in kg, and FFM in kg), the glycemic profile (expressed as glycemia in mg/dL, glycosylated hemoglobin HbA1c in % total Hb, and the HOMA-IR index), and the lipid profile (expressed as total cholesterol, in LDL and HDL cholesterol, and TG in mg/dL) from baseline to follow-up with a VLCKD. Moreover, comparisons between a VLCKD and any other weight loss intervention (i.e., mainly LCD) of the same duration were performed (Fig. 3).

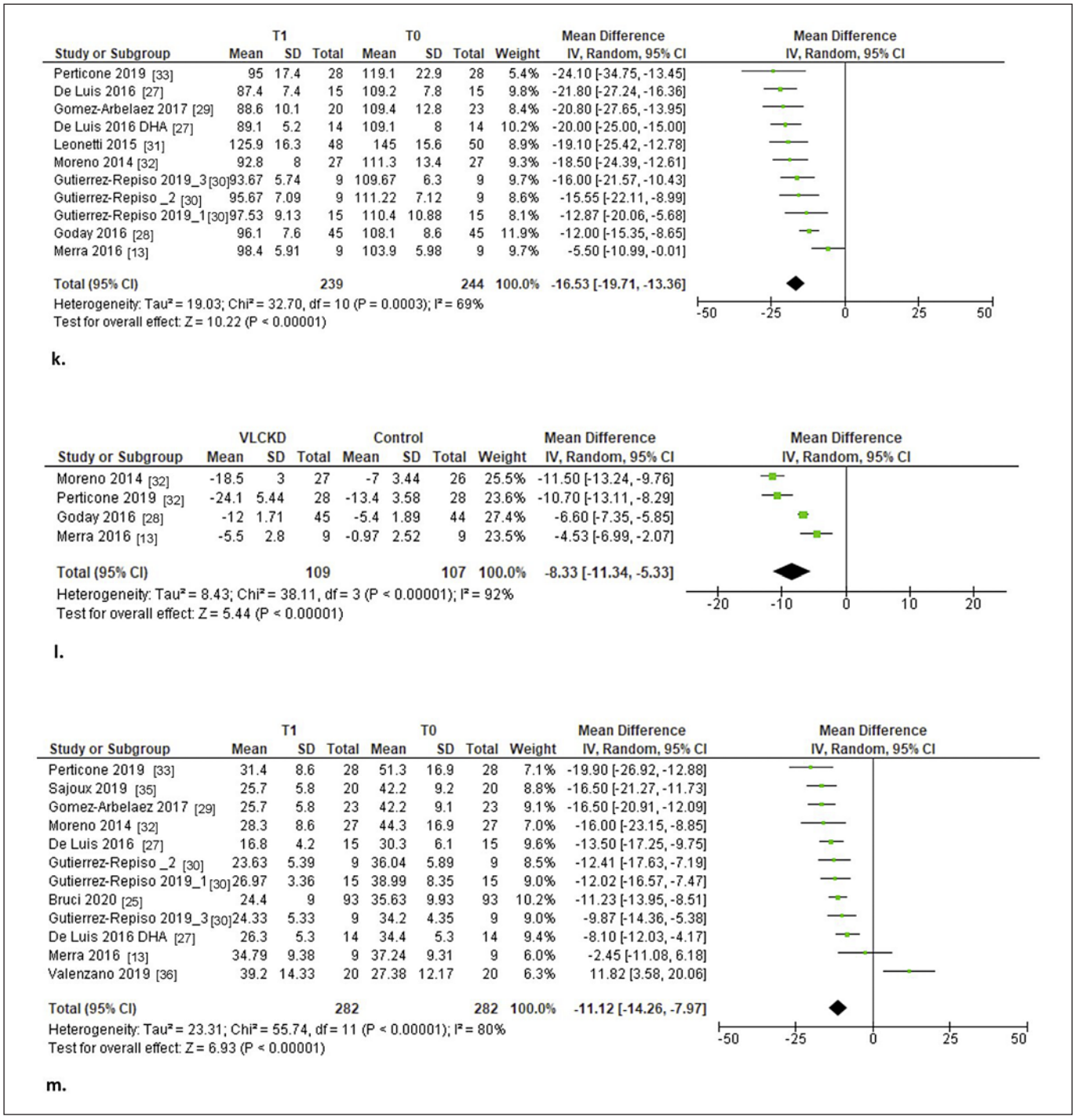


3

(Figure continued on next pages.)

Body Weight Status

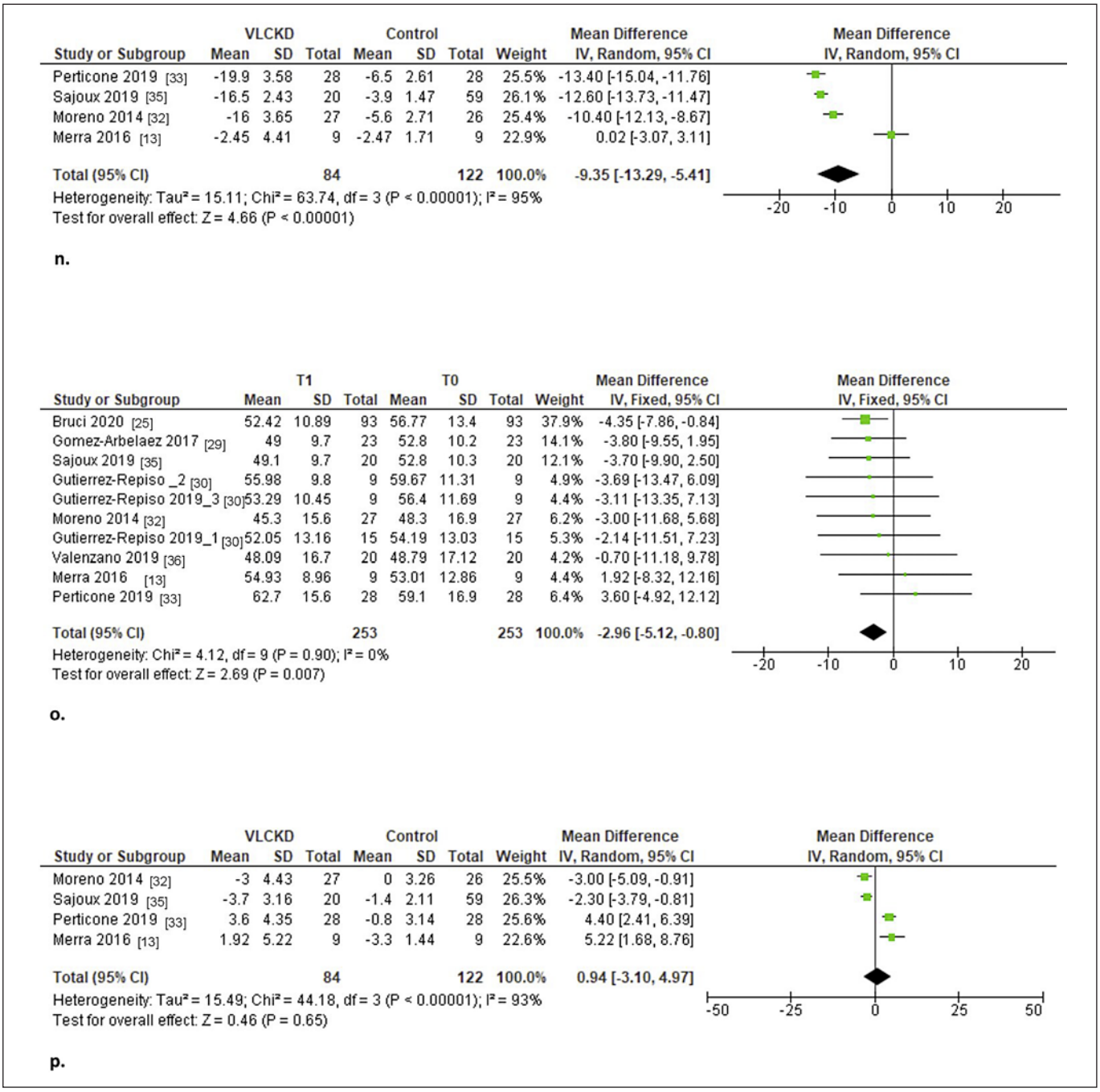
At the 1-month follow-up a VLCKD was associated with a weight loss of –7.48 kg (95% CI –9.63 to –5.34; I^2 = 0%) and a reduction of the BMI of –3.25 (95% CI –3.86 to –2.63; I^2 = 0%; Fig. 3a, b). In the same direction, at the 2-month follow-up a VLCKD was associated with a weight loss of –15.04 kg (95% CI –17.79 to –12.29; I^2 = 0%) and a reduction of the BMI of –5.48 (95% CI –6.14 to –4.83; I^2 = 0%; Fig. 3c, d). At the intermediate weight loss follow-up, i.e., at the 4- to 6-month follow-up, a VLCKD was as-



3

(Figure continued on next pages.)

sociated with a weight loss of –16.76 kg (95% CI –19.08 to –14.43; $I^2 = 25\%$) and a reduction of the BMI of –6.16 (95% CI –7.04 to –5.28; $I^2 = 74\%$; Fig. 3e, f). At the 12-month follow-up, a VLCKD was associated with a weight loss of –21.48 kg (95% CI –28.40 to –14.56; $I^2 = 0\%$) and a reduction of the BMI of –7.11 (95% CI –8.84 to –5.38; $I^2 = 0\%$; Fig. 2g, h). In a comparison between a VLCKD and other weight loss interventions of the same duration, the former showed a major significant mean weight loss ($p = 0.0007$) in terms of body weight (–7.06 kg; 95% CI –11.16 to –2.97; $I^2 = 97\%$; $p = 0.0007$) and BMI (–2.45; 95% CI –3.88 to –1.01; $I^2 = 98\%$; $p = 0.0008$; Fig. 3i, j).

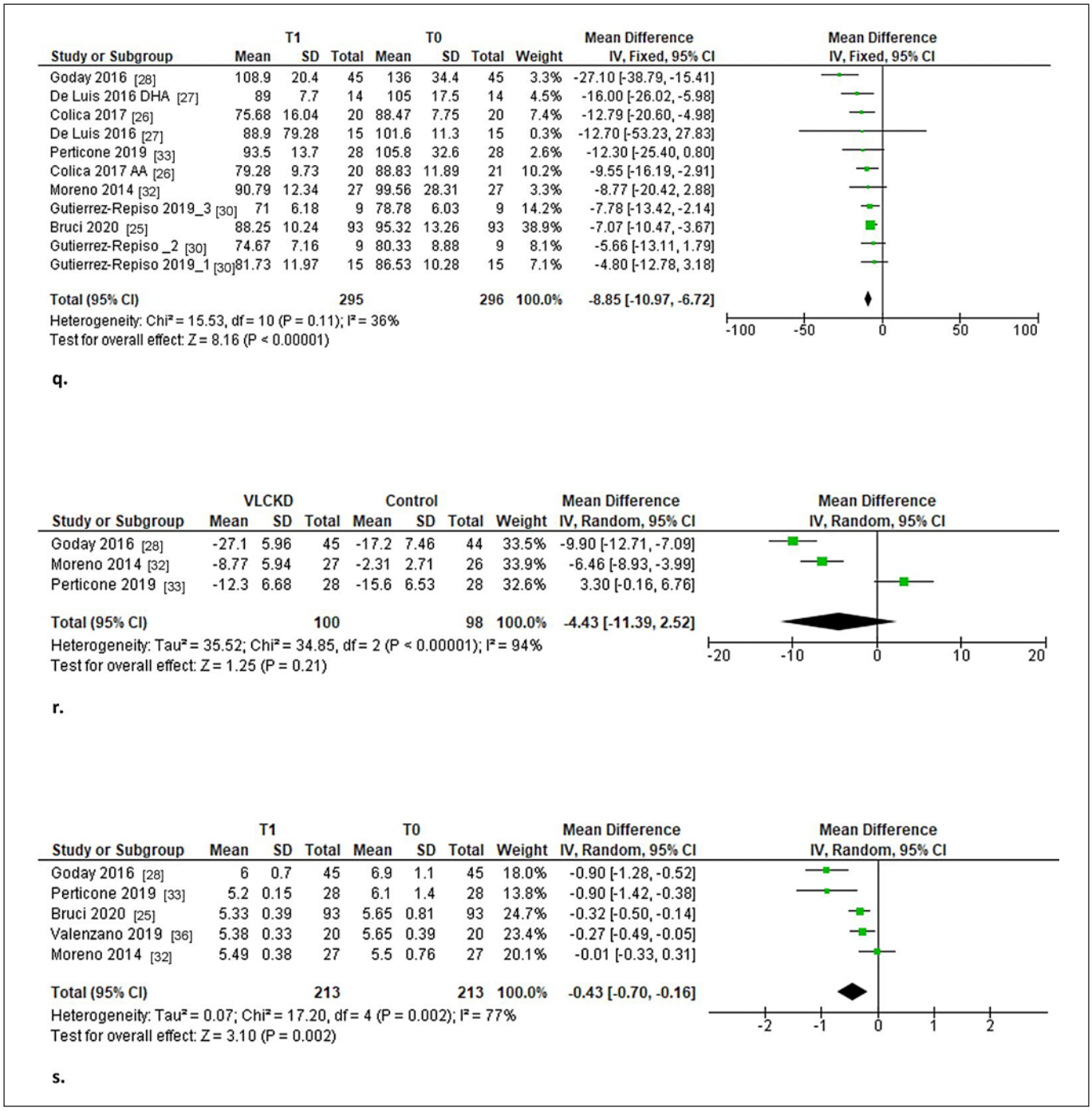


3

(Figure continued on next pages.)

Body Composition

A significant reduction of WC from baseline was observed after VLCKD (–16.53 cm; 95% CI –19.71 to –13.36; $I^2 = 69\%$; Fig. 3k). Moreover, the comparison between VLCKD and other weight loss interventions of same duration showed a larger mean reduction of WC (–8.33 cm; 95% CI –11.34 to –5.33; $I^2 = 92\%$; $p < 0.00001$; Fig. 3l). In the same direction, a significant reduction of FM from baseline was observed after a VLCKD (–11.12 kg; 95% CI –14.26 to –7.97; $I^2 = 80\%$). In addition, compared to any weight loss intervention, a VLCKD showed superiority in the reduction of FM (–9. 35 kg; 95% CI –13.29 to –5.41; $I^2 = 95\%$; $p < 0.00001$; Fig. 3m, n). On the other hand, although the reduction in FFM after a VLCKD was –2.96 kg (95% CI –5.12 to –0.80; $I^2 = 0\%$), this was not significantly different from the reduction in



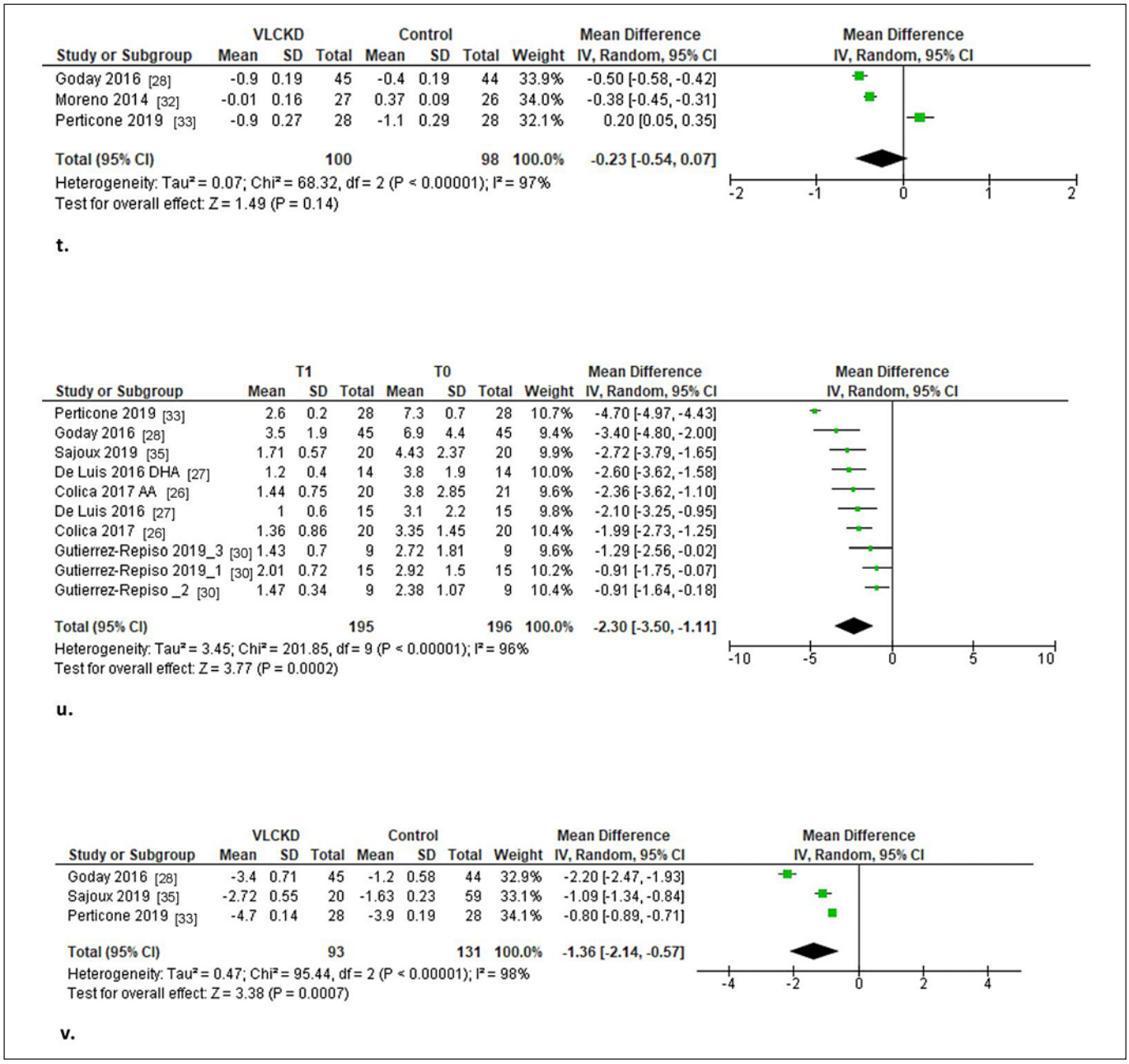
3

(Figure continued on next pages.)

FFM caused by other weight management interventions ($p = 0.65$; Fig. 3o, p).

Glycemic Profile

In terms of fasting glycemia, a significant reduction of –8.85 mg/dL (95% CI –10.97 to –6.72; $I^2 = 36\%$) was observed after a VLCKD, but this effect was not superior to that of other types of weight loss interventions ($p = 0.21$; Fig. 3q, r). In the same way, a significant reduction in HbA1c (–0.43%; 95% CI –0.70 to –0.16; $I^2 = 77\%$) was observed after a VLCKD, without significant differences in comparison to other weight loss treatments ($p = 0.14$; Fig. 3s, t). On the other hand, a reduction in the HOMA-IR index from baseline after a VLCKD (–2.30; 95% CI



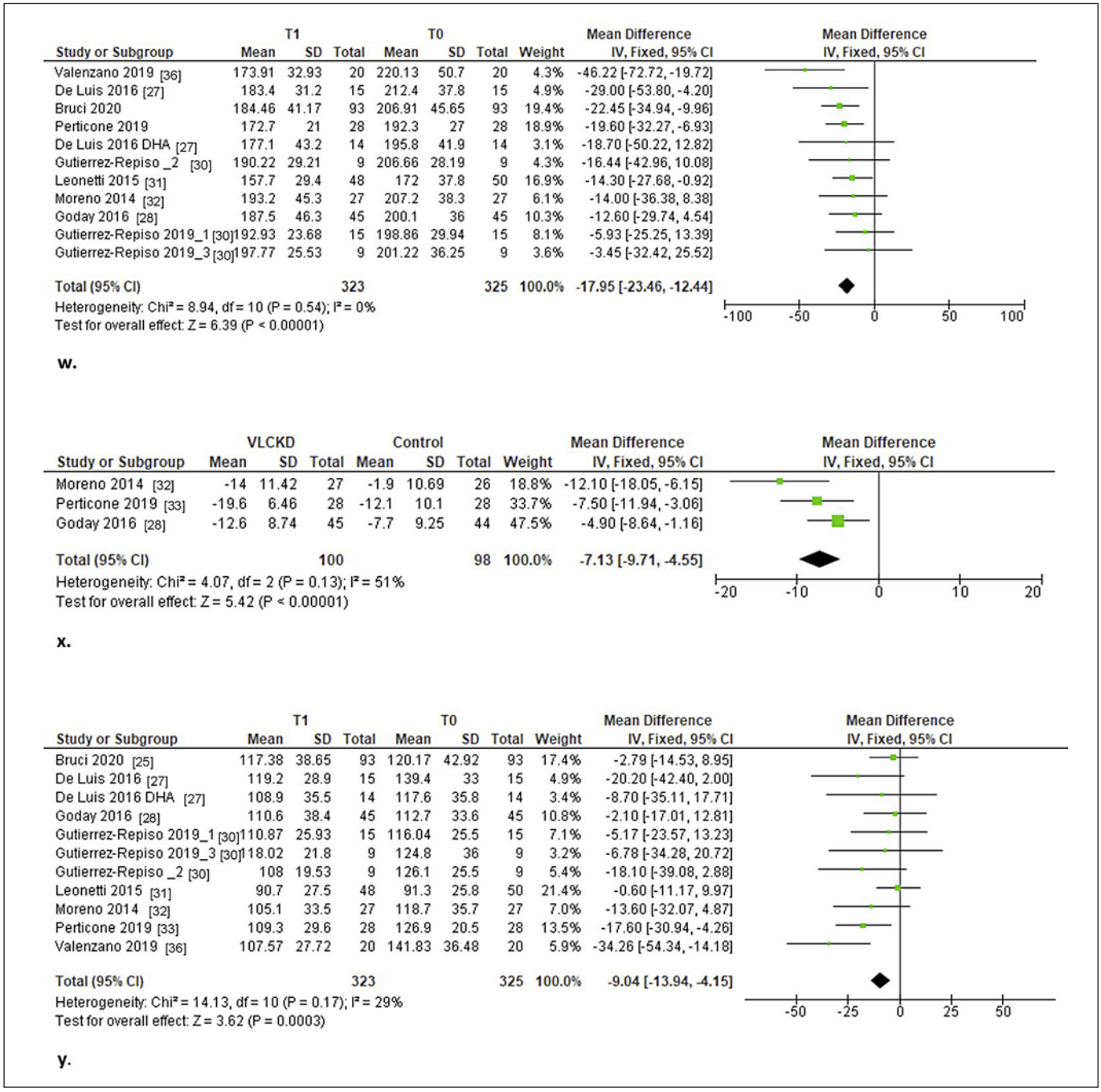
3

(Figure continued on next pages.)

–3.50 to –1.11; I^2 = 96%) was observed. A VLCKD had a superior effect in reducing the HOMA-IR index by –1.36 (95% CI –2.14 to –0.57; I^2 = 98%; p < 0.00001), i.e., more than the other weight loss programs (Fig. 3u, v).

Lipid Profile

A reduction in total cholesterol after VLCKD (–17.95 mg/dL; 95% CI –23.46 to –12.44; I^2 = 0%) was observed, with a VLCKD having a larger effect in reducing total cholesterol by –7.13 mg/dL with respect to other types of weight loss interventions (95% CI –9.71 to –4.55; I^2 = 51%; p < 0.00001; Fig. 3w, x). A significant reduction in LDL of –9.04 mg/dL from baseline to follow-up after a VLCKD (95% CI –13.94 to –4.15; I^2 = 29%) was observed. However, a VLCKD did not demonstrate a superior effect in terms of LDL reduction compared to other weight loss diets (p = 0.12; Fig. 3y, z). HDL showed no change from baseline to follow-up after a VLCKD (p = 0.85), and interestingly when we compare the mean change in HDL cholesterol between a VLCKD and other weight loss in-



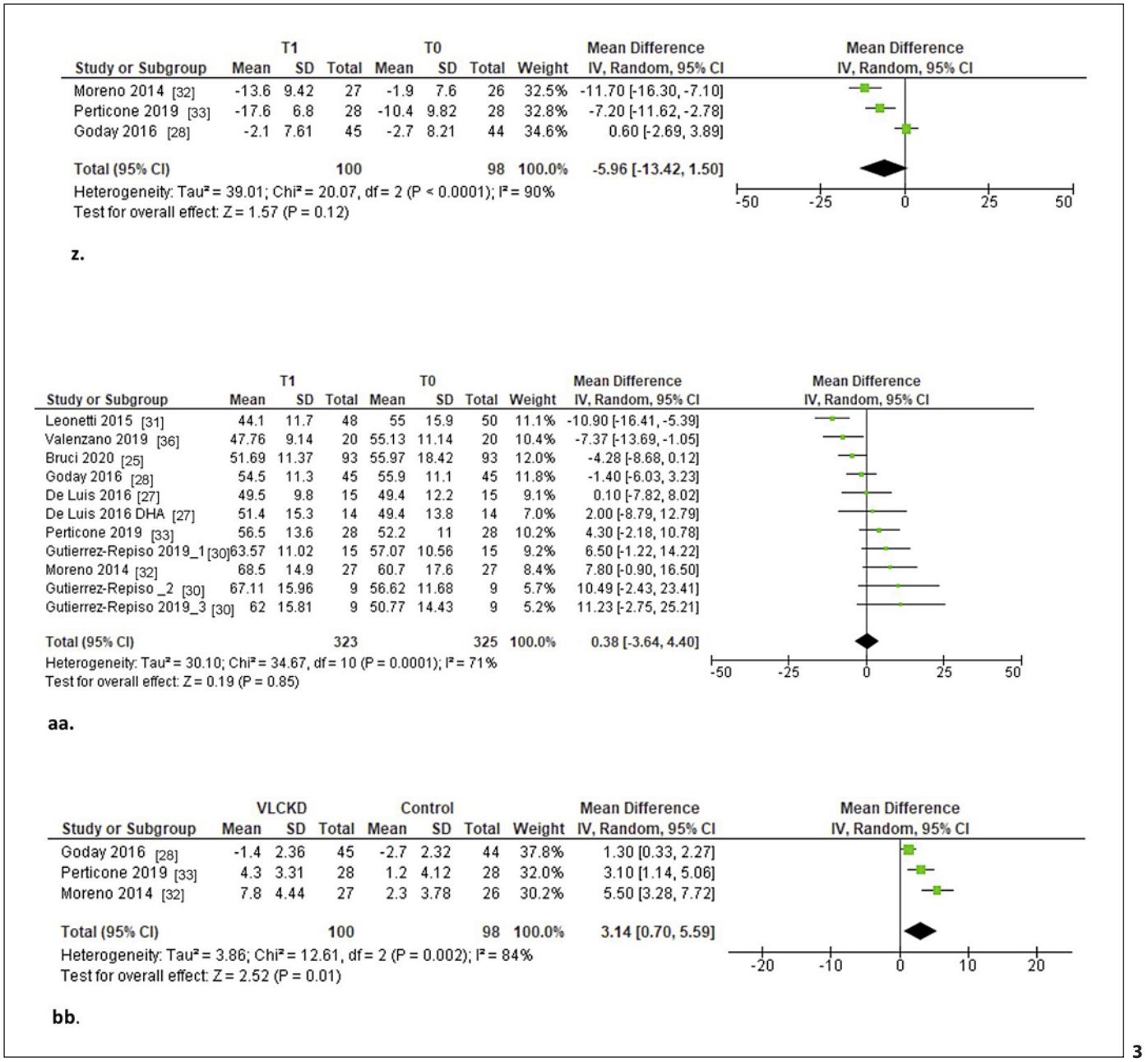
3

(Figure continued on next page.)

terventions we noticed a significant difference between the two (+3.14; 95% CI 0.70–5.59; I^2 = 84%; p = 0.01; Fig. 3aa, 3bb). Finally, a significant reduction in TG (–49.68 mg/dL: 95% CI –58.81 to –40.55; I^2 = 55%) was observed after a VLCKD. The reduction of TG was larger after a VLCKD (~–29.90 mg/dL; 95% CI –42.47 to –17.32; I^2 = 89%; p < 0.00001) compared to other diets (Fig. 3cc, dd).

Indications and Contraindications of VLCKD

The main indications for the use of VLCKD in obesity are: severe obesity, treatment of obesity with bariatric indications in the preoperative period before the bariatric procedure, sarcopenic obesity, and obesity associated with hypertriglyceridemia and/or hypertension and/or type 2 diabetes and/or metabolic syndrome



3

and/or NAFLD and/or obstructive sleep apnea syndrome and/or bone diseases or severe arthropathy [12, 37].

Absolute contraindications are: type 1 diabetes mellitus, latent autoimmune diabetes in adults, β-cell failure in type 2 diabetes mellitus, use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (risk of euglycemic diabetic ketoacidosis), pregnancy and breastfeeding, kidney failure and severe chronic kidney disease, liver failure, hearth failure (NYHA III–IV), respiratory insufficiency, unstable angina, a recent stroke or myocardial infarction (<12 months), cardiac arrhythmias, eating disorders and other severe mental illnesses, alcohol and substance abuse, active/severe infections, frail elderly patients, 48 h prior to an elective surgery or invasive procedures and a perioperative period, rare disorders such as porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders, and pyruvate carboxylase deficiency [12, 37].

Table 2. Parameters monitored during a VLCKD

Parameters	Baseline	During the active stage	At the end of the active stage	At the end of the reintroduction stage
Antropometric assessment				
Weight, height, and BMI	X	X	X	X
Body composition and hydration status (by bioelectrical impedance analysis)	X	X	X	X
Laboratory assessment				
Complete blood count with platelets	X	X	X	X
Sodium, potassium, magnesium, and inorganic phosphate	X	X	X	X
Serum liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine, γ-GT, and total and direct bilirubin)	X	X	X	X
Fasting lipid profile	X			X
25(OH)D, calcium	X			X
Glucose and insulin	X			X
β-hydroxybutyrate (capillary blood or urine)		X		
TSH and FT4	X			
Complete urinalysis and microalbuminuria (urine)	X	X	X	X

Side Effects of VLCKD and Their Medical Management

The VLCKD is a nutritional approach that has significant beneficial effects on anthropometric and metabolic parameters and on body composition. To prevent side effects and to assess the efficacy of VLCKD, it is suggested to carry out periodic monitoring through a physical examination and laboratory assessment as reported in Table 2.

Common Side Effects

Dehydration-Related Disorders

Ketone bodies usually produced during the active stage of a VLCKD are passed via frequent and increased urination. This can lead to dehydration and a loss of electrolytes [38]. Dehydration-related disorders are mostly represented by a dry mouth, headache, dizziness/orthostatic hypotension, lethargy, and visual disturbances [8]. Thus, it is advisable to recommend a proper water intake (at least 2 L daily), in particular during the ketogenic state. Since liquid formulations of the analgesic could contain sugar, it is preferable to take analgesics as pills to relieve headache. The most common electrolyte alterations are represented by hyponatremia and hypomagnesemia, which are potentially a link not only to dehydration but also to the scarce intake of these micronutrients. Subjects with a normal sodium equilibrium experience natriuresis for a few days, usually from day 2 to day 6, with the peak natriuresis occurring on day 4, and after that they spontaneously recover. Mild kaliuresis occurs from day 5 to day 7 of the fast, after which there is a return to a positive potassium balance [39]. If there are no contraindications, an increased salt intake (2–3 g/day, except in hypertension, chronic kidney disease, or chronic heart failure) should be recommended to subjects with hypotension-related symptoms. Muscle cramps and sleep disturbances can be attenuated by the administration of magnesium.

Transient Hypoglycemia

Transient hypoglycemia could occur in the initial period of the active stage but also during the initial step-wise increase in caloric intake in the nonfasting protocol [38]. The acute calorie restriction along with the properties of ketone bodies to stimulate insulin secretion may result in transient hypoglycemia [40]. Furthermore, the decrease in FM consequent to weight loss results in decreased oxidation of lipids and increased oxidation of glucose. This net effect of the shift in oxidation of fuels improves glucose metabolism through the reduction of insulin resistance [41].

The decrease in hepatic triacylglycerol as a consequence of the reduced carbohydrate intake usually improves hepatic insulin resistance and thus reduces hepatic glucose production [42]. If hypoglycemia occurs, it is usually clinically mild and not associated with hypoglycemic symptoms. In the rare case where the blood glucose level is < 40 mg/dL and hypoglycemia is symptomatic, carbohydrate-containing beverages such as orange juice are recommended.

Halitosis

Subjects often report bad breath with a fruity smell once they reach full ketosis. This is caused by the increased ketone levels and in particular by an increase of acetone [43]. Chewing sugar-free gum and/or candy could be a strategy to manage this discomfort.

Gastrointestinal Side Effects

Nausea/vomiting, diarrhea, and constipation are the most common gastrointestinal side effects of a VLCKD and they can often lead to VLCKD discontinuation [38]. Diarrhea is usually easily manageable with short-term antidiarrhea medication. Diarrhea could be due to defective absorption and intolerance of fat. The high content of lipids can slow gastric emptying, favoring gastroesophageal reflux disease, nausea, and vomiting. Relief of this symptom could come from small and frequent meals, the sporadic use of gastrointestinal drugs such as antiemetics, gastrointestinal tract regulators, and antiacids. A decreased in water intake, fiber, and/or the volume of food can cause the onset to constipation [44]. If this is the case, it is recommended to increase the water and fiber intake and, in severe cases, the administration of low-calorie bulk laxatives and/or intermittent enemas. If subjects refer preexisting constipation, diverticular disease or hemorrhoids, it is recommended to prescribe extra dietary fiber (psyllium at 3.5 g twice daily) from the beginning of the nutritional protocol [45].

Hyperuricemia

Hyperuricemia could be detected in subjects on a VLCKD. Indeed, plasma uric acid levels usually increase if the diet is low in carbohydrates and they follow a biphasic course, with a peak in 1–2 weeks and then a decrease to baseline [46]. Special attention must be paid to patients with a prior history of gout because they could be more prone to developing exacerbations and they could benefit from allopurinol therapy. However, acute gouty arthritis has been reported in <1% of subjects on a VLCKD [47].

Lipid Profile Changes

A decrease in plasma TG, increased LDL cholesterol, and a neutral effect on HDL cholesterol are usually observed. The increase in LDL cholesterol is mostly due to a high lipid intake [12], but it is transient and values usually return to normal levels at the end of the VLCKD [48]. If the LDL level does not spontaneously improve after returning to a normal diet, the use of cholesterol-reducing medications should be taken into account.

Rare Side Effects

Hypoproteinemia

The glucogenogenic consumption due to carbohydrate restriction could result in hypoproteinemia [49]. Increasing the protein intake from 1 to 1.5 g/kg/day could be a strategy to manage this side effect.

Hypocalcemia and Bone Damage

Although no studies have been carried out in subjects on a VLCKD with the aim of investigating calcium metabolism, it could be hypothesized that a nutritional protocol rich in acid-ash protein could result in an excessive calcium loss because of its acidogenic content because calcium works as a buffer in the skeleton through the active resorption of bone [36]. Calciuria is positively related to net acid excretion and it is not compensated by increasing intestinal calcium absorption [50]. However, calciuria seems to be not so excessive as to increase the risk of developing osteoporosis [50]. Furthermore, in subjects on a VLCKD who are supplemented with a calcium intake (1,200 mg/day), the calcium balance has been reported to be positive [51]. However, since studies mostly on the long-term fracture risk are lacking, it is advisable to recommend an adequate intake of calcium and to treat vitamin D deficiency in order to restore vitamin D levels to normal during a VLCKD. Particular attention should be paid to subjects with osteopenia/osteoporosis who are at a high risk of developing fractures.

Urolithiasis

Chronic acidosis, dehydration, and fat malabsorption occurring during a VLCKD could predispose to urolithiasis [52, 53]. The stones mostly consist of uric acid, calcium oxalate, or a mixture of calcium oxalate and calcium phosphate/uric acid [52, 53]. This disorder is more common if there are risk factors such as a young age, a family history of kidney stones, and a urine Ca/Cr ratio >0.2 [52]. An adequate water intake (at least 2 L daily) along with the administration of oral potassium citrate is recommended to alkalinize urine, mostly in subjects with risk factors.

Gallstones

Weight loss during a VLCKD could increase the risk of developing gallstones, as previously reported after rapid weight loss, either via a VLCD or via bariatric surgery [54]. Supersaturation of bile with cholesterol, leading to cholesterol crystallization and stone formation, and insufficient gallbladder emptying due to impaired motility are the 2 most commonly suggested mechanisms for gall-

stone formation [55]. However, a fat intake of at least 7–10 g daily could be the threshold for maintaining an efficient gallbladder emptying [56].

Hair Loss

A significant negative nitrogen balance could account for hair loss occurring during a VLCKD. Indeed, when the mobilization of body protein plus dietary protein is not able to meet the requirements, the low priority of hair growth for the available protein is responsible for the telogen effluvium [57]. However, the hair loss is transient and hair grows as well as weight stabilizes. An increased protein intake during a VLCKD in order to equilibrate the nitrogen balance contributes to the prevention of hair loss.

Discussion

The aim of this paper was to provide benchmark data on the effects of VLCKD in terms of short- and intermediate-term weight loss and changes/improvement in body composition patterns and glycemic and lipid profiles. The systematic review and meta-analysis included 15 studies who were objectively judged to be of a high quality and yielded 4 main findings. The first finding was that a VLCKD is associated with a significant reduction in body weight and BMI at 1, 2, 4–6, 12, and 24 months, it and appears to be associated with larger weight loss rates compared to other diets with a different energy content (i.e., LCD and VLCD) of the same duration. The second finding is that a VLCKD is associated with a significant reduction of WC (an expression of central fat) and FM, and this reduction is significantly larger than those achieved with other weight loss interventions of the same duration. However, the reduction in FFM after a VLCKD was not significantly different from the reduction in FFM caused by other weight management interventions, meaning that a VLCKD does not have a better effect in conserving the lean mass as has been speculated by some authors. The third finding is in terms of glycemia and HbA1c, with a significant reduction detected after a VLCKD, without superiority in comparison to other types of weight loss interventions. On the other hand, a VLCKD was associated with a reduction of the HOMA-IR index and an improvement in insulin sensitivity, and this effect was superior to that of other weight loss programs. The fourth finding is that a VLCKD was associated with a reduction in total cholesterol and it was noted to have a major effect in reducing the total cholesterol compared to other weight loss programs. In the same direction, a VLCKD led to a significant reduction in LDL from baseline to follow-up after VLCKD; however it did not demonstrate a superior effect compared to other weight loss diets in terms of LDL reduction. On the other hand, no change was detected in HDL from baseline to follow-up after a VLCKD, and interestingly no differences were detected when we comparing the mean change in HDL cholesterol between a VLCKD and other weight loss interventions. Finally, a significant reduction in TG from baseline was associated with a VLCKD and it was shown to be superior compared to other diets.

The main findings of our study should be considered robust, as we strictly adhered to PRISMA guidelines, and this methodological robustness lends weight to the validity of the conclusions. The studies included in this document were extremely well designed, including both randomized samples and appropriate control groups. Finally, the instruments used in all of the studies to assess the anthropometric and metabolic outcomes have been amply validated and acknowledged in both clinical and research settings.

One major concern regards the side effects of VLCKD. Indeed, few studies have been carried out in subjects with obesity and no study has been set up to specifically assess the side effects. Nevertheless, the included studies that did report side effects associated with ketogenic diets found no meaningful common side effects. They are mostly: dehydration-related disorders, transient hypoglycemia, halitosis, gastrointestinal disorders, hyperuricemia, and lipid profile changes. They are reported to be clinically mild and often recovery occurs spontaneously. Side effects could be prevented and managed by adhering to appropriate indications and contraindications for VLCKD, by following well-organized and standardized protocols, and by performing adequate clinical and laboratory monitoring; for instance, close lipid profile monitoring is important since VLCKD are high-fat low-carbohydrate adequate protein diets that may create a subsequent spike in the plasma levels of total cholesterol and TG, which could, in turn, raise the risk for cardiovascular diseases. Therefore, VLCKD should be carried out under the supervision of a health professional.

Conclusions and Recommendations

After a careful systematic review and meta-analysis of the current evidence, and considering the potential side effects, VLCKD can be recommended as an effective di-

etary treatment for individuals with obesity, in particular for patients with severe obesity and/or comorbidities (joint diseases, preoperative period of bariatric surgery, and cardiovascular and metabolic diseases) who need immediate and substantial weight loss. Therefore, VLCKD can be prescribed targeting a specific population of patients with obesity after consideration of the potential contraindications and under medical surveillance. However, it is important to personalize the diet, based on the patient's preferences, allowing food choices within the VLCKD protocol. After achievement of the weight target with VLCKD, implementation of long-term lifestyle strategies (physical activity and nutritional counselling) is strongly recommended to reduce the risk of weight regain in the long term.

Acknowledgement

We would like to thank Mr. Euan Woodward the Executive Director of the European Association for the Study of Obesity (EASO) for his kind assessment.

Statement of Ethics

Ethical approval is not required because this paper includes information freely available in the public domain and the analysis of data sets, either open source or obtained from other researchers, where the data are properly anonymized and informed consent was obtained at the time of the original data collection.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

Funding Sources

This document was written under the auspices of EASO, which covered the article processing fees.

Author Contributions

G.M., M.E.G., and L.B.: conceptualization. A.C.: methodology. V.Y. and M.H.: validation. M.E.G.: formal analysis. G.M.: investigation and resources. M.H.: data curation. G.M. and M.E.G.: writing and original draft preparation. A.C., V.Y., M.H., and L.B.: review and editing. L.B.: visualization and supervision.

References

1 The European Association for the Study of Obesity. Obesity statistics. Available from: https://easo.org/media-portal/statistics/. 2020.
2 Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a Disease: The Obesity Society 2018 Position Statement. Obesity (Silver Spring). 2019 Jan;27(1):7–9.
3 De Lorenzo A, Gratteri S, Gualtieri P, Cammarano A, Bertucci P, Di Renzo L. Why primary obesity is a disease? J Transl Med. 2019 May;17(1):169.
4 Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab. 2003 Apr;88(4):1617–23.
5 Siraj ES, Williams KJ. Another Agent for Obesity—Will This Time Be Different? N Engl J Med. 2015 Jul;373(1):82–3.
6 Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgrad Med. 2018 Mar;130(2):173–82.
7 Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres AJ, Weiner R, et al.; European Association for the Study of Obesity; International Federation for the Surgery of Obesity - European Chapter. Interdisciplinary European Guidelines on metabolic and bariatric surgery. Obes Facts. 2013;6(5):449–68.
8 Muscogiuri G, Barrea L, Laudisio D, Pugliese G, Salzano C, Savastano S, et al. The management of very low-calorie ketogenic diet in obesity outpatient clinic: a practical guide. J Transl Med. 2019 Oct;17(1):356.
9 Westman EC, Feinman RD, Mavropoulos JC, Vernon MC, Volek JS, Wortman JA, et al. Low-carbohydrate nutrition and metabolism. Am J Clin Nutr. 2007 Aug;86(2):276–84.
10 Moreno B, Crujeiras AB, Bellido D, Sajoux I, Casanueva FF. Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. Endocrine. 2016 Dec;54(3):681–90.
11 Gomez-Arbelaez D, Crujeiras AB, Castro AI, Martinez-Olmos MA, Canton A, Ordoñez-Mayan L, et al. Resting metabolic rate of obese patients under very low calorie ketogenic diet. Nutr Metab (Lond). 2018 Feb;15(1):18.
12 Caprio M, Infante M, Moriconi E, Armani A, Fabbri A, Mantovani G, et al.; Cardiovascular Endocrinology Club of the Italian Society of Endocrinology. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE). J Endocrinol Invest. 2019 Nov;42(11):1365–86.
13 Merra G, Miranda R, Barrucco S, Gualtieri P, Mazza M, Moriconi E, et al. Very-low-calorie ketogenic diet with aminoacid supplement versus very low restricted-calorie diet for preserving muscle mass during weight loss: a pilot double-blind study. Eur Rev Med Pharmacol Sci. 2016 Jul;20(12):2613–21.
14 Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995;123(3):A12–3.
15 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009 Aug;151(4):W65–94.
16 Kreidieh D, Itani L, El Kassas G, El Masri D, Calugi S, Dalle Grave R, et al. Long-term Lifestyle-modification Programs for Overweight and Obesity Management in the Arab States: Systematic Review and Meta-analysis. Curr Diabetes Rev. 2018;14(6):550–8.
17 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010 Sep;25(9):603–5.
18 Wang Y, Ji J, Liu YJ, Deng X, He QQ. Passive smoking and risk of type 2 diabetes: a meta-analysis of prospective cohort studies. PLoS One. 2013 Jul;8(7):e69915.
19 Clark HD, Wells GA, Huët C, McAlister FA, Salmi LR, Fergusson D, et al. Assessing the quality of randomized trials: reliability of the Jadad scale. Control Clin Trials. 1999 Oct;20(5):448–52.

20 Kiehna EN, Starke RM, Pouratian N, Dumont AS. Standards for reporting randomized controlled trials in neurosurgery. J Neurosurg. 2011 Feb;114(2):280–5.
21 Chess LE, Gagnier J. Risk of bias of randomized controlled trials published in orthopaedic journals. BMC Med Res Methodol. 2013 Jun;13(1):76.
22 Higgins JP, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions, version 6.0 (updated July 2019). 2019. Available from: www.training.cochrane.org/handbook.
23 Cochrane Software Review Manager (RevMan). Version 5.3 [software]. Copenhagen: The Nordic Cochrane Centre TCC, 2014.
24 Albanese A, Prevedello L, Markovich M, Busetto L, Vettor R, Foletto M. Pre-operative Very Low Calorie Ketogenic Diet (VLCKD) vs. Very Low Calorie Diet (VLCD): surgical Impact. Obes Surg. 2019 Jan;29(1):292–6.
25 Bruci A, Tuccinardi D, Tozzi R, Balena A, Santucci S, Frontani R, et al. Very Low-Calorie Ketogenic Diet: A Safe and Effective Tool for Weight Loss in Patients With Obesity and Mild Kidney Failure. Nutrients. 2020 Jan;12(2):E333.
26 Colica C, Merra G, Gasbarrini A, De Lorenzo A, Cioccoloni G, Gualtieri P, et al. Efficacy and safety of very-low-calorie ketogenic diet: a double blind randomized crossover study. Eur Rev Med Pharmacol Sci. 2017 May;21(9):2274–89.
27 de Luis D, Domingo JC, Izaola O, Casanueva FF, Bellido D, Sajoux I. Effect of DHA supplementation in a very low-calorie ketogenic diet in the treatment of obesity: a randomized clinical trial. Endocrine. 2016 Oct;54(1):111–22.
28 Goday A, Bellido D, Sajoux I, Crujeiras AB, Burguera B, García-Luna PP, et al. Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. Nutr Diabetes. 2016 Sep;6(9):e230.
29 Gomez-Arbelaez D, Bellido D, Castro AI, Ordoñez-Mayan L, Carreira J, Galban C, et al. Body Composition Changes After Very-Low-Calorie Ketogenic Diet in Obesity Evaluated by 3 Standardized Methods. J Clin Endocrinol Metab. 2017 Feb;102(2):488–98.
30 Gutiérrez-Repiso C, Hernández-García C, García-Almeida JM, Bellido D, Martín-Núñez GM, Sánchez-Alcoholado L, et al. Effect of Synbiotic Supplementation in a Very-Low-Calorie Ketogenic Diet on Weight Loss Achievement and Gut Microbiota: A Randomized Controlled Pilot Study. Mol Nutr Food Res. 2019 Oct;63(19):e1900167.
31 Leonetti F, Campanile FC, Coccia F, Capoccia D, Alessandroni L, Puzziello A, et al. Very low-carbohydrate ketogenic diet before bariatric surgery: prospective evaluation of a sequential diet. Obes Surg. 2015 Jan;25(1):64–71.
32 Moreno B, Bellido D, Sajoux I, Goday A, Saavedra D, Crujeiras AB, et al. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. Endocrine. 2014 Dec;47(3):793–805.
33 Perticone M, Maio R, Sciacqua A, Suraci E, Pinto A, Pujia R, et al. Ketogenic Diet-Induced Weight Loss is Associated with an Increase in Vitamin D Levels in Obese Adults. Molecules. 2019 Jul;24(13):E2499.
34 Rubini A, Bosco G, Lodi A, Cenci L, Parmagnani A, Grimaldi K, et al. Effects of Twenty Days of the Ketogenic Diet on Metabolic and Respiratory Parameters in Healthy Subjects. Lung. 2015 Dec;193(6):939–45.
35 Sajoux I, Lorenzo PM, Gomez-Arbelaez D, Zulet MA, Abete I, Castro AI, et al. Effect of a Very-Low-Calorie Ketogenic Diet on Circulating Myokine Levels Compared with the Effect of Bariatric Surgery or a Low-Calorie Diet in Patients with Obesity. Nutrients. 2019 Oct;11(10):E2368.
36 Valenzano A, Polito R, Trimigno V, Di Palma A, Moscatelli F, Corso G, et al. Effects of Very Low Calorie Ketogenic Diet on the Orexinergic System, Visceral Adipose Tissue, and ROS Production. Antioxidants (Basel). 2019 Dec;8(12):643.
37 Associazione Italiana di Dietetica e Nutrizione Clinica. Attualità in dietetica e nutrizione clinica. Available from: https://www.fondazioneadi.com/wp-content/uploads/paper/2018/01/ADI-ATTUALITA-N.-2_2014.pdf.
38 Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004 Sep;45(9):1116–23.
39 Boulter PR, Hoffman RS, Arky RA. Pattern of sodium excretion accompanying starvation. Metabolism. 1973 May;22(5):675–83.
40 Balasse EO, Ooms HA, Lambilliotte JP. Evidence for a stimulatory effect of ketone bodies on insulin secretion in man. Horm Metab Res. 1970 Nov;2(6):371–2.
41 Franssila-Kallunki A, Rissanen A, Ekstrand A, Ollus A, Groop L. Weight loss by very-low-calorie diets: effects on substrate oxidation, energy expenditure, and insulin sensitivity in obese subjects. Am J Clin Nutr. 1992 Jul;56(1 Suppl):247S–8S.
42 Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011 Oct;54(10):2506–14.
43 Musa-Veloso K, Likhodii SS, Cunnane SC. Breath acetone is a reliable indicator of ketosis in adults consuming ketogenic meals. Am J Clin Nutr. 2002 Jul;76(1):65–70.
44 Wheless JW. The ketogenic diet. In: Swaiman KF, editor. Pediatric neurology: principles and practice. Maryland Heights: Mosby; 1999.
45 Leeds AR. Formula food-reducing diets:A new evidence-based addition to the weight management tool box. Nutr Bull. 2014 Sep;39(3):238–46.
46 Atkinson RL. Low and very low calorie diets. Med Clin North Am. 1989 Jan;73(1):203–15.
47 Palgi A, Read JL, Greenberg I, Hoefer MA, Bistrian BR, Blackburn GL. Multidisciplinary treatment of obesity with a protein-sparing modified fast: results in 668 outpatients. Am J Public Health. 1985 Oct;75(10):1190–4.
48 Swink TD, Vining EP, Freeman JM. The ketogenic diet: 1997. Adv Pediatr. 1997;44:297–329.
49 Ballaban-Gil K, Callahan C, O'Dell C, Pappo M, Moshé S, Shinnar S. Complications of the ketogenic diet. Epilepsia. 1998 Jul;39(7):744–8.
50 Fenton TR, Lyon AW, Eliasziw M, Tough SC, Hanley DA. Meta-analysis of the effect of the acid-ash hypothesis of osteoporosis on calcium balance. J Bone Miner Res. 2009 Nov;24(11):1835–40.
51 Davie MW, Abraham RR, Hewins B, Wynn V. Changes in bone and muscle constituents during dieting for obesity. Clin Sci (Lond). 1986 Mar;70(3):285–93.
52 Furth SL, Casey JC, Pyzik PL, Neu AM, Docimo SG, Vining EP, et al. Risk factors for urolithiasis in children on the ketogenic diet. Pediatr Nephrol. 2000 Nov;15(1-2):125–8.
53 Kielb S, Koo HP, Bloom DA, Faerber GJ. Nephrolithiasis associated with the ketogenic diet. J Urol. 2000 Aug;164(2):464–6.
54 Everhart JE. Contributions of obesity and weight loss to gallstone disease. Ann Intern Med. 1993 Nov;119(10):1029–35.
55 Festi D, Colecchia A, Larocca A, Villanova N, Mazzella G, Petroni ML, et al. Review: low caloric intake and gall-bladder motor function. Aliment Pharmacol Ther. 2000 May;14 Suppl 2:51–3.
56 Johansson K, Sundström J, Marcus C, Hemmingsson E, Neovius M. Risk of symptomatic gallstones and cholecystectomy after a very-low-calorie diet or low-calorie diet in a commercial weight loss program: 1-year matched cohort study. Int J Obes. 2014 Feb;38(2):279–84.
57 Blackburn GL, Bistrian BR, Hoag C. Letter: hair loss with rapid weight loss. JAMA. 1976 Jul;236(3):252.

Journal of Clinical Lipidology (2019) 13, 689–711

Journal of Clinical Lipidology

NLA Scienitific Statement

Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: A scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force

Carol F. Kirkpatrick, PhD, MPH, RDN, CLS*, Julie P. Bolick, MS, RDN, CD, CLS, Penny M. Kris-Etherton, PhD, RDN, CLS, Geeta Sikand, MA, RDN, CLS, Karen E. Aspry, MD, MS, Daniel E. Soffer, MD, Kaye-Eileen Willard, MD, Kevin C. Maki, PhD, CLS

Wellness Center, Kasiska Division of Health Sciences, Idaho State University, Pocatello, ID, USA (Dr Kirkpatrick); Dietitian Nutritionist Specialist II and Clinical Lipid Specialist, Intermountain Health Care, Live Well Center, Salt Lake City, UT, USA (Dr Bolick); Distinguished Professor of Nutrition, Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA (Dr Kris-Etherton); Associate Clinical Professor of Medicine (Cardiology Division) and Director of Nutrition, University of California Irvine Preventive Cardiology Program, Irvine, CA, USA (Dr Sikand); Brown University Alpert Medical School, Lipid and Prevention Program, Lifespan Cardiovascular Institute, East Greenwich, RI, USA (Dr Aspry); University of Pennsylvania, Preventive Cardiology Heart and Vascular Center, Philadelphia, PA, USA (Dr Soffer); Physician Advisor for Patient Quality and Safety, Ascension Wisconsin All Saints, Racine, WI, USA (Dr Willard); and Midwest Biomedical Research, Center for Metabolic & Cardiovascular Health, Addison, IL, USA (Dr Maki)

KEYWORDS:
Cardiometabolic risk factors;
Glycemic control;
Ketogenic diet;

Abstract: Historically, low-carbohydrate (CHO) and very-low-CHO diets have been used for weight loss. Recently, these diets have been promoted for type 2 diabetes (T2D) management. This scientific statement provides a comprehensive review of the current evidence base available from recent systematic reviews and meta-analyses on the effects of low-CHO and very-low-CHO diets on body weight, lipoprotein lipids, glycemic control, and other cardiometabolic risk factors. In addition, evidence on emerging risk

* Corresponding author. Wellness Center, Kasiska Division of Health Sciences, Idaho State University, 921 S. 8th Ave., Stop 8134, Pocatello, ID, 83209-8134, USA.
E-mail address: fellcaro@isu.edu
Submitted August 13, 2019. Accepted for publication August 13, 2019.

https://doi.org/10.1016/j.jacl.2019.08.003

Lipoproteins;
Low-carbohydrate diet;
Medical nutrition therapy;
Obesity;
Triglycerides;
Weight loss;
Very-low-carbohydrate diet

factors and potential safety concerns of low-CHO and very-low-CHO diets, especially for high-risk individuals, such as those with genetic lipid disorders, was reviewed. Based on the evidence reviewed, low-CHO and very-low-CHO diets are not superior to other dietary approaches for weight loss. These diets may have advantages related to appetite control, triglyceride reduction, and reduction in the use of medication in T2D management. The evidence reviewed showed mixed effects on low-density lipoprotein cholesterol levels with some studies showing an increase. There was no clear evidence for advantages regarding effects on other cardiometabolic risk markers. Minimal data are available regarding long-term (>2 years) efficacy and safety. Clinicians are encouraged to consider the evidence discussed in this scientific statement when counseling patients on the use of low-CHO and very-low-CHO diets.

Introduction

Historically, dietary strategies that restrict carbohydrate (CHO) have been used for weight loss.[1–4] There is growing interest in low-CHO and very-low-CHO diets for patients with prediabetes and type 2 diabetes (T2D) to improve glycemic control and other cardiometabolic risk factors (eg, high blood pressure and atherogenic dyslipidemia).[1–6] There are proposed benefits of these diets for other conditions (eg, acne, cancer, neurological diseases, and polycystic ovary syndrome)[3] and performance enhancement in athletes.[7] There have been anecdotal reports of improved mood, cognitive function, and energy levels with the use of low-CHO and very-low-CHO diets for weight loss, which have not generally been supported by findings from controlled studies.[8–11] In addition, very-low-CHO diets have become popular because of the perception they are healthier than currently recommended dietary patterns.[12]

There are several types of CHO-restricted diets, some of which restrict CHO to very low levels without restricting dietary protein and fat (eg, Atkins-style diet), whereas others allow moderate CHO intake with moderate protein and fat intake (eg, South Beach, Zone). Contemporary very-low-CHO diets limit protein to moderate levels to induce ketosis without restricting fat or total calories.[1] A very-low-CHO ketogenic diet (KD) has been used for the treatment of intractable epilepsy since the 1920s. The classic KD is precisely calculated to induce ketosis while providing adequate nutrition to prevent malnutrition and promote normal growth and development in children.[13,14] Some individuals participate in medically supervised low-CHO and very-low-CHO diets for weight loss and/or T2D management; however, many follow these diets without medical supervision. In a 2018 survey of Americans between 18 and 80 years of age (n = 1009), 16% reported following some type of low-CHO eating pattern in the past year.[15]

There is some evidence that low-CHO and very-low-CHO diets elicit weight loss with *ad libitum* intake and without feelings of deprivation and hunger.[1] In addition, reduced CHO intake results in decreased insulin levels, which has been hypothesized to produce cardiometabolic benefits.[3,4,16] However, low-CHO and very-low-CHO diets that are high in saturated fatty acid (SFA)-rich foods and low in nutrient-dense CHO foods are inconsistent with evidence-based dietary strategies recommended by professional organizations.[17–20]

This National Lipid Association (NLA) Scientific Statement reviews the characteristics of low- and very-low-CHO diets and their impacts on metabolic pathways, examines the evidence on the effects of these diets on weight loss, dyslipidemia, and other cardiometabolic risk factors, and makes recommendations for clinicians about the use of these diets in adults in clinical practice. The specific content of this scientific statement includes:

- a description of CHO-restricted diets;
- a brief review of very-low-calorie KDs;
- the impact of nutritional ketosis on energy and cholesterol metabolism;
- the differential effects of CHO-restricted diets on the determinants of energy balance and body weight;
- the evidence base for short- and long-term effects on weight loss, body composition, and cardiometabolic risk factors;
- safety concerns and adverse effects; and
- points to consider for the clinician-patient discussion on the use of low-CHO and very-low-CHO diets.

Definition of CHO-restricted diets

The terminology and definitions used for CHO-restricted diets vary considerably and are often defined based on the proportion of total daily energy (TDE) from CHO and/or absolute CHO intake. In this review, a CHO-restricted diet is defined as CHO intake below the lower boundary of the acceptable macronutrient distribution range for healthy adults (45–65% TDE).[20,21] A moderate-CHO diet is defined as 26–44% TDE from CHO (130–225 grams CHO/d for a reference 2000 kcal diet), a low-CHO diet as 10–25% TDE from CHO (50–130 grams CHO/d), and a very-low-CHO diet as <10% TDE from CHO (<50 grams CHO/d) (Table 1).

Description of CHO-restricted and ketogenic diets

Low- and moderate-CHO diets can be moderate or high in fat and moderate or high in protein and do not result in

Table 1 Diet classification based on amount of TDE and grams per day from CHO[20,22–24]

Diet description	Ketogenic	Calories/d	CHO % TDE	Protein % TDE	Fat % TDE
VLCHF/KD	Yes	>1000	<10* (<20–50 g/d)	~10% TDE (1.2–1.5 g/kg)	70–80% TDE
Low-CHO	No	>1000	10–25† (38–97 g/d)	10–30% TDE	25–45% TDE
Moderate-CHO	No	>1000	26–44† (98–168 g/d)	10–30% TDE	25–35% TDE
High-CHO	No	>1000	45–65† (169–244 g/d)	10–30% TDE	25–35% TDE
Very-high-CHO	No	>1000	>65† (>244 g/d)	10–30% TDE	25–35% TDE
VLCalD‡	Varies	<800	Varies	Varies	Varies
Classic KD	Yes	Varies	3	7	90

CHO, carbohydrate; VLCHF/KD, very-low-CHO, high-fat ketogenic diet; VLCalD, very-low-calorie diet; PSMF, protein sparing modified fast; TDE, total daily energy.

*Typically the amount of CHO required to induce ketosis in most people.[22]

†Based on 1500 calories/d, an energy intake considered hypocaloric for most individuals.

‡VLCalDs vary in macronutrient composition—some may be ketogenic if CHO content is low enough; others may not be if CHO content is >50 g/d. The PSMF is a subset of VLCalDs and is typically higher in protein to spare LBM with a macronutrient composition of <20 to 50 g CHO/d, 1.2 to 1.5 g/kg protein/d, and <10 to 15% TDE fat.

nutritional ketosis due to higher contents of both CHO and protein.[4,22] Ketosis can be predicted for a CHO-restricted diet based on its ketogenic ratio (the ratio of the sum of ketogenic factors to the sum of anti-ketogenic factors):

KR = (0.9 F + 0.46 P)/(1.0 C + 0.58 P + 0.1 F), where F is grams of fat, P is grams of protein, and C is grams of CHO.[25]

The ratio that consistently induces ketogenesis is ≥2,[25] with 1.5 typically being the lower ketogenic threshold.[25,26] Zilberter and Zilberter[25] reviewed 62 studies that reported on prescribed dietary interventions described as "ketogenic" and found that only 25 of the 62 studies had a ketogenic ratio >1.5, which illustrates the complexity of interpreting the available evidence on KDs, much of which appears to be from investigations that did not truly assess KDs.

Low- and moderate-CHO diets allow the consumption of CHO-containing foods that are components of cardioprotective dietary patterns, including vegetables, fruits, whole grains, nuts, seeds, and legumes.[17–20,27] These foods are important sources of fiber, magnesium, B-vitamins, and bioactive compounds, such as polyphenols, all of which have been associated with lower risks for dyslipidemia, atherosclerotic cardiovascular disease (ASCVD) events, and incident T2D.[17–20,27,28]

Contemporary very-low-CHO KDs have become popular among the lay public,[12,29] as well as some clinicians and nutrition scientists.[1,29] The current popular version is very low in CHO (~20–50 g/d or 5–10% TDE), high in fat (70–80% TDE),[22] and emphasizes the replacement of CHO with fat; thus, it is a very-low-CHO, high-fat (VLCHF) diet,[2] which results in ketosis.[4,22] Achieving ketosis is highly individualized[30] and less than 20 g/d of CHO may be needed in some people.[31] In addition, at a given level of CHO intake, protein quantity appears to influence the degree of ketosis because some amino acids are used for gluconeogenesis and stimulate insulin secretion,[4] which may reduce hepatic ketone production.[30] Therefore, current VLCHF/KDs are typically moderate in protein intake (1.2–1.5 g/kg/d).[4,22] Typically, there is little emphasis on the type of fat that replaces CHO in VLCHF/KDs, which may result in a high intake of SFAs and cholesterol. Furthermore, the severe restriction of CHO in a VLCHF/KD limits CHO intake to nonstarchy vegetables[31] and eliminates fiber-rich starchy vegetables, as well as most fruits, legumes, and whole grains,[30] which are foods that have been associated with reduced cardiometabolic risk.[27]

Medically supervised very-low-calorie ketogenic diets for the treatment of obesity

Medically supervised very-low-calorie diets (VLCalDs) have been used for over 40 years for the treatment of obesity (body mass index [BMI] ≥30 kg/m^2 or a BMI of ≥27 kg/m^2 with one or more comorbidities).[23,32,33] The energy level of a VLCalD has been defined as <800 kcal/d[33,34] The macronutrient composition of VLCalDs is typically 0.8–1.5 g protein/kg ideal body weight to induce rapid weight loss and preserve lean body mass (LBM) and 15–30 g fat/d. An important point is that the CHO content in some VLCalDs is 20–50 g/d, which may induce ketosis, but can be as high as 80 g/d[33]; thus, not all VLCalDs are ketogenic[23] (Table 1). The protein-sparing modified fast (PSMF) is a medically supervised VLCalD with 500–800 kcal/d, primarily from protein (1.2–1.5 g/kg ideal body weight). Fat is restricted to only that found in the protein foods allowed on the diet, such as lean meat, fish and seafood, and poultry. CHO is restricted to 20–50 g/d, resulting in ketosis.[23,33,35] VLCalDs or PSMFs should be prescribed only in limited circumstances by trained clinicians. Patients must be medically supervised due to rapid weight loss and possible

health complications, including possible medication adjustments to avoid hypoglycemia and hypotension.[23] Although some medically supervised programs utilize VLCalDs or PSMFs that are very low in CHO, they are not the focus of this scientific statement. Readers interested in the specific details of VLCalDs and PSMFs for adults are encouraged to read relevant articles.[23,32,33,35]

The impact of nutritional ketosis on energy metabolism

Glucose is typically the sole fuel for the human brain because fatty acids (FA) cannot cross the blood-brain barrier. When CHO intake is adequate, insulin promotes lipogenesis and suppresses ketone production; thus, ketone concentration is very low (<0.3 mmol/L) vs glucose (~4 mmol/L).[4] After a few days of severe CHO restriction (<20 g/d), the body's glucose production from gluconeogenesis becomes insufficient and the central nervous system (CNS) requires an additional energy source. During restricted CHO intake, insulin levels decrease and glucagon levels increase, which impact metabolic pathways in the liver resulting in decreased lipogenesis and increased mitochondrial FA oxidation.[30,36] The increased FA oxidation causes overproduction of acetyl-CoA and the production of ketone bodies in the hepatic mitochondria. Acetoacetate is the main ketone body produced and is converted to β-hydroxybutyrate and acetone. Ketosis is typically defined as a blood level of β-hydroxybutyrate ≥0.3 mmol/L.[37,38] Ketone bodies are used as a source of energy for all tissues, especially skeletal and cardiac muscle, after conversion back to acetyl-CoA, which is used in the tricarboxylic acid cycle.[4] Because ketone bodies have a similar binding affinity (a.k.a., Michaelis-Menten [kM] constant) as glucose for transport to the brain, the CNS begins to use ketone bodies for energy at a plasma concentration of ~4 mmol/L. Ketone levels in healthy people do not generally exceed 8 mmol/L because the CNS efficiently uses these molecules for energy in place of glucose.[3,4,39]

In ketogenesis, glucose levels remain within normal levels via gluconeogenesis from glucogenic amino acids and glycerol from hydrolyzed triglycerides (TG). During the first 3 to 4 days of a KD, the main source of glucose is via gluconeogenesis from amino acids. If the circumstances that promote ketogenesis continue, the contribution of amino acids decreases and the amount of glucose derived from glycerol increases.[4] Based on research examining the effects of fasting and very-low-CHO diets, metabolic adaptation to ketosis takes two weeks or longer to achieve a steady-state ketone level.[16,40,41]

The impact of nutritional ketosis on cholesterol metabolism

Low-CHO and very-low-CHO/KDs appear to have variable effects on low-density lipoprotein cholesterol (LDL-C) levels (discussed in a later section) due, in part, to the hepatocellular effects of low insulin levels. A higher CHO intake increases insulin levels, which activates HMG-CoA reductase and increases hepatic cholesterol synthesis.[3,4] A lower CHO intake decreases insulin levels and inhibits HMG-CoA reductase activation and cholesterol synthesis while activating HMG-CoA lyase, an enzyme involved in ketone body production, thus favoring ketogenesis.[30] There are secondary effects on lipoprotein lipase (and co-factors), as well as LDL-receptor and PCSK9 expression affecting very-low-density lipoprotein (VLDL) and LDL clearance and lipoprotein remodeling. The net impact on serum LDL-C levels is thus mediated by complex mechanisms. It has been proposed that, by lowering insulin levels, low-CHO diets may inhibit hepatic cholesterol synthesis.[3,4,30] Unless this is counteracted by other mechanisms, the expected result would be decreased total cholesterol (total-C) and LDL-C,[3,4,30] especially when intakes of SFA and dietary cholesterol are not increased[4] when CHO consumption is lowered. Thus, LDL-C response cannot be predicted in the individual, and should be evaluated in those who choose to follow a low-CHO or very-low-CHO/KD.

Effects of low-CHO and very-low-CHO diets on determinants of energy balance and body weight

CHO-restricted diets have significant effects on factors that influence energy expenditure (EE) and intake. Results from well-controlled studies have shown that substitution of fat for CHO results in a higher EE. Hall et al.[42] examined changes in EE in 17 men with overweight or obesity consuming an isocaloric habitual high-CHO diet (50% TDE CHO, 15% TDE protein, 35% TDE fat) for 4 weeks followed by a VLCHF/KD (5% TDE CHO, 15% TDE protein, 80% TDE fat) for 4 weeks. Participants spent two consecutive days each week in a metabolic chamber to measure changes in EE using the doubly labeled water method during the last two weeks of each dietary phase. During the VLCHF/KD phase, EE was 57 kcal/d higher as measured by the metabolic chamber and 151 kcal/d higher as measured by the doubly labeled water method.

In a randomized controlled trial (RCT), participants who had lost an average of 12% of body weight were randomly assigned to weight maintenance diets varying in dietary CHO, i.e., low (20% TDE), moderate (40% TDE), or high (60% TDE).[43] Protein intake was held constant and energy from fat was substituted for CHO. Total EE measured with doubly labeled water was 91 kcal/d higher with the moderate-CHO group and 209 kcal/d higher in the low-CHO group compared with the high-CHO group, with a linear trend of 52 kcal/d per 10% reduction in dietary CHO.[43]

Although EE appears to be higher with low-CHO diets and very-low-CHO/KDs, the mechanisms contributing to this are incompletely understood. It has been proposed

that changes in catecholamines and thyroid hormone levels influence the EE of individuals following these diets, but associated changes have not been observed in all studies. In the trial by Hall et al.[42] (discussed previously), there was a significant increase in thyroid-stimulating hormone and free thyroxine (T4) levels, significantly decreased free and total tri-iodothyronine levels, and significantly decreased levels of leptin and norepinephrine in the 17 participants during the VLCHF/KD phase of their study.

Results from controlled investigations have suggested a reduced appetite also occurs with CHO restriction, due to various mechanisms, and contributes to weight loss.[4,38,39,44,45] Westman et al.[45] reported that there was a "spontaneous reduction in calorie intake" in studies that examined the effects of low-CHO diets and very-low-CHO/KDs on appetite and satiety, which may be partly mediated through effects of nutritional ketosis on appetite. Participants report less hunger when they are in ketosis, although the mechanisms of action of ketosis on hunger and appetite suppression are not completely understood and evidence suggests both direct and indirect actions of ketone bodies and their oxidation.[3,30,38,39] The degree to which ketosis contributes to appetite reduction, independent of other variables, such as the quantities of CHO and protein consumed and oxidized, is uncertain.[38] Protein appears to provide greater satiety than CHO.[22,30,38,45,46] However, well-controlled studies that matched protein intake found that a ketogenic, high-protein diet suppressed appetite more than a high-protein diet that was not ketogenic, suggesting that circulating ketone levels have an impact, independent of protein intake.[38] Longer-term, well-controlled studies are needed to assess the degree to which appetite suppression occurs with CHO restriction above the threshold for ketosis, which would allow a higher intake of nutrient-dense CHO foods (eg, vegetables, fruits, whole grains, and legumes) that reflect evidence-based cardioprotective dietary patterns.[38]

Low-CHO diets may reduce hunger by influencing circulating levels of hormones that impact hunger and appetite control, including ghrelin, leptin, and cholecystokinin, but study results have been inconsistent.[37–39,43,44,47] Ghrelin and cholecystokinin levels were mildly decreased during ketosis in participants following a low-CHO, VLCalD/KD,[37] whereas ghrelin and leptin were significantly lower in participants assigned to a low-CHO (but non-ketogenic) weight maintenance diet (20% TDE CHO) compared with participants following a moderate-CHO (40% TDE) or high-CHO (60% TDE) weight maintenance diet.[43] Hu et al.[47] found no difference in change in ghrelin levels or self-reported change in appetite between the participants consuming a very-low-CHO diet (<40 g/d) or a low-fat (<30% TDE), high-CHO (~55% TDE) diet over 12 months. These results illustrate the many potential factors that influence EE and appetite during weight loss with low-CHO diets and very-low-CHO/KDs.

Other possible effects of low-CHO and very-low-CHO diets on energy balance and body weight are: 1) diuretic effects of ketosis[48,49] and reduced insulin concentration[50]; 2) increased adipose tissue lipolysis[4,48,51,52]; 3) reduction in resting respiratory quotient, reflecting a higher proportion of fat being oxidized for energy[4,53–55]; and 4) increased metabolic costs of gluconeogenesis and the thermic effect of protein.[4,32,48,56]

Key points

- Low-CHO diets and very-low-CHO/KDs appear to increase EE. The mechanisms contributing to this effect are incompletely understood.
- Changes in catecholamines and thyroid hormone levels may influence the EE of individuals following low-CHO diets and very-low-CHO/KDs.
- Individuals following low-CHO diets and very-low-CHO/KDs in RCTs reported reduced appetite and hunger. The mechanisms that contribute to this are not clear but may include changes in gastrointestinal hormones.

Evidence for the effect of low-CHO and very-low-CHO diets on weight loss

Weight loss in adults with overweight or obesity

Despite favorable effects of low-CHO and very-low-CHO diets on EE and intake, long-term effects on weight loss may not be superior to more conventional strategies. According to the 2013 American Heart Association/American Cardiology/The Obesity Society (AHA/ACC/TOS) Guideline for the Management of Overweight and Obesity in Adults,[34] research has not demonstrated any advantage of a very-low-CHO diet on weight loss at 6 months compared with a calorie-restricted, low-fat diet. More recently, several systematic reviews and meta-analyses of RCTs have examined the effectiveness of low-CHO, high-fat (LCHF) (>30% TDE fat) vs high-CHO, low-fat (HCLF) diets (<30% TDE fat) for weight loss in individuals with overweight or obesity at 3 to 6 months[57] or 1 to 2 years.[57–60] Participants assigned to both LCHF and HCLF diets achieved clinically meaningful weight loss (Table 2, Fig. 1). However, weight loss was significantly greater with LCHF diets vs HCLF diets when the prescribed diets were hypocaloric,[59] when the prescribed *ad libitum* LCHF diets were hypocaloric (even though not required or encouraged),[60] and the study duration was less than 2 years.[58]

Results for patients with prediabetes[63] and T2D[57,64–67] were similar, with no significant difference for weight loss between the low-CHO and HCLF diet groups in long-term studies (Table 2, Fig. 1). Sainsbury et al.[68] found a significant decrease in weight with low-CHO vs HCLF diets at 3 months (weighted mean difference [WMD] −1.08 kg, 95% CI: −1.93, −0.23, n = 12 studies), but no difference at >6 months (WMD −0.14 kg, 95% CI: −0.94, 0.65, n = 9 studies). van Zuuren et al.[69] reported

Table 2 Effect of low-CHO and very-low-CHO diets compared with HCLF diets on weight, lipids, HbA1c, and blood pressures at 1–2 years follow-up reported in meta-analyses

Author	# of RCTs	Weight WMD (95% CI), kg	LDL-C, WMD (95% CI), mg/dL	HDL-C, WMD (95% CI), mg/dL
Meta-analyses of studies of adults with overweight and/or obesity				
Naude et al. 2014[57]	14	−0.48 (−1.44 to 0.49)	2.71 (−0.39 to 6.19)	1.55 (0.39 to 3.09)
Bueno et al. 2013[58]	13	−0.91 (−1.65 to −0.17)	4.64 (1.55 to 7.73)	3.48 (2.32 to 4.64)
Schwingshackl & Hoffmann 2013[59]	32	0.15 (−0.50 to 0.80); −0.59* (−1.04 to −0.15)	3.11 (1.71 to 4.51)	2.35 (1.29 to 3.42)
Mansoor et al. 2016[60]	11	−2.17 (−3.36 to −0.99)	6.19 (0.12 to 12.8)	5.41 (3.48 to 7.35)
Gjuladin-Hellon et al. 2019[61]	5†	NR	1.55 (−1.55 to 4.64)	3.48 (0.77 to 5.80)
Sackner-Bernstein et al. 2016[62]	17	−2.04‡ (−3.15, −0.93)	8.6‡ (3.6 to 13.7)	5.1‡ (3.5 to 6.7)
Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes				
Naude et al. 2014[57]	5	0.91 (−2.08 to 3.89)	3.87 (−2.32 to 10.44)	0.00 (−3.48 to 3.09)
Schwingshackl & Hoffmann 2014[63]	14§	−0.47 (−1.85 to 0.92)	1.55 (−5.41 to 8.89)	1.55 (0.00 to 3.09)
Meng et al. 2017[64]	9	−0.24 (−2.18 to 1.70)	1.55 (−3.09 to 6.19)	2.71 (1.16 to 4.25)
Snorgaard et al. 2017[65]	10	0.20 (−0.97 to 1.36)	−0.39 (−3.87 to 2.71)	NR
Huntriss et al. 2018[66]	5–7‖	0.28 (−1.37 to 1.92)	1.93 (−3.87 to 7.35)	2.32 (1.55 to 3.48)
Korsmo-Haugen et al. 2019[67]	7–10¶	0.14 (−0.29 to 0.57)	1.16 (−3.87 to 6.19)	2.32 (−0.39 to 5.03)
Sainsbury et al. 2018[68]	25	−0.43 (−0.93 to 0.07)	NR	NR
van Zuuren et al. 2018[69]	2–3**	−0.14 (−1.64 to 1.35)	2.32 (−3.09 to 8.12)	4.64 (2.71 to 6.57)

HCLF, high-carbohydrate, low-fat; RCT, randomized control trials; WMD, weight mean difference; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; NR, not reported.

If all values in the confidence interval are on the same side of zero (either all positive or all negative), the findings are significant.

In this meta-analysis, 14 RCTs were included in the full meta-analysis, but the number of RCTs varied in the analyses involving only participants with T2D: 5 RCTs were included for SBP, 6 RCTs were included for DBP, 7 RCTs were included for LDL-C, 8 RCTs were included for weight, 9 RCTs were included for HDL-C, and 10 RCTs were included for TG and HbA1c.

*For hypocaloric diet comparisons only.

†In the Gjuladin-Hellon et al.[61] meta-analysis, 8 RCTs were included in the full meta-analysis, but only 5 RCTs were included in the 12 mo + meta-analysis for LDL-C, HDL-C, and TG.

‡The decimal places reported reflect those reported in the published article.

§In the Schwingshackl & Hoffmann[63] meta-analysis, the authors included RCTs of high-fat diets (>30% TDE total fat) of which 6 studies were classified as low-CHO and 4 were classified as moderate-CHO.

‖In the Huntriss et al.[66] meta-analysis, 18 RCTs were included in the full meta-analysis, but only 7 RCTs were included in the 12 mo + meta-analysis for HDL-C, TG, HbA1c, SBP, and DBP, 6 RCTs were included for weight, and 5 RCTs were included for LDL-C.

¶In the Korsmo-Haugen et al.[67] meta-analysis, 23 RCTs were included in the full meta-analysis, but the number of RCTs varied in the 12 mo + meta-analyses, which is what is reported in Table 2: 7 RCTs were included for DBP, 8 RCTs were included for SBP, 9 RCTs were included for LDL-C and TG, and 10 were included for weight, HDL-C, and HbA1c.

**In the van Zuuren et al.[69] meta-analysis, 33 RCTs and 3 clinical control trials were included in the full meta-analysis, but the number of RCTs varied in the 12 mo + meta-analyses, which is what is reported in Table 2: 2 RCTs were included for weight, LDL-C, HDL-C, TG, SBP, and DBP, and 3 RCTs were included for HbA1c.

a significantly greater weight loss at 8–16 weeks (WMD −2.04 kg, 95% CI: −3.23, −0.85; P = .0008; n = 4 studies) with low-CHO vs HCLF diets, but no difference at any other time. In addition, Snorgaard et al.[65] reported no difference in BMI and waist circumference in their meta-analysis.

Points to consider regarding the effects of low-CHO and very-low-CHO diets on weight loss

The results from the meta-analyses discussed previously support the view that low- and very-low-CHO diets are not superior for weight loss compared with diets with a higher quantity of CHO and are difficult to maintain in clinical trials of adults with overweight and obesity, with or without prediabetes or diabetes.[57–60,63,65–69] In the studies included in the meta-analyses, mean CHO intake in the low- and very-low-CHO diet groups at the end of follow-up exceeded 50 g/d in all except one study.[70] Mean CHO intake in the remaining studies was between 33–47% TDE by study end.[58–60] Attrition was ∼30% for both the LCHF and HCLF diet groups in some studies.[60]

Gardner et al.[71] found that when individuals are educated to consume foods with high dietary quality for both low-fat and low-CHO diets, weight loss was similar in both groups. Sacks et al.[72] found that satisfaction was similar among study completers assigned to four different hypocaloric diets (n = 645): low-fat, average-protein; low-fat, high-protein; high-fat, average-protein; and high-fat, high-protein. However, there was substantial variation in weight loss achieved with each of the diet conditions with some individuals in each showing well-above-average weight loss, suggesting that personal preference in the selection of a weight loss diet is important and should be considered.

Table 2 (continued)

TG, WMD (95% CI), mg/dL	HbA1c WMD (95% CI), %	SBP, WMD (95% CI), mm/Hg	DBP, WMD (95% CI), mm/Hg
−5.31 (−12.4 to 2.66)	NR	−2.00 (−5.00 to 1.00)	−0.03 (−1.68 to 1.62)
−15.9 (−23.9 to −7.09)	−0.24 (−0.55 to 0.06)	−1.47 (−3.44 to 0.50)	−1.43 (−2.49 to −0.37)
−8.38 (−13.5 to −3.25)	NR	NR	NR
−23.0 (−32.8 to −13.3)	NR	−1.02 (−2.98 to 0.94)	−1.01 (−2.75 to 0.74)
−9.74 (−15.9 to −2.66)	NR	NR	NR
−28.8‡ (−39.1 to −18.5)	NR	−1.7‡ (−3.5 to 0.2)	NR
−7.09 (−43.4 to 23.0)	0.01 (−0.28 to 0.30)	0.31 (−3.1 to 3.72)	0.09 (−1.95 to 2.13)
−15.9 (−21.3 to −11.5)	−0.17 (−0.39 to 0.06)	−1.35 (0.35 to 2.35)	−1.35 (−1.79 to −0.92)
−29.2 (−39.9 to −18.6)	−0.44 (−0.61 to −0.26)	NR	NR
NR	0.04 (−0.04 to 0.13)	NR	NR
−21.3 (−31.0 to −11.5)	−0.28 (−0.53 to −0.02)	−2.74 (−5.27 to −0.20)	−0.99 (−2.24 to 0.25)
−8.86 (−20.4 to 2.66)	0.00 (−0.10 to 0.09)	−1.39 (−3.20 to 0.43)	−0.55 (−2.17 to 1.06)
NR	−0.09 (−0.21 to 0.03)	NR	NR
−16.8 (−28.3 to −4.43)	−0.02 (−0.37 to 0.41)	1.60 (−1.50 to 4.70)	0.88 (−1.25 to 3.02)

Key points

- Short-term (≤6 months) hypocaloric low-CHO and very-low-CHO diets may result in greater weight loss than hypocaloric high-CHO, low-fat (HCLF) diets.
- Longer-term (>6 months) results suggest that low-CHO and very-low-CHO diets may result in weight loss that is equivalent to that of HCLF diets.
- Very-low-CHO diets are difficult to maintain and are not clearly superior for weight loss compared with diets that

Cardiometabolic risk factor	Adults with overweight or obesity	Adults with overweight or obesity and T2D
Weight	↓**	↑↓*
LDL-C	↑**	↑*
HDL-C	↑***	↑**
TG	↓**	↓**
HbA1c	↓*	↑ ⇔ ↓**
SBP	↓*	↑↓**
DBP	↓**	↑↓**

Figure 1 Effects of low-CHO and very-low-CHO diets vs high-CHO, low-fat diets on cardiometabolic risk markers at 1–2 years follow-up.[57–69] LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; T2D, type II diabetes; TG, triglycerides; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure. *No significant difference between diet groups. **Mixed results on significant difference between diet groups—some meta-analyses found a significant difference between diet groups, while others did not. ***Significant difference between diet groups.

Key recommendations for weight loss in adults with overweight or obesity*	COR	LOE
Because a specific distribution of CHO, protein, and fat has not been shown to be superior for weight loss, it **is reasonable** to counsel patients on achieving a calorie reduction by limiting the intake of multiple energy sources (ie, CHO, fat) vs limiting calories from a single energy source (ie, CHO).[34,57–60,63–69,71,72]	IIa	B-R
A low-CHO diet (50–130 g CHO/d) or very-low-CHO/KD (~20–49 g CHO/d) **is a reasonable option** for some patients for a limited period of time (2–6 months) to induce weight loss.[57,68,69]	IIa	B-R
Because low-CHO diets or very-low-CHO/KDs are difficult to maintain long-term, a more moderate CHO intake (>130–225 g/d) **is reasonable** for longer-term (>6 months) weight loss and maintenance.[57–60,63,65–69]	IIa	B-R

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

allow a higher amount of CHO in adults with overweight and obesity with or without diabetes.
- Long-term participation in any weight loss intervention is difficult, but adherence to the assigned macronutrient distribution (ie, CHO, protein, and fat) is lower with low-CHO and, especially, very-low-CHO diets.
- Personal preference should be considered when selecting a weight loss diet.

Evidence for the effect of low-CHO and very-low-CHO diets, including ketogenic diets, on body composition changes

Body water loss

The initial weight loss that occurs with low-CHO diets and very-low-CHO/KDs is largely attributable to the loss of body water, not fat loss.[30] This body water loss occurs due to at least two major mechanisms, ketonuria-induced natriuresis and glycogen-depletion, although other mechanisms may also play some role.[48,74,75] Renal losses of sodium and water are also promoted by lower average insulin levels during low-CHO diets, because insulin promotes renal reabsorption of sodium.[76] Glycogen depletion to maintain blood glucose levels results in a loss of body water (3 grams of water per 1 gram stored glycogen).[2,30,48,49,75] Gomez-Arbelaez et al.[75] found that the peak amount of water loss (as measured by multifrequency-bioelectrical impedance) coincided with the phase of maximum ketosis in study participants and, as ketosis decreased, body water was recovered.

Lean body mass or fat-free mass and body fat mass

A concern with any weight loss intervention is the potential to decrease LBM while decreasing fat mass as individuals lose weight.[4] VLCalDs and protein-sparing–modified fast interventions were intended to promote rapid weight loss while preserving LBM.[33] Results from RCTs suggest that a higher protein intake has a protective effect for preserving LBM during weight loss. Adam-Perrot et al.[30] reviewed studies that demonstrated when participants consumed a LCHF diet vs a hypocaloric low-fat diet, they achieved equivalent or higher fat mass loss, but also a higher loss of LBM, unless accompanied by higher protein intake. A hypocaloric high-protein, low-fat diet vs an isocaloric HCLF diet resulted in less LBM loss, suggesting a high-protein diet was more effective at preserving LBM.[30,77]

Krieger et al.[78] conducted a meta-regression analysis of RCTs (n = 87) to examine the effects of varying amounts of protein and CHO intake on body composition during energy restriction (minimum of 1000 kcal/d). After controlling for energy intake, diets with <41.4% TDE from CHO (mean intake 79–97 g/d) were associated with 6.56 kg more body mass loss, 1.74 kg more fat-free mass (FFM) loss, and 5.57 kg more fat mass loss at >12 weeks. When protein intake was >1.05 g/kg/d, there was 1.21 kg more FFM retained compared with protein intake ≤1.05 g/kg/d at >12 weeks.[78] Thus, low-CHO diets that have a higher protein content from partially replacing CHO with protein rather than fat alone appear to promote fat mass loss and result in a lower percentage of LBM lost.[79] Other RCTs with small sample sizes found a greater loss of FFM with very-low-CHO/KDs compared with moderate-CHO (35% TDE; 30% TDE protein)[44] or high-CHO (50% TDE; 15% TDE protein)[42] diets.

Key points

- Ketosis is associated with body water loss.

Table 3 2015 ACC/AHA clinical practice guideline recommendation classification system[74]

CLASS (STRENGTH) OF RECOMMENDATION
CLASS I (STRONG) **Benefit >>> Risk**

Suggested phrases for writing recommendations:
• Is recommended
• Is indicated/useful/effective/beneficial
• Should be performed/administrated/other
• Comparative-Effectiveness Phrases:
  ○ Treatment / strategy A is recommended / indicated in preference to treatment B
  ○ Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:
• Is reasonable
• Can be useful/effective/beneficial
• Comparative-Effectiveness Phrases:
  ○ Treatment/strategy A is probably recommended/indicted in preference to treatment B
  ○ It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) **Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered Usefulness/effectiveness is unknown/unclear/uncertain or not well established
CLASS III: No Benefit (MODERATE) **Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other
CLASS III: Harm (STRONG) **Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE
LEVEL A
• High-quality evidence from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
LEVEL B-R (Randomized)
• Moderate-quality evidence from 1 or more RCTs • Meta-analysis of moderate-quality RCTS
LEVEL B-NR (Nonrandomized)
• Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
LEVEL C-LD (Limited Data)
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
LEVEL C-EO (Expert Opinion)
• Consensus of expert opinion based on clinical experience

Modified from the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System

- The initial weight loss that occurs with low-CHO diets and very-low-CHO/KDs is primarily due to loss of body water.
- All weight loss interventions using CHO-restriction appear to result in greater loss of lean body mass (LBM) compared with more macronutrient balanced hypocaloric diets.
- Higher protein content in low-CHO diets may result in less LBM loss during weight loss.

Key recommendation for body weight and composition*	COR	LOE
In patients choosing to lose weight using a CHO-restricted diet, it **is reasonable** to recommend a higher protein intake (1.0–1.5 g/kg/d) to preserve LBM during weight loss.[77,78]	IIa	B-R

LBM, lean body mass.

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

Evidence for the effect of low-CHO and very-low-CHO diets on traditional cardiometabolic risk factors

Effects on blood lipids and lipoproteins

Recent systematic reviews and meta-analyses of RCTs of adults with overweight or obesity without diabetes have reported conflicting results on the effects of low-CHO and very-low-CHO diets on total-C and LDL-C[57–62] (Table 2). In a meta-analysis of 14 RCTs that examined the differences in blood lipids between low-CHO and isocaloric balanced diets, there was a trend in the low-CHO diet groups for a higher total-C (WMD 3.09 mg/dL, 95% CI: −0.77, 6.57, n = 12 studies) and LDL-C (WMD 3.48 mg/dL, 95% CI: 0.0, 6.96, n = 12 studies) at 3–6 months follow-up and 1–2 years follow-up (total-C WMD 2.32 mg/dL, 95% CI: −1.16, 6.19, n = 6 studies; LDL-C WMD 2.71 mg/dL, 95% CI: −0.39, 6.19, n = 6 studies).[57]

A meta-analysis of 8 large RCTs (each n > 100) over 6–24 months examined the effects of CHO-restricted diets vs low-fat (LF) diets on LDL-C and other lipid markers in adults with overweight or obesity.[61] The CHO-restricted diets were divided into two subgroups: moderate-CHO (4 trials; 35–40% TDE CHO or 130–225 g/d) and very-low-CHO (4 trials; <10% TDE CHO or <50 g/d). The LF diets were 50–65% TDE CHO and 20–35% TDE fat, except one study (70% TDE CHO, <10% TDE fat). Overall, significantly higher LDL-C (WMD 2.71 mg/dL; 95% CI, 0.77, 5.03; $P = .009$; n = 8 studies) was reported in the pooled analysis of CHO-restricted diets vs LF diets. However, a subgroup analysis based on CHO content reported no significant difference in LDL-C levels between CHO-restricted vs LF diets (for very-low-CHO: 2.71 mg/dL; 95% CI: −1.93, 6.96; $P = .27$, n = 4 studies; for moderate-CHO: 1.93 mg/dL; 95% CI: −0.77, 4.64; $P = .16$, n = 4 studies).[61]

Contrary to the results from these two meta-analyses,[57,61] four other meta-analyses examining the effects of low-CHO diets vs HCLF diets in adults with overweight or obesity found significantly higher LDL-C levels during the CHO-restricted diets.[58–60,62] Systematic reviews and meta-analyses of RCTs examining the effects of low-CHO and very-low-CHO diets on blood lipids in patients with T2D and prediabetes found no significant difference in total-C[57,63–67,80] and LDL-C levels[57,63–67,69,80] between low-CHO and HCLF diets (Table 2, Fig. 1).

None of the meta-analyses discussed previously examined the effect of low-CHO or very-low-CHO diets on VLDL-C, non–high-density lipoprotein cholesterol (non–HDL-C), apolipoprotein B (apoB), or LDL particle number or size in adults with T2D and there is very little evidence from RCTs of adults with overweight or obesity. Gjuladin-Hellon et al.[61] identified only three large (n > 100) RCTs that examined the impact of CHO-restricted diets on VLDL-C,[81] apoB levels,[82] or LDL-C particle size.[83] Although the results of these large RCTs showed improvement in these variables for the CHO-restricted diet groups vs the HCLF diets groups, results were limited by the CHO restriction in the diet interventions ranging from ketogenic to nonketogenic and the intensive lifestyle interventions provided to participants may have affected the results.

Similar to total-C and LDL-C, recent systematic reviews and meta-analyses of RCTs have found varying results on the effects of low-CHO and very-low-CHO diets on TG and HDL-C levels (Table 2, Fig. 1). In their meta-analysis of adults with overweight or obesity (14 RCTs), Naude et al.[57] reported a significant difference for HDL-C at 1–2 years follow-up, but no significant difference for TG between diet groups. Furthermore, both Naude et al.[57] and Korsmo-Haugen et al.[67] reported no significant differences between diet groups for TG and HDL-C levels at 1–2 years follow-up in adults with overweight or obesity and T2D.

Conversely, other meta-analyses reported significant improvements in both TG and HDL-C levels with low-CHO diets vs HCLF diets at 1–2 years follow-up in adults with overweight and obesity[58–62] and prediabetes or T2D.[63,64,66,69] Gjuladin-Hellon et al.[61] reported a significantly greater decrease in TG levels and a significantly greater increase in HDL-C levels with CHO-restricted diets vs LF diets at 6 and 12 months in adults with overweight or obesity, but no significant difference at 24 months, except in the very-low-CHO diet group, which maintained significantly higher HDL-C levels than the other diet groups at 24 months.

Points to consider regarding the effects of low-CHO and very-low-CHO diets on blood lipids and lipoproteins

The conflicting results of the studies examining the effect of low-CHO and very-low-CHO diets on blood lipids

and lipoprotein levels in adults with overweight or obesity with and without T2D may be due to variations in CHO and fat quantity and quality of the diet interventions in the RCTs, and/or differences in adherence to the prescribed diets over the course of the study periods.[57,63,78,80] Participants began with a CHO-restriction that was ketogenic (<20–50 g/d) at study start in very few studies included in the meta-analyses and adherence to the diet was not maintained to the study end, except in the Brinkworth et al.[70] study; thus, at 2-year follow-up, there was little difference between the diets.[57–61,66,67] In one meta-analysis of RCTs of adults with overweight or obesity without T2D, the TDE SFA in the HCLF diets was ~9.3%, whereas the low-CHO and comparison control diets were ~12.5–15% TDE SFA.[59] Thus, the greater SFA in the low-CHO and control diets may have resulted in higher LDL-C levels vs the HCLF diet. The lack of significant difference between the diet groups in RCTs involving adults with T2D or prediabetes may be attributed to similar SFA content between diets,[66] SFA intake did not increase from baseline in the diet groups,[80] or CHO was replaced with unsaturated fatty acids in the low-CHO diets.[67] Taken together, the available data suggest that controlling SFA intake is crucial to prevent significant increases in LDL-C and for achieving improved cardiovascular (CV) health with low-CHO diets. Furthermore, improvements in TG and HDL-C levels were achieved at a CHO intake considered low (<130 g/d) or moderate (130–225 g/d), but not ketogenic, which may promote more successful adherence.[66]

In addition to the points discussed previously, weight loss can impact lipids and lipoproteins and modifications in macronutrients can influence the response to some extent. Negative energy balance and weight loss, regardless of the dietary strategy, tend to improve TG, LDL-C, and HDL-C.[19] A 3 kg weight loss can decrease TG by at least 15 mg/dL, and a 5 to 8 kg weight loss can decrease LDL-C by ~5 mg/dL and increase HDL-C by 2 to 3 mg/dL.[34] The macronutrient content of the dietary strategy used for weight loss can affect LDL-C levels in that a higher intake of unsaturated fatty acids tends to lower LDL-C, whereas a higher intake of SFA, cholesterol, and *trans* fatty acids tends to raise LDL-C. Higher protein intake, particularly from plant proteins such as soy protein, tends to lower LDL-C relative to protein from animal sources. Thus, the effect on LDL-C is variable and likely depends in part on the net impact of the various factors discussed previously. Weight loss with a low-CHO diet that is also low in SFA, cholesterol, and *trans* fatty acids will tend to reduce LDL-C, but LDL-C may increase with a low-CHO diet that is high in SFA, cholesterol, *trans* fatty acids, and animal proteins.[19] In regard to TG levels, reducing dietary CHO will generally lower TG levels with a resultant decrease in VLDL-C, particularly in individuals with elevated TG. The TG-lowering effect will be enhanced by weight loss and negative energy balance. Lowering TG will generally raise HDL-C once weight has stabilized, but HDL-C may go down during weight loss or negative energy balance. Weight stabilization after weight loss also tends to raise HDL-C. The reduction in TG levels due to weight loss, with or without CHO restriction, will also tend to shift toward larger HDL and LDL particles.[19]

Although the results from some studies may not show a significant difference in lipid and lipoprotein parameters between diet groups, there may be individuals who experience extreme effects of low-CHO and VLCHF diets, which may be related to genetic factors and the variable response to substrate availability and neurohormonal reactivity. Two RCTs[84,85] reported considerable variability in LDL-C levels in adults with obesity consuming a VLCHF diet (4% TDE, 61% TDE total fat, 20% TDE SFA)[84] or adults with a normal weight following a very-low-CHO diet (<20 g/d; *ad libitum* with no restriction on fat or protein intake)[85] compared with a HCLF or control diet. The increase in LDL-C ranged between 5–10% in one RCT[84] and 44% (range 5% to 107%) in the other RCT.[85] In their narrative review on nutrigenetics and blood cholesterol levels, Vazquez-Vidal et al. reviewed gene-nutrient interaction studies that examined inter-individual variability in blood cholesterol responses.[86] Some studies have shown significant associations between the *APOE4* allele and an increased LDL-C response to dietary interventions while others found no association indicating the LDL-C response varies based on different types of dietary interventions (ie, amount and type of fat and cholesterol) or specific foods.[86,87] Thus, it is essential to assess the lipid profile of patients who choose to follow low-CHO or very-low-CHO diets and KDs.

Key points

- Results from meta-analyses demonstrate a variable total-C and LDL-C response to low-CHO and very-low-CHO diets.
- A high saturated fatty acid (SFA) content in low-CHO and very-low-CHO diets is a key factor for an increase in LDL-C.
- Compared with high-CHO, low-fat (HCLF) diets, low-CHO diets generally decrease TG levels.
- Compared with HCLF diets, low-CHO diets generally result in a short-term increase in HDL-C levels, which is typically not maintained for longer durations.
- Improvements in TG and HDL-C levels were achieved at low- and moderate-CHO intakes vs very-low-CHO intakes, which may result in better long-term adherence.
- Genetic factors have been shown to play a role in the individual variability of LDL-C levels with low-CHO and very-low-CHO diets.
- Baseline and follow-up lipid/lipoprotein assessments are essential for individuals following low-CHO and very-low-CHO diets to identify extreme responses.

Effects on glucose, hemoglobin A1c, insulin and insulin sensitivity, and hypoglycemic medication use

Systematic reviews and meta-analyses of low-CHO and very-low-CHO diets compared with HCLF diets in RCTs of adults without T2D[57,60] or that included a small number of adults with T2D[58] found no significant difference for fasting blood glucose (FBG), hemoglobin A1c (HbA1c), and insulin levels between diet groups, although there were trends in favor of the low-CHO diets for these endpoints. However, only one RCT[70] included in the meta-analyses reported CHO intake <50 g/d by the end of study.[58,60]

Systematic reviews and meta-analyses of RCTs comparing low-CHO and very-low-CHO diets to HCLF diets in adults with T2D and prediabetes found no significant difference between glucose levels[57,64] or insulin levels.[80] In short-term (≤6 months) studies, HbA1c was significantly lower with low-CHO diets compared with HCLF diets.[63–69,80] At ≥1 year, HbA1c was similar between the low-CHO and HCLF diet groups,[57,63,65,67–69,80] except in two meta-analyses.[64,66] Meng et al.[64] (WMD -0.44%; 95% CI: −0.61, −0.26; $P = .00$; n = 9 studies) and Huntriss et al.[66] (WMD −0.28%; 95% CI: −0.53, −0.02; $P = .03$; n = 7 studies) reported a significantly decreased HbA1c in the low-CHO diet groups at 1 year (Table 2, Fig. 1).

Although there were no significant differences in HbA1c responses between CHO-restricted and HCLF diets in most meta-analyses of RCTs, a greater reduction in the use of diabetes medications was found in low-CHO diet groups compared with HCLF diet groups at the end of study,[64–69] primarily lower insulin dosages,[64,67] suggesting a clinically relevant impact on glycemic control. In 4 of 5 RCTs examining medication changes in one meta-analysis,[69] there was a dose reduction of glucose-lowering medications. In their meta-analysis of 18 RCTs, Huntriss et al.[66] reported a statistically significant reduction in the use of diabetes medications, including reductions in insulin, oral hypoglycemic agents (OHAs), or a combined diabetes medication score in the low-CHO diet groups. Fourteen RCTs included in the Huntriss et al.[66] meta-analysis reported a reduced requirement for diabetes medications in the low-CHO diet group vs control group, of which 9 studies found a statistically significant reduction in insulin (2 RCTs), OHAs (2 RCTs), or a combined diabetes medication score (5 RCTs) in the low-CHO diet groups. Importantly, the average CHO intake in 12 RCTs included in the overall meta-analysis was 106 g/d indicating that reductions in the use of diabetes medications can be achieved at CHO levels considered low, but not ketogenic.[66]

Effects of dietary patterns on lipids and glycemic control in people with type 2 diabetes

Recent network meta-analyses (NMAs) compared the impact of different dietary approaches in clinical trials on glycemic control[88] (primary outcome was HbA1c; n = 56; 4937 participants) and blood lipids[89] (n = 52; 5360 participants) in patients with T2D. Eight dietary approaches with a minimum intervention period of 12 weeks and compared with a control (minimal intervention or no intervention) were included in the NMAs:

- low-CHO (<25% TDE CHO; high intake animal and/or plant protein, often high fat);
- moderate-CHO (25–45% TDE CHO, 10–20% TDE protein);
- high-protein (20% TDE protein from animal and/or plant sources, <35% TDE fat);
- low-fat (<30% TDE fat; high intake of cereals and grains; 10–15% TDE protein);
- low glycemic index (GI)/glycemic load (GL);
- vegetarian (no meat and fish)/vegan (no animal products);
- Mediterranean (rich in fruit, vegetables, olive oil, legumes, cereals, fish, and moderate intake of red wine during meals); and
- Paleolithic[88] (includes lean meat, fish, shellfish, fruits, vegetables, roots, eggs and nuts; excludes grains, dairy products, salt or refined fats and sugar).[90]

All eight dietary approaches significantly reduced HbA1c vs the control diet. Based on the surface under the cumulative ranking curves (SUCRA), the low-CHO diet reduced HbA1c the most (SUCRA = 84%) followed by the Mediterranean diet (SUCRA = 80%), whereas the Mediterranean diet reduced FBG the most (SUCRA = 88%) followed by the Paleolithic (SUCRA = 71%) and vegetarian (SUCRA = 63%) diets. Subgroup analyses found that low-CHO diets reduced HbA1c more than the other diets in smaller and shorter-term (<12 months) studies that included patients <60 years of age. The Mediterranean, moderate-CHO, low GI/GL, high-protein, and low-fat diets reduced HbA1c more in larger and longer-term studies with patients >60 years of age. Furthermore, univariate meta-regression analysis showed that the mean reduction in HbA1c was significantly related to the mean difference in weight change between dietary approaches.[88]

The NMA by Neuenschwander et al.[89] compared the effect of the eight dietary patterns to a control diet on LDL-C, HDL-C, and TG in patients with T2D. The results demonstrated that moderate-CHO and vegan/vegetarian diets were more effective at reducing LDL-C compared with the control diet, and low-CHO, high-protein, and low-fat dietary patterns. The Mediterranean diet was the only dietary pattern that increased HDL-C. The Mediterranean and low-CHO diets significantly reduced TG levels compared with low-fat and control diets. Based on the SUCRA ranking for the combined effect on LDL-C, HDL-C, and TG, the Mediterranean diet (SUCRA: 79%) had the most beneficial effects with Paleolithic (SUCRA: 73%) and low-CHO (SUCRA: 62%) ranking next. The authors cautioned about interpreting the results

for the Paleolithic SUCRA given their NMA included only one study.[89]

Key points

- Low-CHO diets did not reduce FBG or insulin levels more than high-CHO, low-fat (HCLF) diets in clinical trials.
- Low-CHO diets result in a greater short-term (<6 months) reduction in HbA1c vs HCLF diets, but there was less difference between diets beyond 1 year.
- Low-CHO diets resulted in a reduction in the use of diabetes medications, and reductions in the use of diabetes medications were achieved at CHO intake levels that do not induce ketosis.
- The Mediterranean dietary pattern produced improvements in TG, HDL-C, and HbA1c levels in individuals with T2D compared with low-CHO diets.

Effects on blood pressures

Reductions in systolic blood pressure (SBP) (3 mm Hg) and diastolic blood pressure (DBP) (2 mm Hg) typically occur with a 5% weight loss.[34] Systematic reviews and meta-analyses of low-CHO and very-low-CHO diets compared with HCLF diets in RCTs of adults without T2D[57,60,62] or that included a small number of adults with T2D[58] reported conflicting results for the impact on blood pressure. One meta-analysis reported no statistically significant difference in SBP (WMD −1.47 mm Hg; 95% CI: −3.44, 0.50; $P = .14$; n = 11 studies), but found a significant difference in DBP between diet groups (WMD −1.43 mm Hg; 95% CI: −2.49, −0.37; $P = .008$; n = 11 studies).[58] Other meta-analyses did not find a significant difference between diet groups for either SBP or DBP.[57,60,62]

Similarly, systematic reviews and meta-analyses of RCTs comparing low-CHO and very-low-CHO diets to HCLF diets in adults with T2D and prediabetes found conflicting results for the effect on blood pressure (Table 2, Fig. 1). One meta-analysis found a significant difference in SBP between diet groups in favor of low-CHO diets (WMD −2.74 mm Hg; 95% CI: −5.27, −0.20, $P = .03$; n = 7 studies), but no significant difference in DBP,[66] whereas another meta-analysis found a significant decrease in DBP with high-fat diets (WMD −1.35; 95% CI: −1.79, −0.92; $P < .00001$; n = 6 studies), but not SBP.[63] van Zuuren et al.[69] found a significant decrease in DBP (WMD −1.91; 95% CI: −3.63, −0.18; $P = .03$; n = 4 studies) with low-CHO diets at 6 months, but no significant difference between diet groups for SBP or DBP past 6 months. Two other meta-analyses did not find a significant difference between diet groups for either SBP or DBP.[57,67] A critical review[80] of 12 RCTs reported no difference between low-CHO and HCLF diets, except in two studies: one showed a greater reduction in SBP (−3.03 mm Hg, $P = .04$) in the HCLF group[91] and the other showed a greater reduction in DBP in the low-CHO diet group (−2 mm Hg, $P = .020$, diet × time).[92]

Key point

- Low-CHO and very-low-CHO diets produced inconsistent effects on blood pressures in adults with overweight or obesity with and without prediabetes or T2D compared with high-CHO, low-fat diets.

Key recommendations for cardiometabolic risk factors*	COR	LOE
To achieve an improvement in a patient's cardiometabolic risk factor profile, a weight reduction diet that achieves a clinically significant weight loss (5–10% of body weight) **is recommended.**[18,19,34]	I	A
As part of low-CHO and very-low-CHO diets, it **is reasonable** for a patient to choose unsaturated fatty acids over SFAs.[19,59,66,67,80]	IIa	B-R
In patients with overweight or obesity with or without T2D and with elevated TG levels, a low-CHO diet **is reasonable** for lowering TG levels (and VLDL-C) compared to an HCLF diet.[58–64,66,69]	IIa	B-R
Because substantial variation in lipid responses has been observed in patients choosing to follow low-CHO and very-low-CHO diets, baseline and follow-up lipid profiles **are reasonable.**[57–67,69]	IIa	B-R
In patients with T2D, a low-CHO diet **may be reasonable** to achieve an improvement in glycemic control or a reduction in diabetes medications.[64–69]	IIb	B-R
In patients with overweight and obesity with hypertension, weight loss with a low-CHO or very-low-CHO diet **may be reasonable** as a way to lower blood pressure.[58,63,66]	IIb	B-R

HCLF, high-carbohydrate, low-fat; SFA, saturated fatty acids.

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

Evidence for the effect of low-CHO and very-low-CHO diets on emerging risk factors

Effect on C-reactive protein levels

Few systematic reviews or meta-analyses have examined the effect of low-CHO or very-low-CHO diets on systemic inflammation. A meta-analysis identified 4 RCTs that examined the impact on C-reactive protein (CRP) levels and reported no significant differences despite a WMD in favor of very-low-CHO diets.[58] In adults with either prediabetes and/or T2D, CRP was not significantly different between high-fat diet groups (included 6 RCTs that prescribed a low-CHO diet).[63] In one critical review, only one study reported on CRP, which found no significant difference between the diet groups.[80]

Effect on the gut microbiome

There is a theoretical concern about the adverse effects of a marked CHO restriction for low-CHO diets and very-low-CHO/KDs due to the avoidance of CHO-rich foods that provide dietary fiber for the gut microbiome. However, there are no long-term studies; only short-term RCTs have been conducted to date. These studies have reported unfavorable shifts in microflora composition with an energy-restricted VLCHF/KD[93] and with a higher-fat diet.[94] Although potentially unfavorable shifts in gut microbiota have been observed in some studies with low-CHO diets, the clinical relevance of these shifts is currently uncertain.

Effect on trimethylamine N-oxide production

Another emerging concern with low-CHO and very-low-CHO diets is the potential effect on ASCVD risk due to trimethylamine N-oxide (TMAO) production. Many individuals following low-CHO and very-low-CHO diets consume more animal products, which are associated with an increase in TMAO levels.[95,96] High levels of TMAO have been associated with major adverse cardiac events and increased mortality in secondary prevention patients,[97,98] as well as major adverse cardiac events or all-cause mortality.[99]

Until recently, the impact of low-CHO and very-low-CHO diets on TMAO production has been largely unknown. Park et al.[96] reported the effect of three isocaloric diets (LCHF [Atkins] diet, Mediterranean [South Beach] diet, and a very-low-fat, plant-based [Ornish] diet) consumed by healthy, normolipidemic participants (n = 26) for 4 weeks on levels of systemic TMAO levels and its nutrient precursors in a post hoc analysis of plasma samples from an earlier randomized crossover study. Compared with both the baseline and the low-fat diet phase, the LCHF diet phase was associated with higher levels of TMAO.[96] Thus, short-term exposure to a LCHF diet vs a very-low-fat, plant-based diet was associated with increased TMAO levels, whereas the plant-based diet was associated with decreased levels of TMAO.

Key points

- Weight loss lowers CRP. However, current evidence does not support a difference between low-CHO and very-low-CHO diets compared with high-CHO, low-fat diets on the effects on CRP.
- Research suggests unfavorable gut microbiota changes and fecal metabolite shifts associated with low-CHO and very-low-CHO diets; however, the clinical significance of these changes is unknown.
- Short-term exposure to an LCHF diet vs a very-low-fat, plant-based diet was associated with increased TMAO levels; however, the clinical significance of this change is unknown.

Safety concerns associated with low-CHO and very-low-CHO diets, including ketogenic diets

The possible tolerance and safety concerns of low-CHO diets vary depending on the level of CHO restriction and the characteristics of individuals. With VLCHF/KDs, gastrointestinal complaints tend to be the most common adverse effects, including constipation, nausea, and abdominal pain, which are experienced in the first few weeks.[13] Some individuals may experience symptoms described as the "keto flu" within 2 to 4 days of beginning a VLCHF/KD, which may occur as the body adapts to using ketone bodies for fuel, may last a few days to one week, and include lightheadedness, dizziness, fatigue, difficulty exercising, poor sleep, and constipation.[1] Other adverse effects that have been reported in individuals strictly following VLCHF/KDs include headache,[30,45] skin rash,[45] muscle cramps, weakness, diarrhea, dehydration, hypoglycemia,[100] increased levels of blood uric acid, and vitamin/mineral deficiencies.[30] Increased urination can lead to reduced levels of electrolytes, including sodium, magnesium, and potassium, and may be associated with symptoms of hypovolemia, as well as dizziness related to the need to reduce hypertension and/or hyperglycemia medications.[100] Educating individuals to consume protein from whole foods vs supplements will promote an adequate intake of sodium, potassium, and magnesium.[1] Ensuring adequate fluid and electrolyte intake is essential to avoid symptoms of initiating a VLCHF/KD.[13,100] People with certain diseases and disorders may have additional safety concerns to consider with the use of low-CHO diets and VLCHF/KDs.

Caution in patients with lipid disorders and variability with atherogenic lipoprotein response

As discussed previously, there is a high variability in the LDL-C response to low-CHO diets and very-low-CHO/KDs. Gene-nutrient interaction studies demonstrate that genetics contribute to the individual variability of lipid/lipoprotein responses to dietary interventions.[86] Of considerable concern is the use of VLCHF/KDs in patients with hypercholesterolemia, particularly familial hypercholesterolemia (FH). Patients with known hypercholesterolemia and FH may have a genetic predisposition to increased LDL-C levels with

VLCHF/KDs. VLCHF/KDs are typically not congruent with the medical nutrition therapy recommended for these patients, which includes a reduction in SFAs, *trans* fatty acids, and dietary cholesterol.[101–104] Replacing SFAs with unsaturated fatty acids decreases LDL-C and is associated with reduced ASCVD risk.[17,19,20] Due to the unpredictable response of LDL-C to VLCHF/KDs, all patients who choose to follow these diets should have baseline and follow-up lipoprotein lipid profiles assessed.[85]

Some patients with severe hypertriglyceridemia may have genetic or acquired causes of lipoprotein lipase dysfunction or deficiency, with predisposition to hyperchylomicronemia and acute pancreatitis. In these patients, a VLCHF/KD could cause chylomicronemia and precipitate pancreatitis. Patients with hyperchylomicronemia must adhere to a very-low-fat diet (10–15% TDE or <15–20 g fat/d);[105] thus, a VLCHF/KD is contraindicated in these patients until the chylomicronemia is cleared, and then, only under close observation.

Caution in patients with ASCVD, risk of atrial fibrillation, and a history of heart failure, kidney disease, and liver disease

Based on the previous discussion related to the potential increase in LDL-C and inconsistent effects on HbA1c, SBP, and DBP with low-CHO or very-low-CHO diets, close medical supervision is recommended for patients with established ASCVD who choose to use these diets. The 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults[34] discussed various beneficial effects on CV risk factors with weight loss in adults with overweight or obesity with or without CV risk. However, Jensen et al.[34] stated, "there is insufficient evidence to comment on the cardiovascular risk factor effects of low-carbohydrate diets," and included the recommendation to, "[p]rescribe a calorie-restricted diet, for obese and overweight individuals who would benefit from weight loss, based on the patient's preferences and health status, and preferably refer to a nutrition professional for counseling. A variety of dietary approaches can produce weight loss in overweight and obese adults."

Recently, Zhuang et al.[106] examined the association between CHO intake and the risk of atrial fibrillation (AF) in Atherosclerosis Risk in Communities (ARIC) study participants (n = 13,852) who did not have AF. They found a U-shaped curve between CHO intake and AF with the lowest observed risk associated with a CHO intake of 39–61% TDE and cautioned against the use of low-CHO diets for weight loss due to the increased risk of AF.[106]

Individuals with chronic illnesses may be more susceptible to adverse effects due to the extreme dietary changes that are inherent with low-CHO diets and very-low-CHO/KDs. Because the effects of these diets on patients with chronic illnesses is unknown, it is recommended that patients with heart failure, kidney disease, and liver disease who choose to follow a low-CHO or very-low-CHO/KD should do so under close medical supervision and receive medical nutrition therapy appropriate for their specific diagnosis from a registered dietitian nutritionist (RDN). A VLCHF/KD is contraindicated in patients with a history of pancreatitis and liver failure.[107]

Caution in patients using medications for diabetes, hypertension, and anticoagulation

Patients and clinicians must be aware that individuals with diabetes who choose to follow a very-low-CHO diet or KD are at an increased risk of hypoglycemia because of the effect of the severe CHO restriction on glycemic control and potential need for medication adjustment; thus, individuals following a very-low-CHO diet for T2D management should be medically supervised.[100] OHAs and/or insulin may need to be reduced or discontinued after initiation of a very-low-CHO or KD.[22,45,100,108] Patients should be instructed to monitor their blood glucose levels before taking OHAs or insulin to prevent hypoglycemia.[100] Patients taking sodium-glucose cotransporter 2 (SGLT2) inhibitors should avoid VLCHF/KDs because of an increased risk of SGLT2 inhibitor–associated ketoacidosis.[109,110] Westman et al.[100] recommended discontinuing SGLT2 inhibitors before initiating a very-low-CHO KD because of the risk of normoglycemic ketoacidosis. Murdoch et al.[111] recently published a practical guide for adapting diabetes medication for patients with T2D following low-CHO diets.

A reduction in blood pressure frequently occurs in patients with hypertension who follow low-CHO or very-low CHO diets. Patients should monitor blood pressure at home or in clinic, and antihypertensive medications may need to be tapered or discontinued, especially if symptoms of orthostatic hypotension occur with a low-CHO or very-low-CHO diet.[45,100] Diuretics may need to be tapered or discontinued to prevent dehydration and/or hypotension.[100] In patients with T2D and microalbuminuria, Westman et al.[100] recommended continuing a low dose of a renal-protective antihypertensive medication if a patient does not become hypotensive.

Patients taking a vitamin K antagonist for anticoagulation should be instructed on consistent vitamin K intake and the potential for increased vitamin K intake from nonstarchy and green leafy vegetables. More frequent monitoring of anticoagulation therapy may be required because of the potential change in vitamin K intake and its effect on anticoagulation therapy.[45,100]

Carbohydrate intake and mortality

The evidence related to CHO intake and mortality is from observational studies. Noto et al.[112] conducted a quantitative meta-analysis of cohort studies that examined the association between low-CHO diets and all-cause mortality and CVD incidence. Their meta-analysis of 4 cohort studies (n = 272,216) found an association between adhering to a low-CHO diet (relative risk [RR] 1.31; 95% CI: 1.07, 1.59; P = .007) or low-CHO, high-protein diet (RR 1.30; 95% CI: 1.01, 1.68; P = .04) and a significantly increased risk for all-cause mortality. Meta-analyses examining the association between a low-CHO diet or a low-CHO, high-protein diet and CVD incidence in 7 cohort studies (a total of 469,963 participants) did not find a significant increase

in the risk of CVD incidence.[112] Most recently, Mazidi et al.[113] examined the association between low-CHO diets and overall or cause-specific mortality from NHANES study data (n = 24,825) and found that participants with the lowest CHO intake (<39% TDE) based on 24-hour recall assessment had the highest risk of overall (hazard ratio [HR] 1.32; 95% CI: 1.14, 2.01, $P < .001$), CVD (HR 1.51; 95% CI: 1.19, 1.91, $P < .001$), cerebrovascular (HR 1.50; 95% CI: 1.12, 2.31, $P < .001$), and cancer (HR 1.36; 95% CI: 1.09, 1.83, $P < .001$) mortality. In addition, analysis of pooled data from 9 prospective cohort studies (n = 462,934 participants) found that participants with the lowest CHO intake had the highest risk of overall (RR 1.22; 95% CI: 1.06, 1.39; $P < .001$; n = 8 studies), CVD (RR 1.13; 95% CI: 1.02, 1.24, $P < .001$; n = 6 studies), and cancer mortality (RR 1.08; 95% CI: 1.01, 1.14, $P = .02$; n = 3 studies).[113] Seidelmann et al.[114] examined the association between CHO intake and all-cause mortality in the ARIC study (n = 15,428), as well as a meta-analysis with data from ARIC plus 7 multinational prospective studies (n = 432,179). Their analyses demonstrated that both low (<40% TDE) and high CHO (>70% TDE) intake was associated with a higher risk of mortality (20% and 23%, respectively) with 50–55% TDE CHO associated with the lowest risk of mortality. Results indicated that, when animal-based protein or fat was substituted for CHO, the associated risk of mortality increased by 18% whereas mortality decreased by 18% when CHO was replaced by plant-based protein or fat.[114] The reasons for the association between CHO restriction and increased mortality are not well understood. Possible explanations include a reduced intake of vegetables, fruits, and grains, and an increased intake of animal-based protein, which results in varying levels of dietary bioactive components (ie, free fatty acids, protein, fiber, minerals, vitamins, and phytochemicals) with CHO restriction. Higher CHO intakes may be associated with lower economic status and lower quality CHO foods (ie, refined and higher GI).[113,114] Based on the results of these observational studies, severe CHO restriction for weight loss, if followed, should be limited to short periods (2–6 months) followed by a transition to a healthy dietary pattern for the long-term with adequate intake of fiber-rich CHO foods and inclusion of plant-based proteins and unsaturated fats to ensure nutritional adequacy and promote overall and CV health.

Key points

- Close medical supervision is essential for individuals with ASCVD, risk of atrial fibrillation, or the presence or history of heart failure, kidney disease, or liver disease who choose to follow a very-low-CHO diet or KD.
- VLCHF/KDs are contraindicated in patients with a history of hypertriglyceridemia-associated acute pancreatitis, severe hypertriglyceridemia, or inherited causes of severe hypercholesterolemia.
- Individuals with T2D should receive medical supervision and cardiometabolic monitoring while on very-low-CHO diets or KDs.
- Low-CHO and very-low-CHO diets can lead to hypoglycemia or hypotension and may require adjustment in diabetes or hypertension medications.
- Patients taking SGLT2 inhibitors should avoid very-low-CHO KDs because of an increased risk of SGLT2 inhibitor–associated ketoacidosis.
- More frequent monitoring of vitamin K–dependent anticoagulation therapy may be required with very-low-CHO diets due to the potential change in vitamin K bioavailability and its effect on anticoagulation therapy.

Key recommendations—safety concerns*	COR	LOE
For individuals with ASCVD, risk of atrial fibrillation, the presence or history of heart failure, kidney disease, or liver disease who choose to follow a low-CHO or very-low-CHO diet, **close medical supervision is recommended.**[106,107]	III: Potential Harm	C-EO
Because VLCHF/KDs are **contraindicated** in patients with a history of hypertriglyceridemia-associated acute pancreatitis, severe hypertriglyceridemia, or inherited severe hypercholesterolemia, they are **not recommended** for these patients.[101–105]	III: Potential Harm	C-EO
Because low-CHO diets and very-low-CHO/KDs can increase the risk of hypoglycemia, it **is reasonable** to monitor glycemic control and make adjustments in diabetes medication.[100,108]	III: Potential Harm	B-R
SGLT2 inhibitors **should not be used** in patients choosing to follow very-low-CHO/KDs due to an increased risk of SGLT2 inhibitor–associated ketoacidosis.[100,109,110]	III: Harm	B-NR
More frequent monitoring of vitamin K–dependent anticoagulation therapy **may be reasonable** with a very-low-CHO/KD due to the potential change in vitamin K intake and its effect on anticoagulation therapy.[45,100]	III: Potential Harm	C-EO
Long-term consumption of extreme CHO intakes (low and high) **has been associated with all-cause, CV, and cancer mortality** in the general population.[112–114]	III: Potential Harm	B-NR

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

- Both low- and high-CHO intake has been associated with a higher risk of mortality in the general population; moderate-CHO intake has been associated with the lowest risk of mortality in the general population.

Points for the clinician-patient discussion regarding low-CHO and very-low-CHO diets, including ketogenic diets

Health professionals are a trusted source of nutrition information.[15] In a systematic literature review (9 studies with 9564 subjects) that evaluated the effectiveness of nutrition care provided by primary care physicians, 5 studies reported an observed improvement in nutrition behavior and 7 reported improvements in cardiometabolic risk factors.[115] Health professionals are uniquely positioned to use their expertise to help patients seeking guidance about effective diets for weight loss and cardiometabolic health. Based on current treatment guidelines and recommendations for weight loss, there are a variety of dietary approaches that can produce weight loss in adults with overweight or obesity.[34] The treatment objective is to achieve ideal CV health and, thus, target not only weight loss, but also other health behaviors (nonsmoking, body mass index <25 kg/m^2, physical activity at goal levels, and a dietary pattern that is consistent with current evidence-based recommendations) and ideal health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure $<120/<80$ mm Hg, and FBG <100 mg/dL).[116] A systematic review of the prevalence and outcomes of ideal CV health in both US and other populations reported an inverse association between increasing number of ideal CV health metrics and all-cause and CVD-related mortality risk.[117] Moreover, for each increase in ideal CV health metrics, there is a decreased risk of all-cause and CV mortality by 11% and 19%, respectively.[118] The importance of lifestyle factors was emphasized by a study (n = 55,685) that found a healthy lifestyle was associated with a substantially lower risk of coronary events compared with an unhealthy lifestyle, regardless of the genetic risk for coronary artery disease.[119]

As noted in the ACC/AHA Guideline on the Primary Prevention of CVD,[17] the most important way to prevent ASCVD is to promote a healthy lifestyle throughout the life span. An essential component of this is to meet current food-based dietary recommendations and decrease SFA and *trans* fat, sodium, and added sugars.[17,120] An overall cardioprotective dietary pattern for adults emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish, and minimizes the intake of foods rich in SFA, *trans* fats, and cholesterol, processed meats, refined CHO foods and foods with added sugars, and sweetened beverages.[17–19,120] The dietary recommendations for CVD prevention should be implemented in a way that accommodates cultural, ethnic, or economic influences that shape individual food preferences.[17–20,120]

For adults with overweight and obesity, of the myriad of weight loss diets evaluated, there is no evidence that one is superior or ideal,[121] and counseling and caloric restriction in conjunction with a comprehensive lifestyle intervention are recommended for achieving and maintaining weight loss.[17,34,122] Based on the results of clinical studies, patients with overweight or obesity who receive high-intensity lifestyle interventions, including referral to a nutrition professional (ie, RDN) for multiple nutrition counseling sessions, and participation in $\geq$14 weight loss intervention visits over 6 months with a trained interventionist have improved outcomes compared with those who do not.[34] Guidelines for the treatment of patients with overweight or obesity recommend that a structured lifestyle intervention program with a multidisciplinary team is available to patients and based on the phases of disease prevention (ie, primary, secondary, tertiary).[122] In addition, referral to an RDN, when feasible, for multiple face-to-face visits, can improve results for biomarkers of cardiometabolic risk, including weight loss, lipids, and glycemic control.[123] Information on referral to an RDN and reimbursement is available on the NLA "5-minute Nutrition Tool" tear sheet for providers (www.lipid.org, follow link to "Practice Tools," then "Patient and Clinician Tear Sheets," then "Clinician's Lifestyle Modification Toolbox–Tools for Clinicians").

A comprehensive lifestyle intervention program includes reduced calorie intake, increased physical activity, and behavior change therapy to facilitate weight loss or maintenance of reduced body weight. The behavior change program typically includes regular self-monitoring of weight, food intake, and physical activity.[34,122] Physical activity recommended for weight loss includes increased aerobic activity, such as brisk walking, for $\geq$150 min/wk. To maintain lost weight or minimize weight regain in the long term ($>$1 year), higher levels of physical activity, approximately 200 to 300 min/wk, are recommended.[17,19,34,122,124] As noted by Kahan and Manson,[125] helping patients manage weight loss expectations is important. It may be unrealistic for many patients to achieve a "normal" weight. Nonetheless, a sustained weight loss of 5–10% is often achievable and improves health. Additional weight loss can be pursued over time.

Although a low-CHO diet (initially <20 g/d and transitioning to <30 g/d) can be used in practice with medical supervision, if this is the preferred weight loss strategy chosen by a patient, it is strongly recommended that the patient transition to a healthier dietary pattern that meets current dietary recommendations for ideal cardiometabolic and CV health. As discussed previously, studies have shown that long-term adherence to a very-low-CHO/KD is challenging and, noted by Brouns,[2] over time many individuals appear to shift to higher CHO intakes (130–160 g/d). Professional guidance, preferably from an RDN whenever feasible, increases the likelihood that individuals will transition to a healthy dietary pattern that is sustained and promotes maintenance of a reduced body weight.[17,19,34,108,122]

Important to this NLA Scientific Statement, the 2019 *Nutrition Therapy for Adults with Diabetes or Prediabetes:*

Consensus Report[108] and the American Diabetes Association (ADA) *Lifestyle Management: Standards of Medical Care in Diabetes*[109] reviewed the current evidence for individualized nutrition therapy for adults with prediabetes or diabetes and recognized that there is convincing evidence from several meta-analyses that a reduction in overall CHO intake improves glycemia and cardiometabolic risk factors in persons with T2D. Moreover, for select adults with T2D who do not meet glycemic targets or when reducing antiglycemic medications is a priority, a reduction in CHO intake with a low-CHO[108,109] or very-low-CHO eating plan[108] is considered a viable approach. Although the *Consensus Report*[108] did not include a discussion of RCTs that varied the SFA content of low- and very-low-CHO diets, a study by Tay et al.[126–128] did show a very-low-CHO (14% TDE; <50 g/d), high-unsaturated/low-saturated fat diet (<10% TDE SFA) and high in dietary fiber (25 g/d) vs an HCLF diet (53% TDE CHO; <10% TDE SFA) elicited similar weight loss, LDL-C, and HbA1c reductions. However, the VLCHF (low SFA) diet achieved greater reduction in diabetes medications, better improvements in diurnal blood glucose stability, greater reductions in TGs, and maintenance of HDL-C levels. Thus, if implemented appropriately with lower SFA intake, there are benefits of CHO-restricted diets, principally on glycemic control, but also on other cardiometabolic risk factors, in persons with T2D. It was recognized by the *Consensus Report*[108] and as illustrated in this NLA Scientific Statement that, to date, the evidence for benefits of low-CHO and very-low-CHO diets for diabetes control are based largely on short-term studies; hence, further research (especially longer term) is needed on low-CHO diets that meet all of the nutrition recommendations of the *Consensus Report*[108] and ADA *Lifestyle Management Standards*,[109] including adequate dietary fiber (14 g/1000 calories) and <2300 mg/d sodium. Weight loss is recommended, if indicated, and an eating pattern should be individualized to achieve long-term adherence. Despite emerging benefits for lower CHO diets on glycemic control in persons with diabetes, if these diets are implemented in clinical settings, they require close medical supervision.

In summary, because a healthy body weight is a key metric for CV health, weight loss in adults with overweight or obesity improves cardiometabolic risk factors.[129] Thus, an energy-reduced diet that meets all dietary recommendations for heart health will promote healthy weight loss and improve CV health. To promote long-term maintenance of a reduced body weight and decreased ASCVD risk, a healthy dietary pattern coupled with behavior change strategies and increased physical activity are essential.

Key points

- There should be a clinician-patient discussion regarding need for and oversight of low-CHO diets or very-low-CHO/KDs before initiation.
- Low-CHO and very-low-CHO diets may be an option for a short-term initial weight loss period (2–6 months).
- For long-term weight maintenance and CV health, it is recommended to gradually increase CHO intake. An emphasis should be placed on CHO foods associated with reduced cardiometabolic risk, including vegetables, fruits, whole grains, and legumes.
- A comprehensive lifestyle intervention program includes reduced calorie intake, increased physical activity, and behavior change therapy to facilitate weight loss or maintenance of reduced body weight.

Key recommendations for long-term weight loss and maintenance*	COR	LOE
Referral to a comprehensive lifestyle intervention program with a multidisciplinary team (which may include physicians, advanced practice nurses, physician assistants, registered dietitian nutritionists, exercise specialists, and psychologists) **is reasonable** as a way to facilitate weight loss or maintenance of reduced body weight.[17,34,122]	IIa	B-NR
Addressing behavioral, family, cultural, and social dynamics and accommodating ethnic or economic influences that shape individual food preferences and physical activity habits **can be useful** to promote long-term success as part of comprehensive lifestyle intervention programs.[17,34,122]	IIa	B-R
A moderate-CHO intake (>130–225 g/d) with an emphasis on including foods known to be associated with improved cardiometabolic health **may be a reasonable** long-term strategy to manage weight and promote health in general.[19,122]	IIb	B-R
It **is recommended** that all patients receive counseling on reducing sedentary activity and increasing physical activity, including both aerobic physical activity, such as brisk walking, for ≥150 min/wk, and strength/resistance activities.[17–19,122,124]	I	A
To maintain long-term (>1 y) weight loss or minimize weight regain, it **is reasonable** to counsel patients on engaging in higher levels of physical activity of approximately 200 to 300 min/wk[17,19,122,124]	IIa	B-R

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

Gaps in the evidence

Based on the review of the evidence for this NLA Scientific Statement, there are gaps in the knowledge base about the long-term effects of low-CHO and very-low-CHO diets, including KDs, on cardiometabolic health, ASCVD risk, and overall health and mortality. Future research is needed to determine:

- the factors that influence EE and appetite with low-CHO diets and very-low-CHO diets, including KDs;
- the effects of different levels of CHO intake on cardiometabolic indices and disease outcomes with well-designed RCTs of longer duration that compare a range of diets, ideally including a very-low-CHO/KD and low-CHO, moderate-CHO, and high-CHO diets, where strong efforts are made to promote adherence with the CHO intake goal through end of study;
- whether a possible threshold exists where CHO intake does not have to be severely restricted and still achieve benefit as suggested by Gibson et al.,[38] thus, whether a moderate-CHO and moderate-fat diet can achieve similar benefits as a very-low-CHO/KD through improved long-term adherence and inclusion of foods associated with more favorable cardiometabolic outcomes; and
- the long-term effects of following a low-CHO diet or very-low-CHO/KD on body weight changes and maintenance of weight loss; the microbiome, TMAO production, and other inflammatory markers associated with higher ASCVD risk; and finally, atherosclerosis and ASCVD risk, as well as other chronic illness (eg, cancer).

Conclusion/summary statement

As discussed in this NLA Scientific Statement, low-CHO diets and very-low-CHO/KDs are increasing in popularity. Results from meta-analyses and guidelines from professional organizations suggest that there is not one macronutrient distribution that is superior for weight loss or for the management of T2D. Evidence suggests that there is a physiological basis for potential metabolic benefits of CHO-restriction compared with dietary strategies with a higher CHO content in some individuals. Results from meta-analyses indicate that low-CHO and very-low-CHO diets may elicit improvements in TG and HDL-C levels, glycemic control, and reductions in diabetes medications, but have variable effects on LDL-C levels; however, by approximately 2 years, there are no differences for most cardiometabolic risk markers. Moreover, three separate observational studies, including a large prospective cohort study with long-term follow-up, have shown that a very-low-CHO intake is associated with increased all-cause mortality. Evidence also demonstrates that adherence to the severe CHO restriction of very-low-CHO diets is challenging and has the potential to cause adverse side effects. In addition, VLCHF diets challenge the nutrition recommendations of various professional organizations, severely restrict or eliminate foods associated with cardioprotective benefits, and encourage a high intake of foods known to increase ASCVD risk (eg, processed meats, foods rich in SFAs). Long-term studies on the potential impact of ASCVD outcomes are lacking.

The decision about whether a patient should consider following a low-CHO or very-low-CHO diet should be made after a clinician-patient discussion about the risks and benefits of these diets and consideration of patient preference. If a very-low-CHO diet is adopted, individuals with overweight or obesity without T2D should, ideally, receive medical supervision, baseline and regular assessment of lipid/lipoproteins, and, when feasible, multiple sessions with an RDN to facilitate dietary adherence with personalized nutrition counseling and behavior modification, as well as replacement of CHO with unsaturated fatty acids and avoidance of excessive intakes of SFA and cholesterol. Individuals following low-CHO or very-low-CHO diets for T2D management should receive medical supervision for adjustment of diabetes and hypertension medications as needed. In addition, referral to a behavioral change support team, including an RDN, when feasible, is recommended to facilitate dietary adherence along with personalized nutrition counseling and behavior modification. Patients taking SGLT2 inhibitors should avoid very-low-CHO/KDs because of an increased risk of SGLT2 inhibitor–associated ketoacidosis. Clinician oversight is essential for patients with chronic medical conditions who want to follow low-CHO or very-low-CHO diets, including those with ASCVD, heart failure, T2D, kidney disease, and liver disease. Some patients should not follow a VLCHF diet because of the presence or history of hypertriglyceridemia-associated acute pancreatitis, severe hypertriglyceridemia (ie, propensity for hyperchylomicronemia), or inherited severe hypercholesterolemia.

Referral to a comprehensive lifestyle intervention for weight loss can increase the likelihood of weight loss success and long-term weight management. Referral to an RDN, when feasible, for medical nutrition therapy and lifestyle counseling can improve cardiometabolic risk and encourage the consumption of vegetables, fruits, nuts, seeds, legumes, and whole grains within the context of a CHO-restricted diet. Achieving a healthy body weight and long-term weight maintenance using a cardioprotective dietary pattern and increased physical activity can promote overall health and decrease the risk of ASCVD.

Financial disclosures

C.F.K. discloses that, in the past 12 months, she has nothing to disclose. J.P.B. discloses that, in the past 12 months, she has nothing to disclose. P.M.K.E. discloses that, in the past 12 months, she has received Principal Investigator honorarium from the Hass Avocado Board. G.S. discloses that in the past 12 months, she has nothing to disclose. K.E.A. discloses that in the past 12 months, she has received speaking honorarium from Medscape and has

been a Site Principle Investigator for clinical trials involving Amgen, Akcea Therapeutics, and Esperion. D.E.S. discloses that in the past 12 months, he has received speaking honorarium from Sanofi; consulting honorarium from Medicure, and Regeneron; and is an investigator in clinical trials sponsored by Amgen Inc., Astra Zeneca, Novartis, Regeneron, and RegenX Bio. K.E.W. discloses that in the past 12 months, she has received speaking honorarium from Amgen, Regeneron, and Sanofi. K.C.M. discloses that in the past 12 months, he has received consulting honoraria or research grants from Acasti, Akcea Therapeutics, Almond Board of California, American Egg Board, Amgen, ChromaDex, Corvidia Therapeutics, General Mills, Ingredion, Kellogg, Matinas BioPharma, National Cattlemen's Beef Association, National Dairy Council, and Regeneron.

Conflict of interest

The authors have no conflicts of interest to disclose.

Acknowledgments

The authors would like to gratefully acknowledge Vivian Grifantini for her assistance in completing this project, especially communicating deadlines and submitting this article. A special thanks to Terry A. Jacobson, MD, FNLA, who provided guidance and valuable comments and feedback during the development of this manuscript.

Authors' contributions: All authors contributed to this scientific statement, drafting and revising it critically for important intellectual content, and have approved the final version.

There was no funding for the study.

References

1. Abbasi J. Interest in the ketogenic diet grows for weight loss and type 2 diabetes. *JAMA*. 2018;319(3):215–217.
2. Brouns F. Overweight and diabetes prevention: is a low-carbohydrate-high-fat diet recommendable? *Eur J Nutr*. 2018;57(4):1301–1312.
3. Paoli A, Rubini A, Volek JS, et al. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr*. 2013;67(8):789–796.
4. Paoli A. Ketogenic diet for obesity-friend or foe. *Int J Environ Res Public Health*. 2014;11(2):2092–2107.
5. Harvey CJDC, Schofield GM, Zinn C, Thornley SJ, Crofts C, Merien FLR. Low-carbohydrate diets differing in carbohydrate restriction improve cardiometabolic and anthropometric markers in healthy adults: a randomised clinical trial. *PeerJ*. 2019;7:e6273.
6. Hyde PN, Sapper TN, Crabtree CD, et al. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. *JCI Insight*. 2019;4(12):128308.
7. Burke LM, Hawley JA. Swifter, higher, stronger: What's on the menu? *Science*. 2018;362(6416):781–787.
8. Brinkworth GD, Buckley JD, Noakes M, Clifton PM, Wilson CJ. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. *Arch Intern Med*. 2009;169(20):1873–1880.
9. Brinkworth GD, Luscombe-Marsh ND, Thompson CH, et al. Long-term effects of very low-carbohydrate and high-carbohydrate weight-loss diets on psychological health in obese adults with type 2 diabetes: randomized controlled trial. *J Intern Med*. 2016;280(4):388–397.
10. El Ghoch M, Calugi S, Dalle Grave R. The effects of low-carbohydrate diets on psychosocial outcomes in obesity/overweight: a systematic review of randomized, controlled studies. *Nutrients*. 2016;8(7):E402.
11. Iacovides S, Goble D, Paterson B, Meiring RM. Three consecutive weeks of nutritional ketosis has no effect on cognitive function, sleep, and mood compared with a high-carbohydrate, low-fat diet in healthy individuals: a randomized, crossover, controlled trial. *Am J Clin Nutr*. 2019;110:349–357.
12. Clarke C, Best T. Low-carbohydrate, high-fat dieters: characteristic food choice motivations, health perceptions and behaviours. *Food Qual Preference*. 2017;62:162–171.
13. Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open*. 2018;3(2):175–192.
14. Roehl K, Sewak SL. Practice paper of the academy of nutrition and dietetics: classic and modified ketogenic diets for treatment of epilepsy. *J Acad Nutr Diet*. 2017;117(8):1279–1292.
15. International Food Information Council Foundation. Food & Health Survey; 2018. Available at: https://foodinsight.org/wp-content/uploads/2018/05/2018-FHS-Report-FINAL.pdf. Accessed July 11, 2019.
16. Ludwig DS, Ebbeling CB. The carbohydrate-insulin model of obesity: beyond "calories in, calories out.". *JAMA Intern Med*. 2018;178(8):1098–1103.
17. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;1097:33877.
18. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;1097:39034.
19. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. *J Clin Lipidol*. 2015;9(6 Suppl):S1–S122.e1.
20. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th Edition; 2015. Available at: http://health.gov/dietaryguidelines/2015/guidelines/. Accessed April 10, 2019.
21. Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids; 2005. Available at: https://www.nap.edu/read/10490/chapter/1. Accessed April 10, 2019.
22. Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition*. 2015;31(1):1–13.
23. Chang J, Kashyap SR. The protein-sparing modified fast for obese patients with type 2 diabetes: what to expect. *Cleve Clin J Med*. 2014;81(9):557–565.
24. Wylie-Rosett J, Aebersold K, Conlon B, et al. Health effects of low-carbohydrate diets: where should new research go? *Curr Diab Rep*. 2013;13(2):271–278.
25. Zilberter T, Zilberter Y. Ketogenic ratio determines metabolic effects of macronutrients and prevents interpretive bias. *Front Nutr*. 2018;5:75.
26. Talbot FB, Metkalf KM, Moriarty ME. Epilepsy: chemical investigations of rational treatment by production of ketosis. *Am J Dis Child*. 1927;33:218–225.

27. Mozaffarian D. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation*. 2016;133(2):187–225.
28. Sikand G, Kris-Etherton P, Boulos NM. Impact of functional foods on prevention of cardiovascular disease and diabetes. *Curr Cardiol Rep*. 2015;17(6):39.
29. Evans M. Keto diets: good, bad or ugly? *J Physiol*. 2018;596(19): 4561.
30. Adam-Perrot A, Clifton P, Brouns F. Low-carbohydrate diets: nutritional and physiological aspects. *Obes Rev*. 2006;7(1):49–58.
31. Miller VJ, Villamena FA, Volek JS. Nutritional ketosis and mitohormesis: potential implications for mitochondrial function and human health. *J Nutr Metab*. 2018;2018:5157645.
32. Blackburn GL, Bistrian BR, Flatt JP. Role of a protein-sparing fast in a comprehensive weight reduction program. In: Howard AN, editor. Recent Advances in Obesity Research. London, UK: Newman Publishing Ltd, 1975.
33. Tsai AG, Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity (Silver Spring)*. 2006;14(8):1283–1293.
34. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(25 Suppl 2):S102–S138Erratum in: Circulation. 2014 Jun 24;129(25 Suppl 2):S139-40.
35. Palgi A, Read JL, Greenberg I, Hoefer MA, Bistrian BR, Blackburn GL. Multidisciplinary treatment of obesity with a protein-sparing modified fast: results in 668 outpatients. *Am J Public Health*. 1985;75(10):1190–1194.
36. McGarry JD, Foster DW. Regulation of hepatic fatty acid oxidation and ketone body production. *Annu Rev Biochem*. 1980;49:395–420.
37. Sumithran P, Prendergast LA, Delbridge E, et al. Ketosis and appetite-mediating nutrients and hormones after weight loss. *Eur J Clin Nutr*. 2013;67(7):759–764.
38. Gibson AA, Seimon RV, Lee CM, et al. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obes Rev*. 2015;16(1):64–76.
39. Paoli A, Bosco G, Camporesi EM, Mangar D. Ketosis, ketogenic diet and food intake control: a complex relationship. *Front Psychol*. 2015;6:27.
40. Owen OE, Caprio S, Reichard GA Jr., Mozzoli MA, Boden G, Owen RS. Ketosis of starvation: a revisit and new perspectives. *Clin Endocrinol Metab*. 1983;12(2):359–379.
41. Yang MU, Van Itallie TB. Composition of weight lost during short-term weight reduction. Metabolic responses of obese subjects to starvation and low-calorie ketogenic and nonketogenic diets. *J Clin Invest*. 1976;58(3):722–730.
42. Hall KD, Chen KY, Guo J, et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am J Clin Nutr*. 2016;104(2):324–333.
43. Ebbeling CB, Feldman HA, Klein GL, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. *BMJ*. 2018;363:k4583.
44. Johnstone AM, Horgan GW, Murison SD, Bremner DM, Lobley GE. Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum. *Am J Clin Nutr*. 2008;87(1):44–55.
45. Westman EC, Feinman RD, Mavropoulos JC, et al. Low-carbohydrate nutrition and metabolism. *Am J Clin Nutr*. 2007;86(2):276–284.
46. Rains TM, Leidy HJ, Sanoshy KD, Lawless AL, Maki KC. A randomized, controlled, crossover trial to assess the acute appetitive and metabolic effects of sausage and egg-based convenience breakfast meals in overweight premenopausal women. *Nutr J*. 2015;14:17.
47. Hu T, Yao L, Reynolds K, et al. The effects of a low-carbohydrate diet on appetite: A randomized controlled trial. *Nutr Metab Cardiovasc Dis*. 2016;26(6):476–488.
48. Frigolet ME, Ramos Barragán VE, Tamez González M. Low-carbohydrate diets: a matter of love or hate. *Ann Nutr Metab*. 2011;58(4): 320–334.
49. Husain AM, Yancy WS Jr., Carwile ST, et al. Diet therapy for narcolepsy. *Neurology*. 2004;62:2300–2302.
50. Brands MW. Role of insulin-mediated antinatriuresis in sodium homeostasis and hypertension. *Hypertension*. 2018;72(6):1255–1262.
51. Cahill GF Jr. Fuel metabolism in starvation. *Annu Rev Nutr*. 2006;26: 1–22.
52. Kather H, Wieland E, Scheurer A, Vogel G, Wildenberg U, Joost C. Influences of variation in total energy intake and dietary composition on regulation of fat cell lipolysis in ideal-weight subjects. *J Clin Invest*. 1987;80(2):566–572.
53. Paoli A, Cenci L, Fancelli M, et al. Ketogenic diet and phytoextracts comparison of the efficacy of Mediterranean, Zone and Tisanoreica diet on some health risk factors. *Agro Food Industry Hi Tech*. 2010;21(4):24–29.
54. Paoli A, Grimaldi K, Bianco A, Lodi A, Cenci L, Parmagnani A. Medium term effects of a ketogenic diet and a mediterranean diet on resting energy expenditure and respiratory ratio. *BMC Proc*. 2012; 6(Suppl 3):37.
55. Tagliabue A, Bertoli S, Trentani C, Borrelli P, Veggiotti P. Effects of the ketogenic diet on nutritional status, resting energy expenditure, and substrate oxidation in patients with medically refractory epilepsy: a 6-month prospective observational study. *Clin Nutr*. 2012; 31(2):246–249.
56. Fine EJ, Feinman RD. Thermodynamics of weight loss diets. *Nutr Metab (Lond)*. 2004;1(1):15.
57. Naude CE, Schoonees, Senekal M, Young T, Garner P, Volmink J. Low carbohydrate versus isoenergetic balanced diets for reducing weight and cardiovascular risk: a systematic review and meta-analysis. *PLoS One*. 2014;9(7):e100652Erratum in: PLoS One. 2018 Jul 2;13(7):e0200284.
58. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2013; 110(7):1178–1187.
59. Schwingshackl L, Hoffmann G. Comparison of effects of long-term low-fat vs high-fat diets on blood lipid levels in overweight or obese patients: a systematic review and meta-analysis. *J Acad Nutr Diet*. 2013;113(12):1640–1661.
60. Mansoor N, Vinknes KJ, Veierød MB, Retterstøl K. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2016;115(3):466–479.
61. Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. *Nutr Rev*. 2019;77(3):161–180.
62. Sackner-Bernstein J, Kanter D, Kaul S. Dietary intervention for overweight and obese adults: comparison of low-carbohydrate and low-fat diets. A meta-analysis. *PLoS One*. 2015;10(10):e0139817.
63. Schwingshackl L, Hoffmann G. Comparison of the long-term effects of high-fat v. low-fat diet consumption on cardiometabolic risk factors in subjects with abnormal glucose metabolism: a systematic review and meta-analysis. *Br J Nutr*. 2014;111(12):2047–2058.
64. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract*. 2017;131:124–131.
65. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2017;5(1): e000354.
66. Huntriss R, Campbell M, Bedwell C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. *Eur J Clin Nutr*. 2018;72(3):311–325.
67. Korsmo-Haugen HK, Brurberg KG, Mann J, Aas AM. Carbohydrate quantity in the dietary management of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2019;21(1):15–27.

68. Sainsbury E, Kizirian NV, Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2018;139:239–252.
69. van Zuuren EJ, Fedorowicz Z, Kuijpers T, Pijl H. Effects of low-carbohydrate- compared with low-fat-diet interventions on metabolic control in people with type 2 diabetes: a systematic review including GRADE assessments. *Am J Clin Nutr*. 2018;108(2):300–331.
70. Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. *Am J Clin Nutr*. 2009;90(1):23–32.
71. Gardner CD, Trepanowski JF, Del Gobbo LC, et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: The DIETFITS Randomized Clinical Trial. *JAMA*. 2018;319(7):667–679.
72. Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med*. 2009;360(9):859–873.
73. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;67(13):1572–1574.
74. Kolanowski J, Bodson A, Desmecht P, Bemelmans S, Stein F, Crabbe J. On the relationship between ketonuria and natriuresis during fasting and upon refeeding in obese patients. *Eur J Clin Invest*. 1978;8(5):277–282.
75. Gomez-Arbelaez D, Bellido D, Castro AI, et al. Body composition changes after very-low-calorie ketogenic diet in obesity evaluated by 3 standardized methods. *J Clin Endocrinol Metab*. 2017;102(2):488–498.
76. Kolanowski J. Influence of glucose, insulin, and glucagon on sodium balance in fasting obese subjects. *Perspect Biol Med*. 1979;22(3):366–376.
77. Layman DK, Boileau RA, Erickson DJ, et al. A reduced ratio of dietary carbohydrate to protein improves body composition and blood lipid profiles during weight loss in adult women. *J Nutr*. 2003;133(2):411–417.
78. Krieger JW, Sitren HS, Daniels MJ, Langkamp-Henken B. Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression 1. *Am J Clin Nutr*. 2006;83(2):260–274.
79. Willoughby D, Hewlings S, Kalman D. Body composition changes in weight loss: strategies and supplementation for maintaining lean body mass, a brief review. *Nutrients*. 2018;10(12):1876.
80. van Wyk HJ, Davis RE, Davies JS. A critical review of low-carbohydrate diets in people with Type 2 diabetes. *Diabet Med*. 2016;33(2):148–157.
81. Foster GD, Wyatt HR, Hill JO, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med*. 2010;153(3):147–157.
82. Klemsdal TO, Holme I, Nerland H, Pedersen TR, Tonstad S. Effects of a low glycemic load diet versus a low-fat diet in subjects with and without the metabolic syndrome. *Nutr Metab Cardiovasc Dis*. 2010;20(3):195–201.
83. Morgan LM, Griffin BA, Millward DJ, et al. Comparison of the effects of four commercially available weight-loss programmes on lipid-based cardiovascular risk factors. *Public Health Nutr*. 2009;12(6):799–807.
84. Tay J, Brinkworth GD, Noakes M, Keogh J, Clifton PM. Metabolic effects of weight loss on a very-low-carbohydrate diet compared with an isocaloric high-carbohydrate diet in abdominally obese subjects. *J Am Coll Cardiol*. 2008;51(1):59–67.
85. Retterstøl K, Svendsen M, Narverud I, Holven KB. Effect of low carbohydrate high fat diet on LDL cholesterol and gene expression in normal-weight, young adults: a randomized controlled study. *Atherosclerosis*. 2018;279:52–61.
86. Vazquez-Vidal I, Desmarchelier C, Jones PJH. Nutrigenetics of blood cholesterol concentrations: towards personalized nutrition. *Curr Cardiol Rep*. 2019;21(5):38.
87. Ordovas JM. Gene-diet interaction and plasma lipid responses to dietary intervention. *Biochem Soc Trans*. 2002;30(2):68–73.
88. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. *Eur J Epidemiol*. 2018;33(2):157–170.
89. Neuenschwander M, Hoffmann G, Schwingshackl L, Schlesinger S. Impact of different dietary approaches on blood lipid control in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *Eur J Epidemiol*. 2019;1–16.
90. Jönsson T, Granfeldt Y, Ahrén B, et al. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. *Cardiovasc Diabetol*. 2009;8:35.
91. Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12-month randomised controlled trial. *Diabetologia*. 2011;54(4):731–740.
92. Wolever TMS, Gibbs AL, Mehling C, et al. The Canadian Trial of Carbohydrates in Diabetes (CCD), a 1-y controlled trial of low-glycemic-index dietary carbohydrate in type 2 diabetes: no effect on glycated hemoglobin but reduction in C-reactive protein. *Am J Clin Nutr*. 2008;87(1):114–125.
93. Brinkworth GD, Noakes M, Clifton PM, Bird AR. Comparative effects of very low-carbohydrate, high-fat and high-carbohydrate, low-fat weight-loss diets on bowel habit and faecal short-chain fatty acids and bacterial populations. *Br J Nutr*. 2009;101(10):1493–1502.
94. Wan Y, Wang F, Yuan J, et al. Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: a 6-month randomised controlled-feeding trial. *Gut*. 2019;68:1417–1429.
95. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19(5):576–585.
96. Park JE, Miller M, Rhyne J, Wang Z, Hazen SL. Differential effect of short-term popular diets on TMAO and other cardio-metabolic risk markers. *Nutr Metab Cardiovasc Dis*. 2019;29(5):513–517.
97. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013;368(17):1575–1584.
98. Senthong V, Wang Z, Li XS, et al. Intestinal Microbiota-Generated Metabolite Trimethylamine-N-Oxide and 5-Year Mortality Risk in Stable Coronary Artery Disease: The Contributory Role of Intestinal Microbiota in a COURAGE-Like Patient Cohort. *J Am Heart Assoc*. 2016;5(6):e002816.
99. Heianza Y, Ma W, Manson JE, Rexrode KM, Qi L. Gut microbiota metabolites and risk of major adverse cardiovascular disease events and death: a systematic review and meta-analysis of prospective studies. *J Am Heart Assoc*. 2017;6(7):e004947.
100. Westman EC, Tondt J, Maguire E, Yancy WS Jr. Implementing a low-carbohydrate, ketogenic diet to manage type 2 diabetes mellitus. *Expert Rev Endocrinol Metab*. 2018;13(5):263–272.
101. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5(3 Suppl):S1–S8.
102. Ito MK, McGowan MP, Moriarty PM. National Lipid Association Expert Panel on Familial Hypercholesterolemia. Management of familial hypercholesterolemias in adult patients: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5(3 Suppl):S38–S45.
103. Feldman DI, Blaha MJ, Santos RD, et al. Recommendations for the management of patients with familial hypercholesterolemia. *Curr Atheroscler Rep*. 2015;17(1):473.

104. Gidding SS. Special Commentary: Is diet management helpful in familial hypercholesterolemia? *Curr Opin Clin Nutr Metab Care*. 2019;22(2):135–140.
105. Williams L, Rhodes KS, Karmally W, Welstead LA, Alexander L, Sutton L. Familial chylomicronemia syndrome: bringing to life dietary recommendations throughout the life span. *J Clin Lipidol*. 2018; 12(4):908–919.
106. Zhuang X, Zhang S, Zhou H, Du Z, Liao X. U-shaped relationship between carbohydrate intake proportion and incident atrial fibrillation. *J Am Coll Cardiol*. 2019;73(9):4.
107. Masood W, Uppaluri KR, Ketogenic Diet. [Updated 2019 Mar 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019. Available at: https://www.ncbi.nlm.nih.gov/books/NBK499830/. Accessed May 21, 2019.
108. Evert AB, Dennison M2, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care*. 2019;42(5):731–754.
109. American Diabetes Association. 5. Lifestyle management: standards of medical care in diabetes – 2019. *Diabetes Care*. 2019;42(Suppl 1): S46–S60.
110. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2019 Executive Summary. *Endocr Pract*. 2019;25(1):69–100.
111. Murdoch C, Unwin D, Cavan D, Cucuzzella M, Patel M. Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. *Br J Gen Pract*. 2019;69(684):360–361.
112. Noto H, Goto A, Tsujimoto T, et al. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. *PLoS One*. 2013;8(1):e55030Erratum: PLoS One. 2019 Feb 7;14(2):e0212203.
113. Mazidi M, Katsiki N, Mikhailidis DP, Sattar N, Banach M. Lower carbohydrate diets and all-cause and cause-specific mortality: a population-based cohort study and pooling of prospective studies. *Eur Heart J*. 2019;ehz174.
114. Seidelmann SB, Claggett B, Cheng S, et al. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health*. 2018;3(9):e419–e428.
115. Ball L, Johnson C, Desbrow B, Leveritt M. General practitioners can offer effective nutrition care to patients with lifestyle-related chronic disease. *J Prim Health Care*. 2013;5(1):59–69.
116. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121(4):586–613.
117. Younus A, Aneni EC, Spatz ES, et al. A systematic review of the prevalence and outcomes of ideal cardiovascular health in us and non-us populations. *Mayo Clin Proc*. 2016;91(5):649–670.
118. Guo L, Zhang S. Association between ideal cardiovascular health metrics and risk of cardiovascular events or mortality: A meta-analysis of prospective studies. *Clin Cardiol*. 2017;40(12): 1339–1346.
119. Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016; 375(24):2349–2358.
120. Van Horn L, Carson JA, Appel LJ, et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement From the American Heart Association. *Circulation*. 2016; 134(22):e505–e529.
121. Jensen MD, Ryan DH. New obesity guidelines: promise and potential. *JAMA*. 2014;311(1):23–24.
122. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. *Endocr Pract*. 2016;22(Suppl 3): 1–203.
123. Sikand G, Cole RE, Handu D, et al. Clinical and cost benefits of medical nutrition therapy by registered dietitian nutritionists for management of dyslipidemia: A systematic review and meta-analysis. *J Clin Lipidol*. 2018;12(5):1113–1122.
124. U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans. 2nd edition Washington, DC: U.S. Department of Health and Human Services; 2018Available at, https://health.gov/PAGuidelines/.
125. Kahan S, Manson JE. Obesity treatment, beyond the guidelines: practical suggestions for clinical practice. *JAMA*. 2019;321: 1349–1350.
126. Tay J, Luscombe-Marsh ND, Thompson CH, et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. *Diabetes Care*. 2014;37(11):2909–2918.
127. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. *Am J Clin Nutr*. 2015;102(4):780–790.
128. Tay J, Thompson CH, Luscombe-Marsh ND, et al. Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. *Diabetes Obes Metab*. 2018;20(4):858–871.
129. Clifton PM, Keogh JB. Effects of different weight loss approaches on CVD risk. *Curr Atheroscler Rep*. 2018;20(6):27.

Appendix

Process of the development of the scientific statement

This scientific statement was developed after the NLA Scientific Statements Committee and the NLA Board of Directors approved a proposal for its development to address the recent popularity of using low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets, for the management of cardiometabolic risk factors and type 2 diabetes. Many authors/researchers have completed high-quality reviews and meta-analyses evaluating low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets; thus, this scientific statement was not meant to be a systematic review and meta-analysis. Rather, this scientific statement was meant to provide a balanced review of the current scientific evidence regarding the potential benefits, risks, and evidence gaps regarding low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets. To that end, at the request of the NLA Executive Committee and Scientific Statements Committee, the NLA Nutrition and Lifestyle Workgroup selected a multidisciplinary team to serve on the NLA Nutrition and Lifestyle Task Force—a writing team and a reviewing/editing team—to develop this scientific statement. The writing team was four registered dietitian nutritionists (RDNs) (CFK, JPB, PMKE, GS), and the reviewing/editing team was three physicians (KEA, DES, KEW) and a clinical nutrition scientist/epidemiologist (KCM).

The Task Force members developed an initial outline for the content of the scientific statement that was approved by the NLA Board of Directors. On approval of the outline, the RDN writing team determined writing assignments based on expertise and conducted the primary research and compilation of evidence on the effects of low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets, on cardiometabolic risk factors. The writing team focused the review of evidence mainly on published systematic reviews and meta-analyses of randomized controlled trials (RCTs). For topics where reviews and meta-analyses were not available, the writing team considered basic research and individual RCTs. Both the writing team and reviewing/editing team were responsible for editing and revision of the scientific statement. The Task Force team graded the key recommendations of this scientific statement using the American College of Cardiology/American Heart Association Evidence-Based Grading System (Table 3).[73] In rating the class (or strength) of the key recommendations, consideration was given to the ''net benefit'' after taking into account potential benefits and risks or harms associated with the dietary interventions examined in the evidence. For rating the level (or quality) of the evidence, consideration was given to obtaining the highest quality evidence to support the key recommendations, such as that from meta-analyses.

The chair of the NLA Scientific Statements Committee reviewed the scientific statement, which was then submitted to the NLA Board of Directors for review and approval by majority vote. This scientific statement presents a high-level discussion of the current evidence and key recommendations to provide guidance to clinicians regarding the use of low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets, for the management of cardiometabolic risk factors.

Muscogiuri *et al. J Transl Med* (2019) 17:356
https://doi.org/10.1186/s12967-019-2104-z

Journal of Translational Medicine

REVIEW Open Access

The management of very low-calorie ketogenic diet in obesity outpatient clinic: a practical guide

Giovanna Muscogiuri[†], Luigi Barrea[*†], Daniela Laudisio, Gabriella Pugliese, Ciro Salzano, Silvia Savastano and Annamaria Colao

Abstract

The epidemic of obesity is growing steadily across the whole world. Obesity is not only a merely aesthetic disease but is the "mother" of most chronic diseases such as associated with a range of type 2 diabetes, cardiovascular disease, obstructive sleep apnea, and cancer. However, although there is a need to find a strategy to stop this epidemic disease, most of the times the current nutritional strategies are not effective in weight loss and in long term weight maintenance. Very low-calorie ketogenic diets (VLCKD) is increasingly establishing as a successful nutritional pattern to manage obesity; this is due to rapid weight loss that gives rise to a positive psychological cycle which in turn increases the compliance to diet. Another important key point of VLCKD is the ability to preserve fatty free mass which is known to play a role of paramount importance in glucose metabolism. Despite the clinical evidence of VLCKD there are paucity of data regarding to its management. Therefore, we will provide a useful guide to be used by nutrition experts taking care of subjects with obesity. In particular, we will report recommendations on the correct use of this therapeutic approach for weight loss and management of side effects.

Keywords: Very low-calorie ketogenic diet (VLCKD), Obesity, Type 2 diabetes mellitus, Diet, Nutritionist

Introduction

Growing evidence reported that obesity is reaching epidemic proportions. It has been reported that in 2008, over 200 million men and nearly 300 million women aged 20 and over were obese, and 65% of the world's population live in countries where overweight [1]. Obesity could be defined as the silent killer; in fact, it significantly increases the risk of contracting diseases, such as: arterial hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), coronary heart disease, cerebral vasculopathy, gallbladder lithiasis, arthropathy, ovarian polycytosis, sleep apnea syndrome, and some neoplasms [2, 3]. In order to reach weight loss, one of the most important challenge in the management of obesity is reducing energy intake and increasing energy output. Although several strategies has been developed to reach this goal, this disorder is increasing in prevalence. The most common used nutritional pattern is characterized by an increase in complex/raw carbohydrate and a reduction in fat intake [4]. The scarce compliance of people with obesity to diet is mostly due to their preference to highly processed foods containing simple sugars rather than complex/raw carbohydrates. This is due because high glycemic index food is able to stimulate serotonin secretion that in turn provides a feeling of well being and favouring the onset of carbohydrates craving [4]. Although new anti-obesity drugs is continuously coming up, they still have some limits such as non trivial costs, potential side effects and contraindications that do not make them suitable for all people with obesity [5, 6]. In addition bariatric surgery has been demonstrated to be a useful tool for weight loss and remission of T2DM and metabolic

*Correspondence: luigi.barrea@unina.it
[†]Giovanna Muscogiuri and Luigi Barrea have equal contribution and should be considered as co-first authors
Dipartimento di Medicina Clinica e Chirurgia, Unit of Endocrinology, Federico II University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy

syndrome; however, there are several complications and sequelae related to surgery and it is restricted to the obese people that do not have contraindications to surgery [7]. In this scenario very low carbohydrate ketogenic diets (VLCKDs) have been recently proposed as an attractive nutritional strategy for the obesity management in individuals who have already attempted to lose weight with diet with more equilibrated distribution of macronutrients without reaching the target weight loss. VLCKD consist of 90% of calories from fat and only 10% from carbohydrates and proteins, resulting in a highly restricted diet [8]. The benefits of VLCKDs have been demonstrated on body composition, metabolic profile, and inflammation and oxidative stress genes expression in people with obesity [9]. Merra et al. randomized people with obesity to three VLCKD protocols in which the daily kcal amount were calculated subtracting to the estimated basal metabolism 1000 kcal/day and the number of carbohydrates were < 50 g/day. However, in VLCKD1 subjects reached the half of the amount of daily protein using synthetic aminoacid supplementation containing whey protein (13.42/bag), carbohydrate (0.03/bag), fat (0.15/bag), isoleucine (0.31/bag), ornithine alpha-ketoglutarate (0.25/bag), L-citrulline (0.25/bag), taurine, (0.25/bag), L-tryptophan (0.05/bag), potassium citrate (0.45/bag), for a total of 64 kCal (268 kJ). The powder of aminoacid is dissolved in water and drunk at breakfast and lunch or dinner. In VLCKD2 and 3 the composition of macronutrient was the same of VLCKD1 while there was a different source of carbohydrate i.e. < 35 g; > 80% from simple sugars and < 30 g; > 35% from complex sugars, respectively. VLCKDs protocol resulted in weight loss and an improvement of metabolic profile. In addition, after VLCKD with synthetic aminoacidic protein replacement (VLCKD1) there was a significant modulation of superoxide dismutase (SOD)-1 gene expression along with a reduction or C-reactive protein, thus suggesting the efficacy of VLCKD with synthetic aminoacidic protein replacement, for the reduction of cardiovascular risk, without the development of sarcopenia and activation of inflammatory and oxidative processes [9]. Regarding gene expression Garbow et al. reported that, in C57BL/6J mice, VLCKD determines a reduction, up to the suppression, of the expression of inflammatory cytokines and chemokines, as well as the production of reactive species oxy-hydrogen (ROS) [10]. Mutations in the gene encoding the enzyme copper/zinc (Cu/Zn) SOD1 were the first mutation identified to be associated with familial amyotrophic lateral sclerosis (ALS). Further, it has been demonstrated that VLCKD in the G93A-SOD1 transgenic mice model of familial amyotrophic lateral sclerosis promotes ATP synthesis and neuroprotection [11]. Ketogenic diets induce a metabolic condition called "physiological ketosis" by Hans Krebs which is different from the pathological diabetic ketosis [12]. In the past the ketogenic diet has been used as treatment of various diseases such as pediatric pharmacoresistant epilepsy [13]. Recently, VLCKDs have undoubtedly demonstrated to be an effective tool to tackle obesity [14], dyslipidemia and most of obesity-related cardiovascular risk factors [15, 16]. The rapid initial weight loss is due to natriuresis and diuresis resulting from the decrease in insulin levels and increase in glucagon levels and ketone production [17, 18]. Even after the initial diuresis, the rate of weight loss remains faster than with other types of diet because the calorie level is so low. Further, because the nutritional pattern is unfamiliar and the diet is perceived to be temporary, patients may have a higher compliance rate than on nutritional patterns that require a longer time to lose the same amount of weight. The relative preservation of protein mass also is an advantage, certainly as compared with starvation [19]. Given the growing use of VLCKDs in the management of obesity, we will provide a practical guide on its clinical indications and contraindications and on the steps involved in ketogenic diet initiation, monitoring, and management of its side effects in outpatient clinic.

Very low-calorie ketogenic diet protocol

VLCKD is a nutritional protocol that resembles fasting through a marked restriction of daily carbohydrate intake, usually lower than 30 g/day (≃ 13% of total energy intake) along with a relative increase in the proportions of fat (≃ 44%) and protein (≃ 43%) and a total daily energy intake < 800 kcal [20]. The VLCKD protocol is a weight loss nutritional program based on a high-biological-value protein (coming from milk, peas, whey and soy) preparations diet and natural foods. Each protein preparation contains 18 g protein, 4 g carbohydrate, 3 g fat (mainly high-oleic vegetable oils) and provides approximately 100–150 kcal. This protocol is divided in three stages: active, re-education, and maintenance.

Active stage

The active stage is characterized by a very low-calorie diet (600–800 kcal/day), low in carbohydrates (< 50 g daily from vegetables) and lipids (only 10 g of olive oil per day). The amount of high-biological-value proteins ranged between 0.8 and 1.2 g per each Kg of ideal body weight in order to preserve lean mass and to meet the minimal daily body requirements. This stage is further divided in 3 ketogenic phases: in phase 1, the patients eat high-biological-value protein preparations five times a day, along with vegetables with low glycemic index. In phase 2, one of the protein servings is replaced by natural proteins such as meat/egg/fish either at lunch or

at dinner. In the phase 3, a second serve of the natural protein low in fat replaced the second serve of biological protein preparation. Being a very low caloric nutritional pattern, it is recommended to supplement patients with micronutrients (vitamins, such as complex B vitamins, vitamin C and E, minerals, including potassium, sodium, magnesium, calcium; and omega-3 fatty acids) according to international recommendations. This active stage is kept until the patient loses most of weight loss target, about 80%. Therefore, the ketogenic phases are variable in time depending on the individual and the weight loss target. The active stage generally lasts between 8 and 12 weeks in total.

Re-education stage

After the ketogenic phases, the patient is switched to low-calorie diet. At this point, the patients will progressively reintroduce different food groups and in the meantime participates in a program of alimentary re-education in order to maintain weight long term. Carbohydrates are gradually reintroduced, starting from foods with the lowest glycemic index (fruit, dairy products—Phase 4), followed by foods with moderate (legumes—Phase 5) and high glycemic index (bread, pasta and cereals—Phase 6). The daily calorie intake in the reintroduction period (Phases 4–6) ranges between 800 and 1500 kcal/day. After the reintroduction of food there is a maintenance stage which includes an eating plan balanced in carbohydrates, protein, and fat. The main target of this stage is to keep lost weight and to promote healthy lifestyle. In this stage the calories consumed ranged between 1.500 and 2.000 kcal/day, depending on individual.

Indications and contraindications

The The European Association for the Study of Obesity (EASO) guidelines defines as very low calorie diets (VLCD) a diet that usually provide less than 800 kcal/day and highlights as it may be used only as part of a comprehensive programme under the supervision of an obesity specialist or another physician trained in nutrition and dietetics. The prescription of VLCD should be limited for specific patients and for short frametime. VLCDs are unsuitable as a unique source of nutrition for children and adolescents, pregnant or lactating women and the elderly [21]. According to the National Institute for Health and Care Excellence (NICE) guidance, VLCD should be considered as part of a multistrategical weight management for people who are obese and who have a clinically assessed need to lose weight rapidly (for example, those who need joint replacement surgery or who are seeking fertility services). VLCD should be is followed for a maximum of 12 weeks (continuously or intermittently) with ongoing clinical Support [22]. The VLCKDs indications of ADI (Associazione Italiana di Dietetica e Nutrizione Clinica) are the following [23]:

1. Morbid obesity or complicated (T2DM, dyslipidemia, hypertension, metabolic syndrome, obstructive sleep apnoea syndrome (OSAS), bone diseases or severe arthropathy);
2. Severe obesity with bariatric surgery indication (in the preoperative period);
3. Patients with severe comorbidities needing a rapid weight loss;
4. Non-alcoholic fatty liver disease (NAFLD);
5. Drug-resistant epilepsy.

The VLCKDs controindications of *Associazione Italiana di dietetica e Nutrizione Clinica* (ADI) are represented by:

1. Pregnancy and lactation;
2. History of mental disorders and behavioral problems, abuse of alcohol and other substances;
3. Hepatic or renal failure;
4. Type 1 Diabetes;
5. Porphyria, unstable angina, recent myocardial infarction (Table 1).

In 2016, VLCKD has also been reported with similar indications in the standards of care in obesity released by the Italian Society of Obesity (SIO) and ADI itself [24]. The recent consensus statement from the Italian Society of Endocrinology (SIE) strongly recommended VLCKDs in:

1. Severe obesity;
2. Management of severe obesity before bariatric surgery;
3. Sarcopenic obesity;
4. Obesity associated with T2DM (preserved beta cell function);
5. Obesity associated with hypertriglyceridemia;
6. Obesity associated with hypertension;
7. Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet.

There is a weak recommendation for:

1. Obesity associated with dysbiosis of the gut microbiota;
2. Obesity associated with high levels of LDL-cholesterol and/or low levels of HDL-cholesterol;
3. Obesity associated with non-alcoholic fatty liver disease (NAFLD);

Table 1 Indications and contraindications to VLCKD of ADI (Associazione Italiana di Dietetica e Nutrizione Clinica) and SIE (Società Italiana di Endocrinologia)

	ADI	SIE
Indications	Morbid obesity or complicated (type 2 diabetes, dyslipidemia, hypertension, metabolic syndrome, OSAS, bone diseases or severe arthropathy) Severe obesity with bariatric surgery indication (in the preoperative period) Patients with severe comorbidities needing a rapid weight loss Non-alcoholic fatty liver disease (NAFLD) Drug-resistant epilepsy	Severe obesity Management of severe obesity before bariatric surgery Sarcopenic obesity Obesity associated with type 2 diabetes (preserved beta cell function) Obesity associated with hypertriglyceridemia Obesity associated with hypertension Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet
Contraindications	Pregnancy and lactation History of mental disorders and behavioral problems, abuse of alcohol and other substances Hepatic or renal failure Type 1 Diabetes Porphyria, unstable angina, recent myocardial infarction	Type 1 diabetes mellitus Latent autoimmune diabetes in adults β-cell failure in type 2 diabetes mellitus Use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (risk for euglycemic diabetic ketoacidosis) Pregnancy and breastfeeding Kidney failure and moderate-to-severe chronic kidney disease Liver failure Hearth failure (NYHA III-IV) Respiratory failure Unstable angina, recent stroke or myocardial infarction (or myocardial infarction (or myocardial infarction (< 12 months) Cardiac arrhythmias Eating disorders and other severe mental illnesses, alcohol and substance abuse Active/severe infections Frail elderly patients 48 h prior to elective surgery or invasive procedures and perioperative period Rare disorders: porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders, pyruvate carboxylase deficiency

4. Obesity associated with heart failure (NYHA I–II);
5. Obesity associated with atherosclerosis;
6. Male obesity secondary hypogonadism;
7. Obesity associated with polycystic ovary syndrome (PCOS);
8. Menopausal transition-related obesity;
9. Neurodegenerative disorders associated with sarcopenic obesity.

The absolute contraindications are represented by type 1 diabetes mellitus, latent autoimmune diabetes in adults, β-cell failure in T2DM, use of sodium/glucose cotransporter 2 (SGLT2) inhibitors (risk for euglycemic diabetic ketoacidosis), pregnancy and breastfeeding kidney failure and moderate-to-severe chronic kidney disease, liver failure, hearth failure (NYHA III–IV), respiratory failure unstable angina, recent stroke or myocardial infarction (< 12 months), cardiac arrhythmias, eating disorders and other severe mental illnesses, alcohol and substance abuse, active/severe infections, frail elderly patients, 48 h prior to elective surgery or invasive procedures and perioperative period, rare disorders: porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders, pyruvate carboxylase deficiency (Table 1) [20]. Finally according to *Società Italiana di Chirurgia dell'OBesità e delle malattie metaboliche* (SICOB) the use of VLCKD from 15 to 30 days prior to surgery allows to get satisfactory results in less time, with less money and fewer side effects than the intragastric balloon [25].

Efficacy and management of the most common side effects

Efficacy

The VLCKD is a nutritional protocol that provides suddenly beneficial effects on anthropometric and metabolic parameters and on body composition [9]. The assessment of anthropometric measurements (BMI, weight, waist circumference and hip circumference), body composition and hydration status (by bioelectrical impedance analysis) is recommended at baseline, during the active state and at the end of the VLCKD program. In order to investigate the efficacy of VLCKD on metabolic parameters glucose, insulin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (serum) should be assessed at baseline and at the end of the VLCKD program (Table 2).

Short term side effects

Dehydration Dehydration is the most common early-onset complication of VLCKD. Signs and symptoms of dehydration are mostly represented by dry mouth, headache, dizziness/orthostatic hypotension and visual disturbance [26]. Therefore, proper water intake (at least 2 L of sugarless fluids daily) is mandatory mostly in the first 3 phases. In order to relieve headache, it is advisable to take mild analgesics as pills instead of liquid formulations because they could contain sugar. However, it should notice that headache is a short term, temporary side effect; in fact, VLCKDs are currently used in the treatment of chronic migraine [27]. Electrolyte abnormalities such as hyponatremia and hypomagnesemia, which are potentially due to dehydration, urinary excretion of ketone bodies and poor intake of micronutrients, could occur mostly in the active stage. It has been reported that in the sodium-equilibrated subjects on a constant sodium intake, the natriuresis of early starvation is transient and lasts typically from days 2 through 6 of the fast, the peak natriuresis occurs with some individual variation on day 4 of the fast. Following the natriuresis, there is a return to positive sodium balance, which will be kept for the duration of fasting. In contrast to the natriuresis, the small and variable kaliuresis that accompanies starvation occurs on days 5 through 7 of the fast, after which there is a return to positive potassium balance [17]. If patient complain hypotension-related symptoms, it is advisable to increase salt intake wherever there are no contraindications. Supplementing with magnesium can help reduce muscle cramps, difficulty sleeping and irritability mostly in the active stage.

Hypoglycemia Transient hypoglycemia could be a complication of the VLCKD, usually in the initial period of protocol [28]. The majority of the glucose lowering effect has been related to calorie restriction, whereas weight loss has an increasing contribution over the time through the decrease in intraabdominal (visceral) adipose tissue. Further, It has been demonstrated that ketone bodies can stimulate insulin secretion in normal humans [29]. The reduction of fat mass consequent to weight reduction during VLCKD is associated with decreased oxidation of lipids and increased oxidation of glucose. The net effect of the shift in oxidation of fuels was enhanced glucose metabolism and improved insulin sensitivity [30].

The reduction in carbohydrate intake is associated with an early and significant decrease in hepatic triacylglycerol content that in turn suppresses hepatic glucose production improving hepatic insulin sensitivity [31].

Table 2 Anthropometric measurements and laboratory assessment to be monitored during the VLCKD

	Parameters	Baseline	During active stages	At the end of VLCKD
Anthropometric assessment	Weight, height, BMI	✓	✓	✓
	Body composition and hydration status (by bioelectrical impedance analysis)	✓	✓	✓
Laboratory assessment	Complete blood count with platelets	✓	✓	✓
	Sodium, potassium, magnesium, and inorganic phosphate	✓	✓	✓
	Serum liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine, γ-GT, total and direct bilirubin)	✓	✓	✓
	Fasting lipid profile	✓		✓
	25(OH)D, calcium	✓		✓
	Glucose, Insulin	✓		✓
	β-Hydroxybutyrate (capillary blood or urine)		✓	
	TSH, FT4	✓		
	Complete urinalysis and microalbuminuria (urine)	✓	✓	✓

BMI body mass index, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *γGT* γ-glutamyltransferase, *25(OH)D* 25-hydroxy vitamin D, *TSH* thyroid-stimulating hormone, *FT4* free thyroxine

However, most patients experiencing transient hypoglycemia recover without assistance and do not show hypoglycemic symptoms. If blood glucose is less than 40 mg/dL and hypoglycemia is symptomatic, it is suggested the assumption of carbo-hydrate-containing beverages such as orange juice.

Lethargy Transitory lethargy could occur in the first days of the protocol and it occurs as the body switches from burning carbohydrates to burning fat for energy. However, if lethargy persists more than few days, medical investigations are recommended, as lethargy could be also a symptom of dehydration, excessive ketosis and nutrient deficiencies. It is also recommended to measure ketonemia/ketonuria and eventually, it is suggested the assumption of carbo-hydrate-containing beverages such as orange juice.

Halitosis Halitosis can occur whilst VLCKD. This is due to ketosis and generally it is caused by an increase in acetone levels. This is characteristic of VLCKD and it could be considered as an additional sign of being in ketosis. The halitosis will only last whilst they are following the active stage; chewing on a low-calorie mint or sugar free chewing gum is recommended to manage it.

Gastrointestinal side effects The most common early complications of VLCKD are represented by gastrointestinal disturbances, involving nausea/vomiting, diarrhea, or constipation. Gastrointestinal (GI) disturbances are often related to scarce tolerance of the diet that result in a significant resistance to the ketogenic diet and even blunting its efficacy. Diarrhea is the most common of these symptoms, but most cases is transient and easily controlled, sometimes using short-term antidiarrhea medication. This is could due to defective absorption and intolerance of fat. In addition, the high-lipid diet ketogenic diet's high-fat content prolongs the gastric emptying time thus favouring gastroesophageal reflux disease, nausea and vomit. A modification of the diet menu such as frequent intake of small amounts, intermittent use of GI drugs such as antiemetics, GI tract regulators, and antacids. Constipation might be caused by a decreased intake of fiber and/or by a decreased volume of food [32]. Constipation can be successfully controlled ensuring an adequate fluid intake and/or using low-calorie bulk laxative and/or intermittent enemas. The supplement of dietary fibre may improve constipation increasing the number of bowel movements. In subjects with pre-existing constipation, diverticular disease or haemorrhoids an extra dietary fibre (psyllium 3.5 g twice daily is recommended) from the beginning of the diet need to be considered [33]. Acute pancreatitis is a rare but serious complication that is often fatal [34]. Pancreatitis can be caused by hypertriglyceridemia [35]. Hepatitis is also a rare complication that could be fatal [28]. Both these conditions may occur more often if there is the concomitant use of antiepileptic drugs [36]. Discontinuation of the VLCKD and adequate supportive treatment are required for successful recovery.

Hyperuricemia Serum uric acid is known to increase in individuals on ketogenic regimens providing less than 900 calories per day. Plasma uric acid levels increase on VLCKDs, especially if the diet is very low in carbohydrate. Uric acid also follows a biphasic course having a peak in 1 to 2 weeks and then decreases toward baseline [19]. Patients with a prior history of gout may be more prone to develop exacerbations. However, attacks of acute gouty arthritis, has been described in less than 1% of subjects following VLCKD [37], (Table 2).

Long term side effects

Hypoproteinemia Hypoproteinemia could occur probably as a consequence of gluconeogenic consumption due to carbohydrate restriction [38]. In order to manage this side effect, it is recommended to increase protein intake from 1 g/kg/day to 1.5 g/kg/day while the lipid-to-non-lipid ratio is kept.

Hypocalcemia and bone damage It has been reported that serum ionized calcium, as well as total serum calcium, plasma parathyroid hormone (PTH) and calcitonin levels remain stable even during the 4-week long VLCD [39]. In particular calcium balance has been reported to be positive in people with obesity undergoing a moderate VLCKD taking high calcium intake (1200 mg/day); the retention of ingested calcium was proportional to the amount of carbohydrate in the diet [40]. Although calcium metabolism seems to be preserved in VLCKD, few evidence reported that very low calorie diet has a negative effect on both bone mineral content (BMC) and bone mineral density (BMD), in particular in the femoral neck and greater trochanter, and that this effect is proportional to the degree of reduction in body weight, as well as in fat and lean mass [41, 42]. However, there are no data to suggest this increases long-term fracture risk. Although no studies have been carried out in VLCKD, diet high in acid-ash proteins have been described to be associated to excessive calcium loss because of its acidogenic content. Calcium is provided as buffer from the skeleton through the active resorption of bone; indeed, calciuria is directly related to net acid excretion and it is not compensate by increasing intestinal calcium absorption [43]. Thus, taken together, all these observations raise some concern about the risk of a moderate loss of bone mineral content during VLCD. To prevent such a consequence of dieting, it is

recommended to provide an adequate high intake of calcium and vitamin D, as well as an appropriate amount of carbohydrate.

Lipid profile changes The effects of VLCKD on plasma lipoproteins in obese patients is characterized by a fall in plasma triglycerides, an increase in LDL-cholesterol and a neutral effect on HDL-cholesterol. The prolonged ingestion of high lipid diets could be responsible of increase in LDL cholesterol [20]. However, this seems to be a transient effect as demonstreated by the reabsorption of ateroma produce by ketogenic diet, after returning to a normal diet [44]. Since the increase in LDL has been reported to spontaneously improve, the decrease of the lipid-to-nonlipid ratio to 3:1 or the use of cholesterol-reducing medication should be taken into account if LDL does not normalize after returning to normal diet.

Urolithiasis Urolithiasis is another possible complication of the VLCKD [45, 46]. The stones are mostly are mostly made of uric acid, calcium oxalate, or a mixture of calcium oxalate and calcium phosphate/uric acid. [45, 46]. The cause of VLCKD—related urolithiasis are represented by chronic acidosis, dehydration, and fat malabsorption. Risk factors of developing urolithiasis include young age, family history of kidney stones, and a urine Ca/Cr ratio of >0.2 [45]. In order to prevent the onset of urolithiasis it is suggested to recommend an adequate daily fluid intake (at leat 2 L) and to alkalinize urine using oral potassium citrate.

Gallstones The low fat content and/ore the rapid weight loss increases the risk of developing gallstones. In fact it has been already reported that rapid weight loss, either by VLCD or bariatric surgery, is a known risk factor for gallstone formation [47]. This is due to the supersaturation of bile with cholesterol, leading to cholesterol crystallization and stone formation, and to the insufficient gallbladder emptying caused by blunted due to impaired motility. Both mechanisms happen in VLCD: supersaturation is mostly due to decreased bile salt levels and increased cholesterol levels whilst impaired motility is due to reduced gallbladder stimulation because of the low-fat content [48, 49]. In order to prevent the risk of gallstones, a fat intake of 7–10 g per day has been reported as a threshold for maintaining an efficient gallbladder emptying [50].

Hair loss Hair loss occurs mostly in patients in whom weight loss is associated with the loss of body cell mass (e.g., a significant negative nitrogen balance). When mobilized body protein plus dietary protein are not enough to meet requirements, the low priority of hair growth for available protein accounts for the telogen effluvium [51]. The hair loss is transient and hair grows back well as weight stabilizes. However, an increase in protein intake during fasting in order to preserve nitrogen balance, contribute to eliminate almost completely hair loss, (Table 2).

Conclusions

VLCKD is an ideal therapeutic tool for people with obesity and in particular for that subjects who have already experienced unsuccessful diet in the past and/or have urgently need to lose weight (people with obesity with joint diseases, people with obesity with bariatric surgery indications, people with obesity with cardiovascular risk factor etc.). Given the potential of VLCKD in determining remission of T2DM, VLCKD should be also taken into account in people with obesity with short T2DM duration.

Once weight goal is achieved, it is mandatory to suggest an appropriate healthy lifestyle (physical activity and a balanced nutritional pattern such as Mediterranean Diet) for long-term body weight maintenance. The scheme of the stages of VLCKD is reported in Fig. 1.

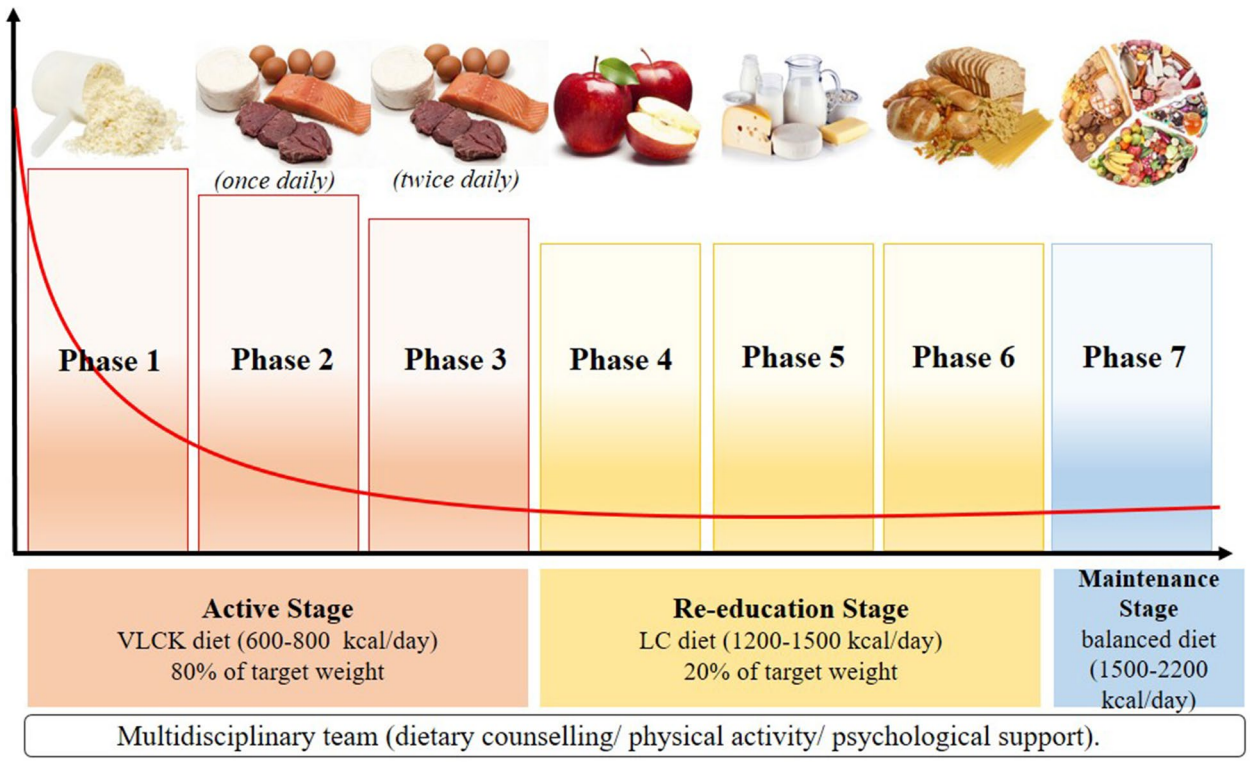


Fig. 1 Scheme of the stages of VLCKD

Abbreviations
T2DM: type 2 diabetes mellitus; VLCKDs: very low-calorie ketogenic diets; ADI: Associazione Italiana di Dietetica e Nutrizione Clinica; NAFLD: non-alcoholic fatty liver disease; SIO: Italian Society of Obesity; SIE: Italian Society of Endocrinology; LDL: low-density lipoprotein; HDL: high-density lipoprotein; PCOS: polycystic ovary syndrome; SICOB: Italian Society of Bariatric Surgery and Metabolic Diseases; PTH: parathyroid hormone; BMC: bone mineral content; BMD: bone mineral density.

Acknowledgements
Not applicable.

Authors' contributions
The authors' responsibilities were as follows: GM, LB and AC were responsible for the concept of this paper and drafted the manuscript; DL, GP, CS and SS provided a critical review of the paper. All Authors contributed to and agreed on the final version of the manuscript. All authors read and approved the final manuscript.

Funding
The open access of this article has been sponsored by the Laboratoire Therascience, 3 Rue de l'Industrie, 98000 Monaco. www.therascience.com.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The Authors declare that they have no competing interests.

Received: 28 June 2019 Accepted: 19 October 2019
Published online: 29 October 2019

References

1. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 21 May 2019.
2. Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a disease: the obesity society 2018 position statement. Obesity (Silver Spring). 2019;27:7–9.
3. De Lorenzo A, Gratteri S, Gualtieri P, Cammarano A, Bertucci P, Di Renzo L. Why primary obesity is a disease? J Transl Med. 2019;17:169.
4. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab. 2003;88:1617–23.
5. Siraj ES, Williams KJ. another agent for obesity-will this time be different? N Engl J Med. 2015;373:82–3.
6. Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgrad Med. 2018;130:173–82.
7. Pories WJ. Bariatric surgery: risks and rewards. J Clin Endocrinol Metab. 2008;93:S89–96.
8. Luat AF, Coyle L, Kamat D. The ketogenic diet: a practical guide for pediatricians. Pediatr Ann. 2016;45:e446–50.
9. Merra G, Gratteri S, De Lorenzo A, Barrucco S, Perrone MA, Avolio E, Bernardini S, Marchetti M, Di Renzo L. Effects of very-low-calorie diet on body composition, metabolic state, and genes expression: a randomized

double-blind placebo-controlled trial. Eur Rev Med Pharmacol Sci. 2017;21:329–45.
10. Garbow JR, Doherty JM, Schugar RC, Travers S, Weber ML, Wentz AE, Ezenwajiaku N, Cotter DG, Brunt EM, Crawford PA. Hepatic steatosis, inflammation, and ER stress in mice maintained long term on a very low-carbohydrate ketogenic diet. Am J Physiol Gastrointest Liver Physiol. 2011;300:G956–67.
11. Zhao Z, Lange DJ, Voustianiouk A, MacGrogan D, Ho L, Suh J, Humala N, Thiyagarajan M, Wang J, Pasinetti GM. A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. BMC Neurosci. 2006;7:29.
12. Krebs HA. The regulation of the release of ketone bodies by the liver. Adv Enzyme Regul. 1966;4:339–54.
13. Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. J Child Neurol. 2009;24:979–88.
14. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr. 2013;110:1178–87.
15. Al-Khalifa A, Mathew TC, Al-Zaid NS, Mathew E, Dashti HM. Therapeutic role of low-carbohydrate ketogenic diet in diabetes. Nutrition. 2009;25:1177–85.
16. Sharman MJ, Kraemer WJ, Love DM, Avery NG, Gomez AL, Scheett TP, Volek JS. A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. J Nutr. 2002;132:1879–85.
17. Boulter PR, Hoffman RS, Arky RA. Pattern of sodium excretion accompanying starvation. Metabolism. 1973;22:675–83.
18. Saudek CD, Boulter PR, Arky RA. The natriuretic effect of glucagon and its role in starvation. J Clin Endocrinol Metab. 1973;36:761–5.
19. Atkinson RL. Low and very low calorie diets. Med Clin North Am. 1989;73:203–15.
20. Caprio M, Infante M, Moriconi E, Armani A, Fabbri A, Mantovani G, Mariani S, Lubrano C, Poggiogalle E, Migliaccio S, et al. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE). J Endocrinol Invest. 2019;42(11):1365–86.
21. Yumuk V, Fruhbeck G, Oppert JM, Woodward E, Toplak H. An EASO position statement on multidisciplinary obesity management in adults. Obes Facts. 2014;7:96–101.
22. Stegenga H, Haines A, Jones K, Wilding J, Guideline Development G. Identification, assessment, and management of overweight and obesity: summary of updated NICE guidance. BMJ. 2014;349:g6608.
23. https://www.fondazioneadi.com/wp-content/uploads/paper/2018/01/ADI-ATTUALITA-N.-2_2014.pdf. Accessed 21 May 2019.
24. Italian Standards for Treatment of Obesity, released by the Italian Society for the Study of Obesity (SIO) and the Italian Association of Dietetics and Clinical Nutrition (ADI) (2016–2017). https://www.sio-obesita.org/wp-content/uploads/2017/09/STANDARD-OBESITA-SIO-ADI.pdf. Accessed 21 May 2019.
25. https://www.sicob.org/00_materiali/linee_guida_2016.pdf. Accessed 21 May 2019.
26. http://www.foodedsoc.org/scoop.pdf. Accessed 21 May 2019.
27. Barbanti P, Fofi L, Aurilia C, Egeo G, Caprio M. Ketogenic diet in migraine: rationale, findings and perspectives. Neurol Sci. 2017;38:111–5.
28. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004;45:1116–23.
29. Balasse EO, Ooms HA, Lambilliotte JP. Evidence for a stimulatory effect of ketone bodies on insulin secretion in man. Horm Metab Res. 1970;2:371–2.
30. Franssila-Kallunki A, Rissanen A, Ekstrand A, Ollus A, Groop L. Weight loss by very-low-calorie diets: effects on substrate oxidation, energy expenditure, and insulin sensitivity in obese subjects. Am J Clin Nutr. 1992;56:247S–8S.
31. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54:2506–14.
32. Wheless JW, Ashwal S. The ketogenic diet. In: Swaiman KF, editor. Pediatric neurology: principles and practice. Philadelphia: Mosby; 1999.
33. Leeds AR. Formula food-reducing diets: a new evidence-based addition to the weight management tool box. Nutr Bull. 2014;39:238–46.
34. Stewart WA, Gordon K, Camfield P. Acute pancreatitis causing death in a child on the ketogenic diet. J Child Neurol. 2001;16:682.
35. Toskes PP. Hyperlipidemic pancreatitis. Gastroenterol Clin North Am. 1990;19:783–91.
36. Chapman SA, Wacksman GP, Patterson BD. Pancreatitis associated with valproic acid: a review of the literature. Pharmacotherapy. 2001;21:1549–60.
37. Palgi A, Read JL, Greenberg I, Hoefer MA, Bistrian BR, Blackburn GL. Multidisciplinary treatment of obesity with a protein-sparing modified fast: results in 668 outpatients. Am J Public Health. 1985;75:1190–4.
38. Ballaban-Gil K, Callahan C, O'Dell C, Pappo M, Moshe S, Shinnar S. Complications of the ketogenic diet. Epilepsia. 1998;39:744–8.
39. Nishizawa Y, Koyama H, Shoji T, Tahara H, Hagiwara S, Aratani H, Nakatsuka K, Miki T, Morii H. Altered calcium homeostasis accompanying changes of regional bone mineral during a very-low-calorie diet. Am J Clin Nutr. 1992;56:265S–7S.
40. Davie MW, Abraham RR, Hewins B, Wynn V. Changes in bone and muscle constituents during dieting for obesity. Clin Sci (Lond). 1986;70:285–93.
41. Andersen RE, Wadden TA, Herzog RJ. Changes in bone mineral content in obese dieting women. Metabolism. 1997;46:857–61.
42. Howard AN, Kreitzman SN. The Swansea trial: body composition and metabolic studies with a very-low-calorie diet (VLCD). London: Smith-Gordon; 1993. ISBN 1854630709.
43. Barzel US, Massey LK. Excess dietary protein can adversely affect bone. J Nutr. 1998;128:1051–3.
44. Swink TD, Vining EP, Freeman JM. The ketogenic diet: 1997. Adv Pediatr. 1997;44:297–329.
45. Furth SL, Casey JC, Pyzik PL, Neu AM, Docimo SG, Vining EP, Freeman JM, Fivush BA. Risk factors for urolithiasis in children on the ketogenic diet. Pediatr Nephrol. 2000;15:125–8.
46. Kielb S, Koo HP, Bloom DA, Faerber GJ. Nephrolithiasis associated with the ketogenic diet. J Urol. 2000;164:464–6.
47. Everhart JE. Contributions of obesity and weight loss to gallstone disease. Ann Intern Med. 1993;119:1029–35.
48. Festi D, Colecchia A, Larocca A, Villanova N, Mazzella G, Petroni ML, Romano F, Roda E. Review: low caloric intake and gall-bladder motor function. Aliment Pharmacol Ther. 2000;14(Suppl 2):51–3.
49. Erlinger S. Gallstones in obesity and weight loss. Eur J Gastroenterol Hepatol. 2000;12:1347–52.
50. Johansson K, Sundstrom J, Marcus C, Hemmingsson E, Neovius M. Risk of symptomatic gallstones and cholecystectomy after a very-low-calorie diet or low-calorie diet in a commercial weight loss program: 1-year matched cohort study. Int J Obes (Lond). 2014;38:279–84.
51. Blackburn GL, Bistrian BR, Hoag C. Letter: hair loss with rapid weight loss. JAMA. 1976;236:252.

Publisher's Note

Journal of Translational Medicine

RESEARCH

Open Access

VLCKD: a real time safety study in obesity

Luigi Barrea[1,3†], Ludovica Verde[2,3†], Claudia Vetrani[2], Francesca Marino[2], Sara Aprano[2], Silvia Savastano[2,3], Annamaria Colao[2,3,4] and Giovanna Muscogiuri[2,3,4*]

Abstract

Background: Very Low-Calorie Ketogenic Diet (VLCKD) is currently a promising approach for the treatment of obesity. However, little is known about the side effects since most of the studies reporting them were carried out in normal weight subjects following Ketogenic Diet for other purposes than obesity. Thus, the aims of the study were: (1) to investigate the safety of VLCKD in subjects with obesity; (2) if VLCKD-related side effects could have an impact on its efficacy.

Methods: In this prospective study we consecutively enrolled 106 subjects with obesity (12 males and 94 females, BMI 34.98 ± 5.43 kg/m^2) that underwent to VLCKD. In all subjects we recorded side effects at the end of ketogenic phase and assessed anthropometric parameters at the baseline and at the end of ketogenic phase. In a subgroup of 25 subjects, we also assessed biochemical parameters.

Results: No serious side effects occurred in our population and those that did occur were clinically mild and did not lead to discontinuation of the dietary protocol as they could be easily managed by healthcare professionals or often resolved spontaneously. Nine (8.5%) subjects stopped VLCKD before the end of the protocol for the following reasons: 2 (1.9%) due to palatability and 7 (6.1%) due to excessive costs. Finally, there were no differences in terms of weight loss percentage (13.5 ± 10.9% *vs* 18.2 ± 8.9%; p = 0.318) in subjects that developed side effects and subjects that did not developed side effects.

Conclusion: Our study demonstrated that VLCKD is a promising, safe and effective therapeutic tool for people with obesity. Despite common misgivings, side effects are mild, transient and can be prevented and managed by adhering to the appropriate indications and contraindications for VLCKD, following well-organized and standardized protocols and performing adequate clinical and laboratory monitoring.

Keywords: Very low calorie ketogenic diet, Side effects, Obesity

Background

There is increasing evidence that obesity has reached an epidemic rate. In 2016, more than 1.9 billion adults over the age of 18 were reportedly overweight and more than 650 million adults were obese [1]. Obesity significantly increases the risk of developing chronic diseases such as arterial hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), coronary heart disease, cerebral vasculopathy, gallbladder lithiasis, arthropathy, polycystic ovary disease, sleep apnea syndrome, and some neoplasms [2, 3]. To achieve weight loss, one of the major challenges in the treatment of obesity is to reduce energy intake and increase energy expenditure [4]. Although various strategies have been developed to achieve this goal, the prevalence of this condition is increasing. The most frequently used dietary strategy is characterized by a reduction in fat intake and an increase in complex carbohydrates [5]. The fact that people with obesity rarely adhere to their diet is mainly because they prefer highly processed foods

*Correspondence: giovanna.muscogiuri@gmail.com
†Luigi Barrea and Ludovica Verde are co-first authors and contributed equally to this article
[2] Department of Clinical Medicine and Surgery, Endocrinology Unit, University Federico II, Via Sergio Pansini 5, 80131 Naples, Italy
Full list of author information is available at the end of the article

with simple sugars over complex/raw carbohydrates [5]. This is because foods with a high glycemic index can stimulate serotonin release, which in turn makes people feel good and promotes the onset of carbohydrate cravings [5]. Although new anti-obesity drugs are constantly appearing on the market, they still have some limitations, such as not insignificant cost, possible side effects and contraindications, which make them not suitable for all people with obesity [6]. Moreover, bariatric surgery has proven to be a useful tool for weight loss and remission of T2DM and metabolic syndrome [7]. However, there are several complications and sequelae associated with surgery, and it is limited to those individuals with severe obesity who do not have contraindications for surgery [8]. In this context, the very low-calorie ketogenic diet (VLCKD) has recently been proposed as an attractive nutritional strategy for the treatment of obesity in individuals who have already attempted to lose weight on a diet with a more balanced distribution of macronutrients without achieving the goal of weight loss. VLCKDs consist of 90% calories from fat and only 10% from carbohydrate and protein, resulting in a severely restricted diet [9]. In individuals with obesity, VLCKD has demonstrated beneficial effects on body composition, metabolic profile, and the expression of inflammation and oxidative stress genes [10–12]. The Obesity Management Task Force (OMTF) of the European Association for the Study of Obesity (EASO) carried out a meta-analysis of 15 studies to assess the efficacy of VLCKD on body weight, body composition, glycemic and lipid parameters in subjects with overweight and obesity [13]. The first finding was that VLCKD was associated with significant reductions in body weight and BMI at 1, 2, 4–6, 12, and 24 months and appeared to be associated with greater rates of weight loss compared with other diets with different energy content (i.e., low-calorie diet and very low-calorie diet) for the same duration. The second finding was that a VLCKD was associated with significant reductions in waist circumference (WC) (an expression of central adipose tissue) and fat mass, and these reductions were significantly greater than those achieved with other weight loss interventions of the same duration. The third outcome concerned blood glucose levels and Glycosilated Haemoglobin A1C (HbA1c) levels. Here, a significant reduction was found after VLCKD, without superiority compared to other weight loss measures. On the other hand, VLCKD was associated with a reduction in the homeostasis model of assessment-IR (HOMA-IR) index and an improvement in insulin sensitivity, and this effect was superior to that of other weight loss programs. The fourth finding was that a VLCKD was associated with a reduction in total cholesterol and had a greater effect in lowering total cholesterol compared with other weight loss programs. In the same vein, VLCKD resulted in a significant reduction in low density lipoproteins (LDL) cholesterol levels from baseline to post-VLCKD follow-up but did not show a superior effect compared to other weight loss diets in terms of LDL reduction. On the other hand, no change in high density lipoproteins (HDL) cholesterol was observed from baseline to follow-up after VLCKD. Interestingly, no differences were also found when we compared the mean change in HDL cholesterol between a VLCKD and other weight loss interventions. Finally, a significant decrease in triglycerides (TG) lv from baseline was associated with a VLCKD and proved to be superior to other diets [13].

Ketogenic Diet (KD) induce a metabolic state termed "physiological ketosis" by Hans Krebs, which is distinct from pathological diabetic ketosis [14]. In the past, the KD has been used to treat various diseases such as pediatric pharmacoresistant epilepsy [15]. More recently, VLCKD has undoubtedly been shown to be effective in tackling obesity [16], dyslipidemia, and most of the cardiovascular risk factors associated with obesity [17, 18]. The rapid initial weight loss is due to natriuresis and diuresis resulting from the decrease in insulin levels and the increase in glucagon levels and ketone production [19, 20]. Even after the initial diuresis, weight loss remains faster than other diets because the amount of calories is very low. In addition, because the dietary pattern is unfamiliar and the diet is perceived as temporary, patients may be able to sustain the diet better than with dietary patterns that require a longer period of time to lose the same amount of weight. Furthermore, during ketosis, subjects reported less hunger and a greater sense of satiety, a useful property to improve adherence to dietary treatments [21]. There are several hypotheses about the effect of a VLCKD on the feeling of satiety and some authors have suggested that there may be a direct effect of ketone bodies, especially B-hydroxybutyrate, on appetite suppression [22, 23]. The relative maintenance of protein mass is also an advantage, at least compared with starvation [24].

Although several studies highlighted the efficacy of VLCKD in obesity, however, the major concerns are represented by the side effects. Indeed, no studies have been carried out in subjects with obesity to specifically investigate the VLCKD-related side effects. Since the ketogenic phase of VLCKD is the most effective in weight loss and it is the phase that potentially could be associated more frequently to side effects, the primary objective of our study was to investigate the VLCKD-related side effects in obesity focusing on the time of onset and on the duration in subjects with obesity in the ketogenic phase of VLCKD. The second objective of our study was to investigate the impact of side effects on efficacy of VLCKD.

Methods

Subjects

We prospectively recruited 106 (12 males and 94 females, BMI 34.98 ± 5.43 kg/m^2) consecutive patients clinically referred for weight loss treatment at the Centro Italiano per la cura e il Benessere del paziente con Obesità (C.I.B.O), Endocrinology Unit, Department of Clinical Medicine and Surgery, University Federico II of Naples (Italy), from March 2021 to September 2021. The study has been approved by the Local Ethical Committee (n. 50/20) and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments that involved humans. The aim of the study was clearly explained to all the study participants and a written informed consent was obtained.

Inclusion criteria were: age 18 years or older, BMI ≥ 30 kg/m^2, naive subjects, i.e. who had not already tried treatment with anti-obesity drugs or bariatric surgery. Exclusion criteria were: type 1 diabetes mellitus, latent autoimmune diabetes in adults, T2DM on insulin therapy, pregnancy and breastfeeding, kidney failure and severe chronic kidney disease, liver failure, hearth failure (NYHA III–IV), respiratory insufficiency, unstable angina, a recent stroke or myocardial infarction (< 12 months), cardiac arrhythmias, eating disorders and other severe mental illnesses, alcohol and substance abuse, active/severe infections, frail elderly patients, 48 h prior to an elective surgery or invasive procedures and a perioperative period, rare disorders such as porphyria, carnitine deficiency, carnitine palmitoyltransferase deficiency, carnitine-acylcarnitine translocase deficiency, mitochondrial fatty acid β-oxidation disorders, and pyruvate carboxylase deficiency.

Anthropometric measurements and physical activity

Anthropometric measurements were assessed at baseline and at the end of ketogenic phase. Measurements were performed between 8 a.m. and 12 p.m. and all the subjects were measured after an overnight fast. The anthropometric measurements were performed by the same operator, according to the International Society for the Advancement of Kinanthropometry (ISAK 2006). All the anthropometric measurements were taken with subjects only wearing light clothes and without shoes. Body weight was determined to the nearest 0.1 kg while using a calibrated balance beam scale (Seca 711; Seca, Hamburg, Germany) as well as height was measured to the nearest 0.5 cm with a wall-mounted stadiometer (Seca 711; Seca, Hamburg, Germany). In each subject, weight and height were measured to calculate the body mass index (BMI) [weight (kg)/height^2 (m^2)]. BMI was classified according to World Health Organization's criteria with normal weight: 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; grade I obesity, 30.0–34.9 kg/m^2; grade II obesity, 35.0–39.9 kg/m^2. WC was measured to the nearest 0.1 cm with a no stretch tape measure at the natural indentation or halfway between the lower edge of the rib cage and the iliac crest if no natural indentation was visible, according to the National Center for Health Statistics. Finally, the Weight Loss Percentage (WLP) was calculated using the following formula: WLP (%) = [(Starting Weight − Current Weight)/Starting Weight] × 100. Measurements were taken at baseline and at each end step of the VLCKD protocol. Participants who habitually exercised at least 30 min per day (YES /NO) were defined as physically active.

Laboratory assay

In a subgroup of 25 subjects with obesity we assessed biochemical parameters. Blood samples were collected by venipuncture between 8 a.m. and 10 a.m. after an overnight fast. Samples were then transferred to the local laboratory and handled according to the local standards of practice. Insulin, glucose, HbA1C, lipid profile, electrolytes, uric acid, liver enzymes, and renal function were measured. The HOMA-IR [fasting glucose (mmol/l) × fasting insulin (mU/ml)/22.5] was also calculated for each subject, as previously detailed [25]. The Glomerular Filtration Rate (GFR) was calculated as follows: eGFR (ml/min/ 1.73 m^2) = 175 × serum creatinine $^{-1.234}$ × age $^{-0.179}$ (× 0.742 if female) (× 1.212 if black) [26]. Ketosis was confirmed by the detection of acetoacetate in urine using commercially available urine reagent strips (Ketur test, Roche Diagnostics, Switzerland).

Nutritional intervention

Subjects who met the inclusion criteria underwent to the VLCKD with the use of replacement meals following a protocol consisting in three stages: active, re-education, and maintenance. The replacement meals used for all subjects were from the same company. After the anthropometric assessment, the diet was prepared by qualified nutritionists and prescribed by the endocrinologist. The VLCKD provided a total daily energy intake of < 800 kcal depending on the quantity and quality of the preparations. The breakdown of macronutrients was as follows: ≃ 13% glucides, generally less than 30 g/day; ≃ 43% protein, daily protein intake of about 1.2–1.5 g/kg ideal body weight, ≃ 44% lipids, olive oil predominating. The VLCKD was based on protein from high biological value preparations derived from peas, eggs, soy and whey. Each protein preparation consisted of approximately 18 g protein, 4 g carbohydrates, 3 g fat (mainly vegetable oils with a high oleic acid content) and provided approximately 100–150 kcal. The weight loss program was structured in several phases. During Phase 1 (21 days), patients

consumed 4–6 protein preparations (depending on ideal body weight) and low-carbohydrate vegetables, establishing the state of ketosis. In subsequent phases, the state of ketosis was still maintained. During Phase 2 (30 days) 1/2 of the meals provided (lunch and/or dinner) were gradually replaced by meals based on natural proteins (meat/fish/eggs/soy). The ketogenic period (Phases 1–2), which provided ≃ 600–800 kcal/day, was about 50 days in total. As it is a very low calorie diet, it is recommended to provide patients with micronutrients (vitamins, such as complex B vitamins, vitamins C and E, minerals, including potassium, sodium, magnesium, calcium and omega-3 fatty acids) according to international recommendations.

Side effects assessments

The assessment of side effects was carried out through a questionnaire, periodic physical examination and laboratory assessment. The questionnaire was formulated reporting all the side effects already known to be associated with KD although in other setting of subjects i.e. migraine, dry mouth, dizziness, low blood pressure, visual disturbances, low blood sugar, lethargy, halitosis, diarrhoea, constipation, vomiting/nausea, hyperuricemia, urolithiasis, gallbladder disease, hair loss [13, 27]. It has been proposed a preliminary version of the questionnaire that was first tested in 10 patients, who were asked to comment on any aspect (content, wording and choice of answer). Questions that were ambiguous, misunderstood or rarely answered were reformulated. This resulted in a final version of 15 questions. This list of 15 potential side effects was administered and it included headache, dry mouth, dizziness, low blood pressure, visual disturbances, low blood sugar, lethargy, halitosis, diarrhoea, constipation, vomiting/nausea, hyperuricemia, urolithiasis, gallbladder disease, hair loss and whether the diet was stopped early (and why) than the end of the protocol. All questions used nominal variables (YES/NO) and were completed with information on the day of onset and duration of symptoms. Finally, information was also collected on how the symptom was managed and whether drugs and/or supplements were taken. Subjects were screened for side effects at the end of ketogenic phase.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) when normally distributed. Categorical variables are expressed as numbers and percentage (%). Variations were analyzed through the paired t-test for normally distributed variables. The p values were considered significant at $p < 0.05$ with 95% confidence interval. Statistical analysis was performed according to standard methods using the Statistical Package for Social Sciences software 26.0 (SPSS/PC; SPSS, Chicago, IL, USA).

Results

Between March 2021 to September 2021, a total of 106 (12 males and 94 females; BMI 34.98 ± 5.43 kg/m^2) subjects aged 39 ± 13.82 years underwent to the VLCKD and were included in the analyses. The main clinical characteristics of the study population are reported in Table 1. WC was 106.16 ± 14.20 cm while waist to hip ratio (WHR) was 0.88 ± 0.08. Most of the participants were sedentary (78, 73.6%). The prevalence of cardiometabolic diseases were the following: 2 (1.9%) subjects with T2DM, 9 (8.5%) with hypertension, 19 (17.9%) with dyslipidaemia, 19 (17.9%) with hypercholesterolaemia and 7 (6.6%) with hypertriglyceridaemia.

Safety

Table 2 shows the side effects that occurred in our population, their onset and duration, and any medical treatment that they took to relieve side effects.

Regarding the kidney function, there was no significant change between GFR from baseline to the end of ketogenic phase (94.13 ± 19.00 mL/min *vs* 89.00 ± 20.83 mL/min; p = 0.123) (Table 3). With regard to liver function, we observed significant increase and decrease in AST e ALT levels, respectively (AST 20.50 ± 6.60 U/L *vs* 20.92 ± 6.32 U/L; p = 0.022, ALT 23.43 ± 9.85 U/L *vs* 22.90 ± 12.15 U/L; p = 0.001). Lastly, subjects showed a significant reduction in mean GGT from 17.82 ± 6.48 U/L to 14.72 ± 5.25 U/L (p = 0.003).

Table 1 Demographic and clinical characteristics at baseline

Parameters	Subjects (N = 106)
Gender	
Male	12 (11.3)
Female	94 (88.7)
Age	39 ± 13.82
BMI (kg/m^2)	34.98 ± 5.43
WC (cm)	106.16 ± 14.20
HC (cm)	120.53 ± 10.8
WHR	0.88 ± 0.08
Physical activity	
Sedentary	78 (73.6)
Moderate	28 (26.4)
CVD	
T2DM	2 (1.9)
Hypertension	9 (8.5)
Dyslipidaemia	19 (17.9)
Hypercholesterolaemia	19 (17.9)
Hypertriglyceridaemia	7 (6.6)

Data are expressed as mean ± SD or n (%)

BMI body mass index, *WC* waist circumference, *HC* hip circumference, *WHR* waist-to-hip-ratio, *CVD* cardiovascular disease, *T2DM* type 2 diabetes mellitus

Table 2 Side effects occurring during ketogenic phase

Parameters	N (%)	Time to onset from the beginning of VLCKD ± SD (days)	Duration (mean ± SD) (days)	Medically treated N (%) and which remedy N (%)
Headache	48 (45.3)	4.23 ± 4.99	7.43 ± 8.84	19 (17.9)9 (47.36) ibuprofen 9 (47.36) paracetamol 1 (5.26) indomethacin
Dry mouth	41 (43.5)	3.83 ± 3.22	19.95 ± 10.35	–
Dizziness	17 (16)	6.12 ± 7.26	9.35 ± 7.37	–
Hypotension	19 (17.9)	4.68 ± 4.69	11.31 ± 10.99	–
Visual disturbances	5 (4.7)	5.40 ± 4.72	8 ± 5.43	–
Low blood sugar	1 (0.9)	2	1	–
Lethargy	49 (46.2)	4.66 ± 4.40	15.9 ± 9.6	–
Halitosis	49 (46.2)	2.90 ± 1.52	22.06 ± 8.24	18 (17) 15(83.33) chewing gum 2 (11.11) oral spray 1 (5.55) mouthwash
Diarrhoea	13 (12.3)	13.31 ± 11.48	10.08 ± 11.48	–
Constipation	30 (28.3)	11.2 ± 16.20	16.37 ± 8.95	8 (7.5) 8 (100) osmotic laxative
Vomiting/nausea	16 (15.1)	4.81 ± 4.94	4.19 ± 3.25	2 (1.9) 1 (50) metoclopramide 1 (50) antacid
Hyperuricemia	11 (10.4)	–	–	8 (7.5) 8 (100) allopurinol
Urolithiasis	0	–	–	–
Gallbladder disease	0	–	–	–
Hair loss	16 (15.1)	15 ± 9.75	15 ± 20.19	3 (2.8) 3 (100) hair supplement

Data are expressed as mean ± SD or n (%)

No significant changes were detected in terms of serum potassium (4.41 ± 0.30 mmol/L *vs* 4.43 ± 0.33 mmol/L; p = 0.452) and serum calcium levels (9.70 ± 0.75 mg/dL *vs* 9.90 ± 0.61 mg/dL; p = 0.056) (Table 3). A significant increase of serum sodium levels has been detected (140.34 ± 2.72 mmol/L vs 140.53 ± 2.22 mmol/L; p = 0.001) Finally, there were no differences in terms of WLP (13.50 ± 10.88% *vs* 18.18 ± 8.91%; p = 0.318) in subjects that developed side effects and subjects that did not developed side effects (Fig. 1).

Efficacy

Table 3 shows clinical and laboratory differences between baseline and the end of ketogenic phase. The weight from baseline to the end ketogenic phase was significantly reduced (94.38 ± 17.34 kg *vs* 87.29 ± 15.99 kg; p < 0.001) as well as the BMI (34.98 ± 5.43 kg/m^2 *vs* 32.35 ± 5.02 kg/m^2; p < 0.001). We also observed a significant reduction of waist and hip circumferences (106.16 ± 14.20 cm vs 99.24 ± 13.57 cm, p < 0.001 and 120.53 ± 10.81 cm vs 115.91 ± 9.70 cm, p < 0.001, respectively) and as can be expected there was also a reduction of WHR (0.88 ± 0.08 vs 115.91 ± 9.70; p < 0.001), from baseline to the end of ketogenic phase. Similarly, fasting plasma glucose (88.04 ± 8.95 mg/dL vs 82.60 ± 10.08 mg/dL; p = 0.072), insulin (17.35 mg/dL ± 13.83 mg/dL *vs* 8.05 ± 5.48 mg/dL; p = 0.286) and HOMA-IR (3.80 ± 2.79 vs 1.74 ± 1.29; p = 0.332) shows an improving trend despite not reaching statistically significant levels. Regarding the lipid profile, total cholesterol (170.20 ± 40.77 mg/dL vs 144.72 ± 30.61 mg/dL; p < 0.001) and HDL (52.24 ± 12.17 mg/dL vs 49.86 ± 13.11 mg/dL; p = 0.018) significantly decreased from baseline to the end of ketogenic phase. No significant changes were observed in mean LDL (88.95 ± 30.77 mg/dL vs 86.14 ± 20.57 mg/dL; p = 0.235) and mean TG levels (88.95 ± 30.77 mg/dL vs 86.14 ± 20.57 mg/dL; p = 0.235).

Discussion

Due to the imminent increase in obesity prevalence [1], effective strategies for weight loss and weight maintenance are needed. Although bariatric surgery is an effective treatment option for patients with obesity, its invasiveness, high costs, long waiting lists and potential complications limit its widespread use [8]. Therefore, pharmacological and lifestyle-based treatments are a valuable option for most patients with obesity [6]. Although new anti-obesity drugs are constantly coming

Table 3 Clinical and laboratory differences between baseline and the end of ketogenic phase

Parameters	Baseline	End of phase 1	p value
Weight (kg)	94.38 ± 17.34	87.29 ± 15.99	< 0.001
BMI (kg/m^2)	34.98 ± 5.43	32.35 ± 5.02	< 0.001
WC (cm)	106.16 ± 14.20)	99.24 ± 13.57	< 0.001
HC (cm)	120.53 ± 10.81	115.91 ± 9.70	< 0.001
WHR	0.88 ± 0.08	0.86 ± 0.09	< 0.001
Blood Glucose (mg/dL)	88.04 ± 8.95	82.60 ± 10.08	0.072
Insulin (mg/dL)	17.35 ± 13.83	8.05 ± 5.48	0.286
HOMA—IR	3.80 ± 2.79	1.74 ± 1.29	0.332
Tot Chol (mg/dL)	170.20 ± 40.77	144.72 ± 30.61	< 0.001
LDL Chol (mg/dL)	101.95 ± 29.11	81.40 ± 29.91	0.142
HDL Chol (mg/dL)	52.24 ± 12.17	49.86 ± 13.11	0.018
TG (mg/dL)	88.95 ± 30.77	86.14 ± 20.57	0.235
GFR (mL/min)	94.13 ± 19.00	89.00 ± 20.83	0.123
Creatinine (mg/dL)	0.77 ± 0.11	0.82 ± 0.16	< 0.001
Azotemia (mg/dL)	30.44 ± 8.94	34.89 ± 10.60	0.001
Uricemia (mg/dL)	5.29 ± 1.45	6.23 ± 1.69	0.054
AST (U/L)	20.50 ± 6.60	20.92 ± 6.32	0.022
ALT (U/L)	23.43 ± 9.85	22.90 ± 12.15	0.001
GGT (U/L)	17.82 ± 6.48	14.72 ± 5.25	0.003
Calcemia (mg/dL)	9.70 ± 0.75	9.90 ± 0.61	0.056
Sodiemia (mmol/L)	140.34 ± 2.72	140.53 ± 2.22	0.001
Potassiaemia (mmol/L)	4.41 ± 0.30	4.43 ± 0.33	0.452

Data are expressed as n or mean ± SD

BMI body mass index, *WC* waist circumference, *HC* hip circumference, *WHR* waist-to-hip-ratio, *HOMA-IR* homeostasis model of assessment-IR, *Tot Chol* total cholesterol, *LDL-chol* low-dense-lipoprotein cholesterol, *HDL-chol* high dense lipoprotein cholesterol, *TG* triglycerides, *GFR* glomerular filtration rate, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *GGT* gamma-glutamyl transferase

onto the market, they still have some limitations, such as not inconsiderable cost, potential side effects and contraindications, which make them unsuitable for all people with obesity [6]. In addition, dietary regimens are often characterized by limited efficacy in weight loss and poor adherence in the majority of patients [28]. Alternative dietary strategies have been introduced to achieve greater weight loss and adherence. VLCKD has been demonstrated to be a valid approach in people affected by obesity, since it promotes satiety, rapid weight loss, and muscle sparing [13]. Nevertheless, a major area of concern is the side effects of VLCKD. None of the studies carried out in subjects with obesity have been designed to specifically investigate the side effects.

In this prospective study we found the VLCKD is a safe and effective tool for weight loss and metabolic improvement in subjects with obesity. Interestingly, no severe side effects occurred in our population. In addition, those that did occur were clinically mild and they did not result in the interruption of the dietary protocol as they could be easily managed by healthcare professionals or often resolved spontaneously. The supplementation with vitamins, such as complex B vitamins, vitamin C and E, minerals, including potassium, sodium, magnesium, calcium; and omega-3 fatty acids was adequate to prevent any deficiency. Furthermore, we found that WLP was similar in those who developed side effects and those who did not (Fig. 1). Thus, the onset of side effects does not have any impact on the efficacy and on the adherence to the VLCKD.

The most common side effects that were reported were lethargy (46.2%), halitosis (46.2%), headache (45.3%), dry mouth (43.5%), constipation (28%), hypotension (17.9%), dizziness (16%), vomiting/nausea (15.1%), hair loss (15.1%), diarrhoea (12.3%), hyperuricemia (10.4%) and visual disturbances (4.7%).

Ketone bodies, which are normally produced during the active phase of VLCKD, are excreted via frequent and increased urination. This can lead to dehydration and a loss of electrolytes [29]. In a RCT comparing the efficacy and tolerability of the non-fasting KD (N = 41) and the initial fasting KD (N = 83) in children with intractable epilepsy, moderate dehydration occurred in both groups [30]. Dehydration-related disorders are mostly represented by a dry mouth, headache, dizziness/orthostatic hypotension, lethargy, and visual disturbances [22]. Thus, it is mandatory to recommend a proper water intake (at least 2 L daily), in particular during the ketogenic state. Headache was common in our patients and generally occurred in the first week. In order to relieve headache, it could be recommended to take mild analgesics as pills instead of liquid formulations because they could contain sugar that could interrupt ketogenic state. However, it should be notice that VLCKD-related headache was a short term. A considerable proportion (17.9%) of subjects also experienced hypotension thus carefully monitoring of blood pressure, increasing salt intake when there were no contraindications and the adjustment of antihypertensive drugs in subjects with hypertension is advisable during VLCKD. Another possible effect of dehydration that we have found in our population is an increase in sodiemia. This is mostly due to dehydration, although the serum sodium levels did not reach pathological values and remained in the normal ranges.

Halitosis was very frequent in our subjects (46.2%). Individuals who underwent to a VLCKD often report bad breath with a fruity smell once they reach full ketosis. Indeed, in a study of 12 healthy adults who ate four ketogenic meals over 12 h, the increase in ketone levels, and in particular the increase in acetone, acted as a predictor of ketosis [31]. Chewing sugar-free gum and/or candy and specific oral spray or mouthwash has been used as a successful strategy to manage this discomfort.

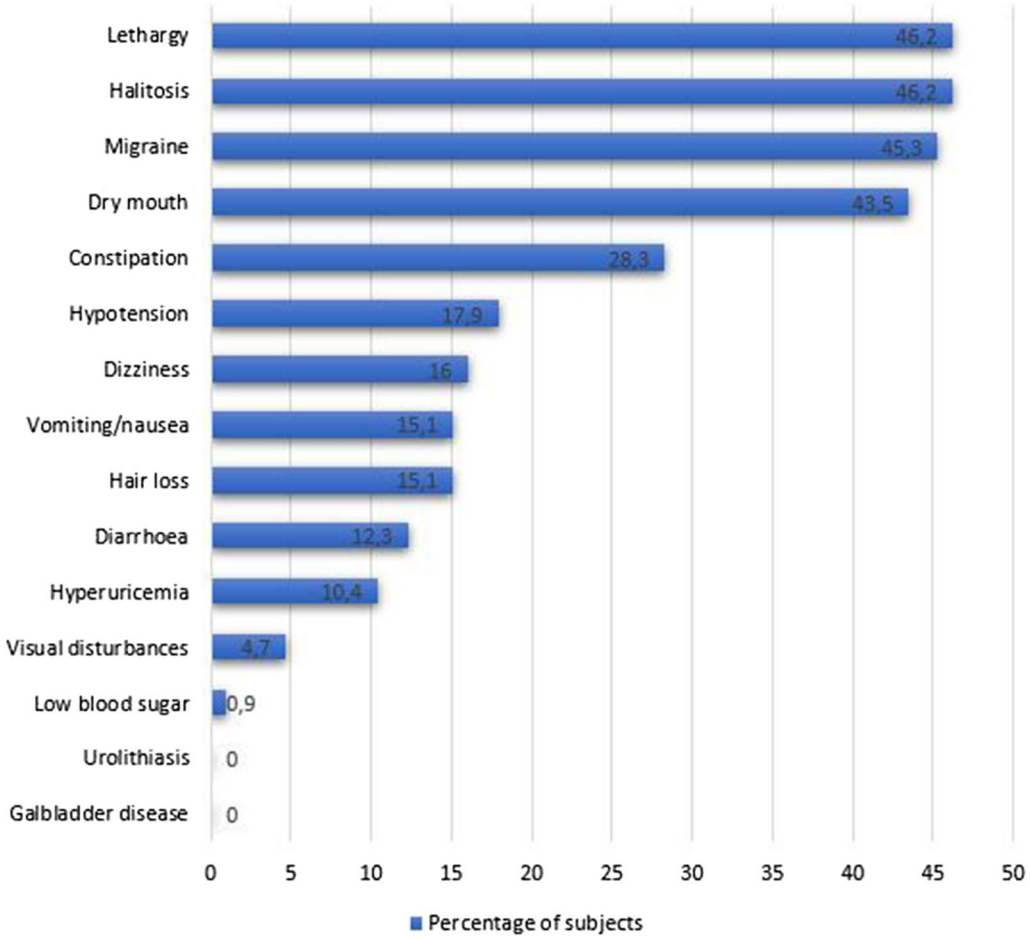


Fig. 1 Differences in weight loss percentages from baseline to end of ketogenic phase

Nausea/vomiting, diarrhea, and constipation are the most common gastrointestinal (GI) side effects of a VLCKD as we also found in our study [constipation (28%), vomiting/nausea (15.1%), diarrhoea (12.3%)] and as already have been reported in studies carried out in normal weight subjects [32–34]. In an RCT, 77 healthy participants were randomized to receive a VLCKD, a low-carbohydrate diet or a low-carbohydrate diet containing 5%, 15% and 25% total energy from carbohydrates, respectively, for 3 weeks [32]. Statistically significant increase in diarrhoea and constipation severity was observed in the VLCKD group [32]. In a prospective study of 147 children with refractory epilepsy conducted to evaluate the efficacy and safety of 6 months KD treatment, the second most common side effect of dietary treatment was diarrhoea [34]. In another similar study of 12 adults with refractory epilepsy treated with KD for 4 months, mild side effects included nausea/vomiting, constipation, and diarrhoea [33]. Diarrhea could be due to defective absorption and intolerance of fat [35]. The high content of lipids can slow gastric emptying, favoring gastroesophageal reflux disease, nausea, and vomiting [35]. For the management of these symptom, it is advisable the intake of small and frequent meals, sporadic use of GI medications such as antiemetics, GI tract regulators and antacids. A decreased in water intake, fiber, and/or the volume of food can cause the onset to constipation [36]. If this was the case, it should be increased water and fiber intake and, in severe cases, the administration of low-calorie osmotic laxative is needed.

Some subjects developed hyperuricemia (10.4%) during the ketogenic phase. However, the occurrence of this adverse event is in line with what has already been reported in a systematic review of 45 studies on the safety and tolerability of the KD used for the treatment of refractory childhood epilepsy, in which hyperuricemia was reported as one of the most frequent side effects [37]. Serum uric acid is known to increase in individuals following a KD [38, 39]. To counteract this side effect,

increasing water intake and, where necessary, allopurinol therapy are recommended.

Hair loss has been reported by 15.1% of enrolled subjects. Significantly negative nitrogen balance can be responsible for the hair loss that occurs during VLCKD [40]. If body protein and dietary protein mobilization are inadequate to meet the requirements, telogen effluvium is due to the low priority of hair growth of the available proteins [41]. However, hair loss is temporary, and hair regrows while weight stabilizes. Increased protein intake during VLCKD to balance nitrogen levels helps prevent or attenuate hair loss.

In addition, the relative protein excess typical of VLCKD has been of great concern among clinicians due to its potential for kidney damage. To investigate this safety outcome GFR was evaluated. GFR was not affected by dietary intervention and no differences were observed between baseline and end of ketogenic phase. Recent evidence suggest that the impact of dietary protein on renal function may depend on the protein source, with red meat intake being detrimental in a dose-dependent manner, and other protein sources such as poultry, fish, eggs and dairy products showing no such deleterious effect [42]. In addition, studies evaluating protein sources of plant origin (soy and plant derivatives) appear to show that these may even play a protective role on kidney [43, 44]. The early stages of VLCKD are based on meal replacements; the protein source of meals is whey and vegetable origin, and—when in the later stages the reintroduction of other protein sources takes place—patients are recommended to favour fish and poultry. The protein intake is never more than 1.5 g/kg/ideal body weight. It therefore seems reasonable to assume that such a dietary intervention is unlikely to have deleterious effects on kidney in individuals with obesity during the ketogenic phase.

The effect of the KD on lipid profile and cardiovascular risk is still debated due to concerns that the frequent increase in animal fat intake may counteract the beneficial effects of weight loss. Regarding the lipid profile, we found out that total cholesterol and HDL significantly decreased from baseline to the end of ketogenic phase. An important element in increasing HDL levels is physical exercise [45], and the reduction in HDL concentration we observed in our subjects is therefore probably due to the recommendation to reduce it in the ketogenic phase as it is characterized by a strong hypocaloric condition. However, a subsequent re-establishment in HDL levels can be expected in the reintroduction phase as reported in other previous studies [46, 47]. No significant changes were observed in mean LDL and mean TG levels, probably due to the prolonged ingestion of high lipid intake. In this regard, a systematic review of 107 studies found no adverse effects on serum lipid parameters, blood pressure, or fasting blood glucose in adults who followed a diet containing less than 60 g/day of carbohydrate [48], although the analysis was complicated by heterogeneity and lack of studies, particularly those that evaluated diet use for > 90 days. A 56-week study of a KD in men with obesity (N = 66) who lost 26% of their body weight found significant reductions in total cholesterol, LDL, and TG and increases in HDL [49]. The positive changes were greater in subjects with hyperlipidemia at baseline [49]. Even in studies of normal-weight subjects (N = 20) with minimal weight loss, slight to moderate increases in total cholesterol and LDL levels were seen in the KD groups [18]. These changes occurred as early as 3 weeks and appeared to return to baseline after 6 weeks in at least one study [18].

KD is also an effective tool for improving glycaemic control variables [50, 51]. In a study of 64 subjects with obesity and high blood glucose levels on a KD for 56 weeks, glucose levels showed significant improvement at the end of treatment [51]. Another study of 363 subjects with overweight or obesity investigated the beneficial effects of the low-carbohydrate ketogenic diet (LCKD) compared with the low-calorie diet in improving glycemic parameters [50]. Both treatments were associated with a reduction in blood glucose and glycated haemoglobin but changes were more significant in subjects who were on the LCKD [50]. Likewise, in our subjects, fasting plasma glucose, insulin and HOMA-IR shows an improving trend despite not reaching statistically significant levels. This is probably due to the drastic reduction in carbohydrates of ketogenic phase, which in turn reduces insulin concentrations and encourages the use of stored fat as fuel, as well as significantly reducing insulin resistance [52].

Finally, there were no differences in WLP between subjects who developed side effects and those who did not. Thus, the occurrence of side effects did not affect efficacy or compliance with VLCKD probably because they were very mild and easily managed. To our knowledge, there are no other studies in the literature that have evaluated the impact that VLCKD side effects might have on the efficacy of dietary treatment.

Conclusions

VLCKD appears to be an ideal therapeutic tool for people with obesity, particularly those who have already tried other nutritional strategies without success and/or who have a rapid need to lose weight (people with obesity with joint diseases, people with obesity with indications for bariatric surgery, people with obesity with cardiovascular risk

factors, etc.). In spite of common misgivings, side effects are mild and preventable thanks to the indications and contraindications provided for VLCKD, by following organised and standardised protocols, and by careful clinical and laboratory monitoring. For this reason, supervision by a healthcare professional is indispensable. Finally, once the goal has been achieved, it is extremely important to recommend an adequate lifestyle (physical activity and a balanced diet such as the Mediterranean diet) for maintaining weight loss in the long term.

Abbreviations

T2DM: Type 2 diabetes mellitus; VLCKD: Very low-calorie ketogenic diet; WC: Waist circumference; HbA1c: Glycosilated haemoglobin A1C; HOMA-IR: Homeostasis model of assessment-IR; LDL: Low density lipoproteins; HDL: High density lipoproteins; TG: Triglycerides; KD: Ketogenic diet; BMI: Body mass index; WLP: Weight loss percentage; WHR: Waist to hip ratio; GFR: Glomerular filtration rate; GI: Gastrointestinal; LCKD: Low-carbohydrate ketogenic diet.

Acknowledgements

Funding was not provided for this study, however all patients used for preparations containing high biological value proteins from New Penta Srl (Castelletto Stura, CN, Italy) who we would like to acknowledge.

Authors' contributions

LB and GM designed the research. LV, SA and FM provided data collection and the clinical samples. CV provided data analysis support. LV and LB wrote the manuscript and GM, SS and AC revised the paper. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study has been approved by the Local Ethical Committee (n. 50/20) and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments that involved humans. The aim of the study was clearly explained to all the study participants and a written informed consent was obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Dipartimento di Scienze Umanistiche, Università Telematica Pegaso, 80143 Napoli, Italy. [2]Department of Clinical Medicine and Surgery, Endocrinology Unit, University Federico II, Via Sergio Pansini 5, 80131 Naples, Italy. [3]Centro Italiano per la cura e il Benessere del Paziente con Obesità (C.I.B.O), Department of Clinical Medicine and Surgery, Endocrinology Unit, Federico II University Medical School of Naples, Naples, Italy. [4]Cattedra Unesco "Educazione alla salute e allo sviluppo sostenibile", Federico II, Naples, Italy.

Received: 28 October 2021 Accepted: 27 December 2021
Published online: 08 January 2022

References

1. WHO. Obesity and overweight. 2021. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 10 Sep 2021.
2. De Lorenzo A, Gratteri S, Gualtieri P, Cammarano A, Bertucci P, Di Renzo L. Why primary obesity is a disease? J Transl Med. 2019;17(1):169.
3. Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a disease: the obesity society 2018 position statement. Obesity (Silver Spring). 2019;27(1):7–9.
4. Howell S, Kones R. "Calories in, calories out" and macronutrient intake: the hope, hype, and science of calories. Am J Physiol Endocrinol Metab. 2017;313(5):E608–12.
5. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab. 2003;88(4):1617–23.
6. Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgrad Med. 2018;130(2):173–82.
7. Hanipah ZN, Schauer PR. Bariatric surgery as a long-term treatment for type 2 diabetes/metabolic syndrome. Annu Rev Med. 2020;71:1–15.
8. Pories WJ. Bariatric surgery: risks and rewards. J Clin Endocrinol Metab. 2008;93(11 Suppl 1):S89-96.
9. Luat AF, Coyle L, Kamat D. The ketogenic diet: a practical guide for pediatricians. Pediatr Ann. 2016;45(12):e446–50.
10. Merra G, Gratteri S, De Lorenzo A, Barrucco S, Perrone MA, Avolio E, et al. Effects of very-low-calorie diet on body composition, metabolic state, and genes expression: a randomized double-blind placebo-controlled trial. Eur Rev Med Pharmacol Sci. 2017;21(2):329–45.
11. Barrea L, Megna M, Cacciapuoti S, Frias-Toral E, Fabbrocini G, Savastano S, et al. Very low-calorie ketogenic diet (VLCKD) in patients with psoriasis and obesity: an update for dermatologists and nutritionists. Crit Rev Food Sci Nutr. 2020;9:1–17.
12. Barrea L, Caprio M, Tuccinardi D, Moriconi E, Di Renzo L, Muscogiuri G, et al. Could ketogenic diet "starve" cancer? Emerging evidence. Crit Rev Food Sci Nutr. 2020;9:1–22.
13. Muscogiuri G, El Ghoch M, Colao A, Hassapidou M, Yumuk V, Busetto L, et al. European guidelines for obesity management in adults with a very low-calorie ketogenic diet: a systematic review and meta-analysis. Obes Facts. 2021;14(2):222–45.
14. Krebs HA. The regulation of the release of ketone bodies by the liver. Adv Enzyme Regul. 1966;4:339–54.
15. Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. J Child Neurol. 2009;24(8):979–88.
16. Bueno NB, de Melo IS, de Oliveira SL, da Rocha AT. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr. 2013;110(7):1178–87.
17. Al-Khalifa A, Mathew TC, Al-Zaid NS, Mathew E, Dashti HM. Therapeutic role of low-carbohydrate ketogenic diet in diabetes. Nutrition. 2009;25(11–12):1177–85.
18. Sharman MJ, Kraemer WJ, Love DM, Avery NG, Gomez AL, Scheett TP, et al. A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. J Nutr. 2002;132(7):1879–85.
19. Boulter PR, Hoffman RS, Arky RA. Pattern of sodium excretion accompanying starvation. Metabolism. 1973;22(5):675–83.
20. Saudek CD, Boulter PR, Arky RA. The natriuretic effect of glucagon and its role in starvation. J Clin Endocrinol Metab. 1973;36(4):761–5.
21. Paoli A, Bosco G, Camporesi EM, Mangar D. Ketosis, ketogenic diet and food intake control: a complex relationship. Front Psychol. 2015;6:27.
22. Muscogiuri G, Barrea L, Laudisio D, Pugliese G, Salzano C, Savastano S, et al. The management of very low-calorie ketogenic diet in obesity outpatient clinic: a practical guide. J Transl Med. 2019;17(1):356.
23. Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr. 2013;67(8):789–96.
24. Atkinson RL. Low and very low calorie diets. Med Clin North Am. 1989;73(1):203–15.
25. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C, et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. Acta Diabetol. 2016;53(2):251–60.
26. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006;17(10):2937–44.

27. Masood W, Annamaraju P, Uppaluri KR. Ketogenic Diet. Treasure Island: StatPearls; 2021.
28. Yannakoulia M, Poulimeneas D, Mamalaki E, Anastasiou CA. Dietary modifications for weight loss and weight loss maintenance. Metabolism. 2019;92:153–62.
29. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004;45(9):1116–23.
30. Kim DW, Kang HC, Park JC, Kim HD. Benefits of the nonfasting ketogenic diet compared with the initial fasting ketogenic diet. Pediatrics. 2004;114(6):1627–30.
31. Musa-Veloso K, Likhodii SS, Cunnane SC. Breath acetone is a reliable indicator of ketosis in adults consuming ketogenic meals. Am J Clin Nutr. 2002;76(1):65–70.
32. Harvey C, Schofield GM, Zinn C, Thornley S. Effects of differing levels of carbohydrate restriction on mood achievement of nutritional ketosis, and symptoms of carbohydrate withdrawal in healthy adults: a randomized clinical trial. Nutrition. 2019;67:100005.
33. Klein P, Janousek J, Barber A, Weissberger R. Ketogenic diet treatment in adults with refractory epilepsy. Epilepsy Behav. 2010;19(4):575–9.
34. Li H, Ouyang M, Zhang P, Fei L, Hu X. The efficacy and safety of a ketogenic diet for children with refractory epilepsy in China: a retrospective single-center cohort study. Transl Pediatr. 2020;9(4):561–6.
35. Zhang M, Yang XJ. Effects of a high fat diet on intestinal microbiota and gastrointestinal diseases. World J Gastroenterol. 2016;22(40):8905–9.
36. Bharucha AE. Constipation. Best Pract Res Clin Gastroenterol. 2007;21(4):709–31.
37. Cai QY, Zhou ZJ, Luo R, Gan J, Li SP, Mu DZ, et al. Safety and tolerability of the ketogenic diet used for the treatment of refractory childhood epilepsy: a systematic review of published prospective studies. World J Pediatr. 2017;13(6):528–36.
38. Castaldo G, Palmieri V, Galdo G, Castaldo L, Molettieri P, Vitale A, et al. Aggressive nutritional strategy in morbid obesity in clinical practice: Safety, feasibility, and effects on metabolic and haemodynamic risk factors. Obes Res Clin Pract. 2016;10(2):169–77.
39. Schwartz RM, Boyes S, Aynsley-Green A. Metabolic effects of three ketogenic diets in the treatment of severe epilepsy. Dev Med Child Neurol. 1989;31(2):152–60.
40. Sherwin RS. The effect of ketone bodies and dietary carbohydrate intake on protein metabolism. Acta Chir Scand Suppl. 1981;507:30–40.
41. Blackburn GL, Bistrian BR, Hoag C. Letter: hair loss with rapid weight loss. JAMA. 1976;236(3):252.
42. Lew QJ, Jafar TH, Koh HW, Jin A, Chow KY, Yuan JM, et al. Red Meat intake and risk of ESRD. J Am Soc Nephrol. 2017;28(1):304–12.
43. Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y, Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. Eur J Clin Nutr. 2003;57(10):1292–4.
44. Jibani MM, Bloodworth LL, Foden E, Griffiths KD, Galpin OP. Predominantly vegetarian diet in patients with incipient and early clinical diabetic nephropathy: effects on albumin excretion rate and nutritional status. Diabet Med. 1991;8(10):949–53.
45. Palazon-Bru A, Hernandez-Lozano D, Gil-Guillen VF. Which physical exercise interventions increase HDL-cholesterol levels? A systematic review of meta-analyses of randomized controlled trials. Sports Med. 2021;51(2):243–53.
46. Castellana M, Conte E, Cignarelli A, Perrini S, Giustina A, Giovanella L, et al. Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: a systematic review and meta-analysis. Rev Endocr Metab Disord. 2020;21(1):5–16.
47. Yuan X, Wang J, Yang S, Gao M, Cao L, Li X, et al. Effect of the ketogenic diet on glycemic control, insulin resistance, and lipid metabolism in patients with T2DM: a systematic review and meta-analysis. Nutr Diabetes. 2020;10(1):38.
48. Bravata DM, Sanders L, Huang J, Krumholz HM, Olkin I, Gardner CD, et al. Efficacy and safety of low-carbohydrate diets: a systematic review. JAMA. 2003;289(14):1837–50.
49. Dashti HM, Al-Zaid NS, Mathew TC, Al-Mousawi M, Talib H, Asfar SK, et al. Long term effects of ketogenic diet in obese subjects with high cholesterol level. Mol Cell Biochem. 2006;286(1–2):1–9.
50. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Nutrition. 2012;28(10):1016–21.
51. Michalczyk MM, Klonek G, Maszczyk A, Zajac A. The effects of a low calorie ketogenic diet on glycaemic control variables in hyperinsulinemic overweight/obese females. Nutrients. 2020;12:6.
52. Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. Ann Intern Med. 2005;142(6):403–11.

Publisher's Note

Journal of Translational Medicine

RESEARCH

Open Access

Supplementation with medium-chain fatty acids increases body weight loss during very low-calorie ketogenic diet: a retrospective analysis in a real-life setting

Claudia Vetrani[1,2†], Ludovica Verde[2,3†], Silvia Savastano[2,3], Annamaria Colao[2,3,4], Giovanna Muscogiuri[2,3,4*] and Luigi Barrea[1,2]

Abstract

Background Very low-calorie ketogenic diet (VLCKD) has shown to significantly reduce body weight and fat mass, as well as inflammation. These effects are supported by nutritional ketosis, which triggers the utilization of the ketone body as an energy source. Medium-chain fatty acids (MCTs) might serve as potential enhancers of ketone bodies production with a greater effect on weight loss. Nevertheless, no clinical studies have evaluated the effect of MCTs supplementation in addition to VLCKD. Therefore, the present study aimed to evaluate whether the supplementation with MCTs can induce a greater weight reduction during the ketogenic phase of VLCKD.

Methods In this retrospective study, 263 women with overweight/obesity (body mass index, BMI: 35.7 ± 5.3 kg/m^2) aged 37.5 ± 14.2 years followed one of these dietary protocols for 45 days: (a) Control group, 83 participants (31.6%) (VLCKD without MCTs), (b) VLCKD + MCTs group, 86 participants (32.7%) (MCTs supplementation — 20 g/day- during VLCKD starting from the first day of the active phase), (c) VLCKD + earlyMCTs, 94 participants (35.7%) (MCTs supplementation — 20 g/day-starting from 5 days before the beginning of the VLCKD active phase. Anthropometric measures, body composition, and c-reactive protein (CRP) concentrations were collected at the beginning and at the end (45 days) of the VLCKD intervention.

Results MCTs supplementation significantly decreased body weight, BMI, and waist circumference as compared to the control group, with a greater effect in the VLCKD + earlyMCTs group. A two-fold decrease in fat mass and an increase in muscle mass were observed in the VLCKD + earlyMCTs group as compared to the control group. As for inflammation, hs-CRP concentrations (assessed as absolute percent change) were significantly lower in the VLCKD + MCTs group ($p = 0.009$) and the VLCKD + earlyMCTs group ($p = 0.011$) than in the control group. A logistic regression model showed that VLCKD + earlyMCTs increase the likelihood of improvement of BMI classes (OR: 1.85, 95% CI 1.02–3.36) also after adjusting for the potential confounding factors.

†Claudia Vetrani and Ludovica Verde are equally contributed to this work

*Correspondence:
Giovanna Muscogiuri
giovanna.muscogiuri@unina.it
Full list of author information is available at the end of the article

Conclusion MCTs supplementation (20 g/day) may be a useful tool to enhance the beneficial effect of VLCKD on the reduction of body weight and fat mass. In particular, MCTs supplementation before the beginning of the VLCKD active phase might facilitate ketosis thus contributing to the effectiveness of the nutritional intervention.

Keywords Obesity, Nutritional ketosis, VLCKD, Ketogenic diet, Ketone bodies, Medium-chain fatty acids (MCTs), Inflammation, Diet

Introduction

Obesity is recognized as a chronic disease that associates with several comorbidities, such as type 2 diabetes mellitus (T2D), hypertension, dyslipidemia, cardiovascular diseases (mainly coronary heart disease and stroke), sleep disturbance, and some cancers [1–4]. These comorbidities—also known as non-communicable diseases (NCDs)—reduce the quality of life and life span and increase public health costs [3, 5].

Although several strategies have been developed to obtain weight loss, the trend of obesity is dramatically increasing, particularly among young adults and middle-income countries [6, 7].

In addition to lifestyle factors such as physical inactivity, smoking, and alcohol intake, also diet has been established as a highly modifiable risk factor for obesity and NCDs [8].

Among dietary approaches, very low-calorie ketogenic diet (VLCKD) has been appointed as one of the most effective interventions for body weight loss [9, 10]. In addition, it has shown to reduce inflammation and insulin resistance which represent two main triggers for the onset of NCDs [11].

VLCKD consists in a multistep protocol with three main stages: active phase, dietary re-education, and maintenance [12]. The active stage is the most important stage of VLCKD since it allows the achievement of 80% of the target weight loss, with a duration ranging 30–45 days depending on the individual response. Rapid weight loss is obtained through a great energy restriction (600–800 kcal/day) and a sharply sustained nutritional ketosis [12].

Nutritional ketosis occurs when carbohydrate intake is < 50 g/day and, because of carbohydrate restriction, it enhances the oxidation of the fatty acids in the adipose tissue for energy purposes [13, 14]. Indeed, acetyl-CoA is the precursor of ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone) which are used as an alternative fuel in various tissues.

Interestingly, only fatty acids with carbon chain lengths ≤ 8 can cross the inner membrane of the mitochondria independent of carnitine palmitoyl transferase I [15]. In this contest, fatty acids C8 (caprylic acid) might have a stronger ketogenic effect compared to C10 (capric acid) and C12 (lauric acid) [16]. Clinical evidence demonstrated that 20 g of C8 produces a significantly stronger ketogenic response than 10 g of C8 [15]. However, Norgren and colleagues [17] reported that to minimize potential side effects, the dose of C8 should be limited to 15–20 g *per* intake. Triglycerides containing medium-chain fatty acids (MCTs) consist in fatty acids with a carbon backbone with 6–12 carbon atoms linked to glycerol [18, 19]. After ingestion with the diet, MCTs are digested by intestinal lipases and absorbed in the gut as triglycerides containing long-chain fatty acids (LCTs, > 12 carbon atoms) [19]. Unlike LCTs, the fatty acids contained in MCTs can bind albumin and skip the formation of chylomicrons. Therefore, MCTs skip the hydrolysis by plasma lipoprotein-lipase and the consequent deposition in adipose tissue [20]. Then, MCTs directly reach the liver where they can be metabolized more quickly by mitochondrial β-oxidation [21]. However, unlike LCTs, MCTs do not require carnitine-mediated transport to enter the mitochondria. Moreover, MCTs, especially C8 and C10, can also be oxidized in peroxisomes, thus representing a more available source of energy than LCTs [21]. Several studies showed that MCTs supplementation increases β-hydroxybutyrate concentrations with a dose-dependent relationship [13, 22–24]. Consequently, MCTs might endorse "nutritional ketosis" during ketogenic diets [24].

Over a faster metabolism and less deposition in adipocytes, MCTs can significantly influence energy balance, favouring body weight loss independently of dietary energy intake [25, 26].

The mechanisms behind this effect are not completely understood possibly due to the high heterogeneity of studies available so far. Some studies have shown that MCTs might increase thermogenesis and, consequently, affect energy expenditure. Furthermore, the replacement of LCTs with MCTs was associated with a greater reduction of adipose tissue in animal models as well as in humans [27, 28]. This effect could be mediated by the specific action of MCTs on a G-protein coupled receptor (GPR84) in the adipose tissue [27]. In addition, MCTs might increase satiety feelings thus limiting food intake while favouring body weight control [28–31]. Indeed, hyperketonaemia can enhance the anorexigenic effect at the hypothalamic level [29, 30]. Furthermore, some studies suggested that MCTs can modulate the secretion of

some gastrointestinal hormones involved in hunger/satiety feelings (ghrelin and YY peptide, respectively) [29, 31].

To date, it is unclear whether the use of MCTs might increase the acute ketogenic response. Nevertheless, a 30 day clinical trial reported that the consumption of caprylic acid (C8; 6 g twice a day) increased plasma β-hydroxybutyrate concentration from ~ 0.1 mmol/L to ~ 0.2 mmol/L [32].

To the best of our knowledge, no previous studies investigated the potential effects of MCTs supplementation during VLCKD for a greater reduction of body weight and fat mass in individuals with overweight and obesity.

Against this background, the present study aimed to evaluate whether the supplementation with MCTs can induce a greater weight reduction during the ketogenic phase of VLCKD. For this purpose, we retrospectively investigated the effect of MCTs supplementation in addition to diet *vs* diet alone in a group of individuals with overweight/obesity undergoing a VLCKD. Over the effect on weight loss, we evaluated whether the association between VLCKD and MCTs supplementation may also affect inflammatory status as demonstrated for VLCKD alone.

Methods

Study design and setting

This study was conducted in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist [33]. Data from consecutive participants undergoing a VLCKD protocol for weight loss at *Centro Italiano per la cura e il Benessere del paziente con Obesità* (C.I.B.O.) of the Federico II University Hospital (Naples, Italy) were retrospectively collected between September 2021 and September 2022. All participants provided written consent after being informed about the study design. The study has been approved by the Local Ethical Committee (n. 50/20). The present analyses included a total of two time points: at baseline and during the VLCKD active stage after 45 days with the collection of anthropometric measures and body composition.

Participants

We included 263 healthy participants as individuals with diseases, such as T2D, might have different metabolic responses [16]. Individuals eligible for this study presented the following features: women aged 18–69 years, body mass index (BMI) 25.0–50.9 kg/m^2 at the beginning of the nutritional treatments. We excluded individuals presenting one or more of the following characteristics: (a) new onset physiological or pathological conditions that represent contraindications for VLCKD (i.e., pregnancy/breastfeeding, individuals with diabetes on insulin therapy, liver or kidney insufficiency, etc.) [10], (b) poor adherence to the dietary intervention (negative test for ketonuria or food behaviours not included in the dietary program referred by the participant); (c) individuals needing treatment with anti-obesity drugs or referred to bariatric surgery; (d) use of drugs, supplements or nutraceuticals that affect energy expenditure or weight loss during the intervention.

Nutritional intervention

Participants included in the present study underwent a VLCKD with the use of replacement meals (New Penta, Cuneo, Italy) following a 3-stages protocol (active phase, re-education, and maintenance) [12]. After the nutritional status assessment, the dietary plan was prescribed by the endocrinologist and planned by a skilled nutritionist. The VLCKD provided a total daily energy intake < 800 kcal, with 13% carbohydrates (< 30 g/day); 43% protein (1.2–1.5 g/kg ideal body weight); 44% lipids (mainly from extra-virgin olive oil). According to the international recommendations, participants were prescribed a multi-vitamin and saline supplement (complex B vitamins, vitamins C and E, potassium, sodium, magnesium, calcium, and omega-3 fatty acids; PentaCal, Penta, s.r.l., Cuneo, Italy), as reported in previous studies [34–36]. In all participants, physical activity (at least 30 min/day aerobic exercise) was assessed using a YES/NO response, as reported in previous studies [37–39].

Participants followed one of these dietary protocols: (a) Control group, VLCKD without MCTs; b) VLCKD + MCTs group, MCTs supplementation (20 g/day) during VLCKD starting from the first day of the active phase; c) VLCKD + earlyMCTs, MCTs supplementation (20 g/day) starting from 5 days before the beginning of the VLCKD active phase.

To reduce potential confounding factors related to the oil composition, all participants in the VLCKD + MCTs and VLCKD + earlyMCTs groups used only 100% MCT oil (Kanso MCToil 100%, for composition details, see: https: //www.kanso.com/en/p/oil-mct-100). MCTs supplementation (20 g/day) provided 163.8 kcal and 18.2 g of fat.

To improve compliance with the recommendations for diet and physical activity, participants were contacted by phone calls by a skilled nutritionist each week. Moreover, the participants were advised to measure blood β-hydroxybutyrate by test strips (Optium Xceed Blood Glucose and Ketone Monitoring System; Abbott Laboratories, Chicago, IL, USA) at fasting in the morning and to notify the results to the nutritionist.

Assessment of anthropometric measures and body composition

Anthropometric measures were collected by a single skilled nutritionist at each visit between 8 a.m. and 10 a.m. Weight, height, and waist circumference were detected in participants wearing light clothing and no shoes, after an overnight fast, according to standard procedures [40, 41]. Weight and height were used to calculate BMI (kg/m^2) [42]. BMI was classified according to the WHO criteria [43]: normal weight (18.5–24.9 kg/m^2); Overweight (25.0–29.9 kg/m^2); Obesity class I (30.0–34.9 kg/m^2); Obesity class II (35.0–39.9 kg/m^2); Obesity class III ($\geq$ 40.0 kg/m^2). All measurements were taken while the subject was standing upright with the feet together and the arms hanging closely by the sides, with the subject standing and breathing normally, as previously reported [36–38].

Body composition was evaluated by bioelectrical impedance analysis (BIA). BIA was performed by a phase-sensitive BIA system (an 800 A current with a frequency of 50 kHz BIA 101 RJL, Akern Bioresearch, Florence, Italy) [44, 45] with BIATRODES electrodes (Akern Srl; Florence, Italy), according to the standard procedures of the European Society of Parenteral and Enteral Nutrition (ESPEN) [46]. All measurements were performed under strictly standardized conditions by the same certified skilled nutritionist and with the same device to avoid inter-observer and inter-device variability as reported in previous studies [36, 47, 48]. Briefly, the device was routinely checked with resistors and capacitors of known values. Reliability for intraday and interday measurements by the same observer was < 2% for resistance (R), < 2.5% for reactance (Xc), and < 3.3% for R, < 2.8% for Xc, respectively. The coefficients of variation (CVs) of repeated measurements of R and Xc at 50 kHz were determined in 10 females by the same observer: CVs were 1.4% for R and 1.3% for Xc.

Assessment of C-reactive protein concentrations

In a subgroup of participants (n = 207), information on c-reactive protein (CRP) was retrieved from electronic medical records. During each visit, fasting blood samples were collected in the morning (8.00–10.00 a.m.), and stored at − 80 °C until processing. Serum high-sensitivity (hs) CRP concentrations were analyzed by CardioPhase® (Siemens Healthcare Diagnostics, Marburg, Germany), based on particle-enhanced immunonephelometry. The CV of intra-and interassay was < 7%.

Statistical analyses

The data distribution was evaluated by Kolmogorov-Smirnov test and variables not normally distributed were normalized by logarithmic transformation. Skewed variables (waist circumference, R, and muscle mass) were back transformed for presentation in tables and figures. Continuous variables were expressed as mean ± standard deviation (SD) whereas categorical variables were reported as numbers and percentages (%). The effect of MCTs supplementation was evaluated as absolute changes (45 days *minus* baseline). Differences between groups were analyzed by analysis of variance (one-way ANOVA) and post hoc analyses for multiple comparisons (Bonferroni). Differences between categorical variables were assessed by χ^2 (chi-square) test. A logistic regression model was used to estimation of the likelihood of BMI changes of WHO classes with MCTs supplementation. BMI improvement was investigated as a dichotomous variable (yes/no) and no MCTs supplementation was designated as reference for ease of comparability. Estimates of the logistic regression coefficients were reported as odds ratios (OR). The analysis was conducted in six steps: Model 1 not adjusted; Model 2 adjusted for age; Model 3 adjusted for age and body weight at baseline; Model 4: adjusted for age, body weight at baseline, and percentage of fat mass at baseline. A p value < 0.05 was considered significant. Statistical analysis was performed according to standard methods using the Statistical Package for Social Sciences software 26.0 (SPSS/PC; SPSS, Chicago, IL, USA).

Results

A total of 263 participants were included in the analyses, with 83 participants (31.6%) in the control group (VLCKD alone without any integration with MCTs), while 86 participants (32.7%) in the VLCKD + MCTs group, and 94 participants (35.7%) in the VLCKD + earlyMCTs group. All individuals of the three groups were evaluated at baseline and at the 45th day (the end of the active phase of VLCKD). At baseline, the three groups did not differ for demographic and anthropometric features, as well as for body composition (Table 1). Absolute changes after the intervention were reported in Table 2. MCTs supplementation significantly decreased body weight, BMI, and waist circumference as compared to the control group, with a greater effect in the VLCKD + earlyMCTs group ($p < 0.001$). MCTs supplementation significantly also affected body composition (Table 2). A two-fold decrease in fat mass and an increase of muscle mass were observed in the VLCKD + earlyMCTs group as compared to the control group ($p < 0.001$). Fat mass and muscle mass were also different when comparing the two groups with MCTs supplementation. Of interest, from baseline, no participant in the three groups changed their physical activity levels during the 45 days of VLCKD ($\chi^2 = 4.22$, $p = 0.121$). All dietary interventions significantly

Table 1 Demographic and anthropometric characteristics, and body composition in the three groups at baseline

Parameters	Control group (n = 83, 31.6%)	VLCKD + MCTs (n = 86, 32.7%)	VLCKD + earlyMCTs (n = 94, 35.7%)	*p* for ANOVA
Age (years)	40.1 ± 15.2	36.8 ± 14.1	35.9 ± 13.1	0.130
Physical activity (yes)	32 (38.6%)	21 (22.3%)	33 (38.4%)	$\chi^2 = 4.22$, $p = 0.121$
Body weight (kg)	92.5 ± 14.9	98.5 ± 16.5	95.7 ± 17.5	0.059
BMI (kg/m^2)	35.1 ± 5.1	35.9 ± 5.2	36.0 ± 5.5	0.475
25.0–29.9 kg/m^2	13 (15.7%)	11 (12.8%)	16 (17.0%)	$\chi^2 = 0.64$, $p = 0.725$
30–34.9 kg/m^2	31 (37.3%)	31 (36.0%)	23 (24.5%)	$\chi^2 = 4.16$, $p = 0.125$
35–39.9 kg/m^2	23 (27.7%)	23 (26.7%)	37 (39.4%)	$\chi^2 = 4.14$, $p = 0.126$
≥ 40.0 kg/m^2	16 (19.3%)	21 (24.4%)	18 (19.1%)	$\chi^2 = 0.95$, $p = 0.622$
Waist circumference (cm)	106.3 ± 13.7	105.8 ± 15.6	102.2 ± 16.4	0.147
R (Ω)	481.6 ± 68.6	467.9 ± 68.1	483.8 ± 80.5	0.296
Xc (Ω)	47.6 ± 9.8	45.9 ± 8.8	45.3 ± 9.4	0.245
FM (%)	41.6 ± 6.4	42.4 ± 7.3	43.0 ± 7.1	0.403
Muscle mass (%)	27.2 ± 4.3	27.8 ± 5.4	26.8 ± 4.8	0.390

Data are expressed as mean ± SD or n (%). One-way ANOVA and post hoc test for multiple comparisons (Bonferroni) and χ^2 (chi-square) test

VLCKD Very low-calorie ketogenic diet, *MCTs* Medium chain fatty acids, *BMI* body mass index, *R* resistance, *Xc* reactance, *FM* fat mass

Table 2 Absolute changes in anthropometric characteristics and body composition in the three groups

Parameters	Control group (n = 83, 31.6%)	VLCKD + MCTs (n = 86, 32.7%)	VLCKD + earlyMCTs (n = 94, 35.7%)	*p* for ANOVA
Body weight (kg)	− 4.8 ± 2.64	− 7.2 ± 1.9[a]	− 8.8 ± 2.9[a,b]	**< 0.001**
BMI (kg/m^2)	− 1.8 ± 0.9	− 2.6 ± 0.6[a]	− 3.3 ± 1.1[a,b]	**< 0.001**
18.5–24.9 kg/m^2	2 (2.4%)	2 (2.3%)	6 (6.4%)	$\chi^2 = 2.66$, $p = 0.263$
25.0–29.9 kg/m^2	23 (27.7%)	25 (29.1%)	24 (25.5%)	$\chi^2 = 0.29$, $p = 0.865$
30–34.9 kg/m^2	28 (33.7%)	26 (30.2%)	35 (37.2%)	$\chi^2 = 0.98$, $p = 0.611$
35–39.9 kg/m^2	24 (28.9%)	24 (27.9%)	19 (20.2%)	$\chi^2 = 2.16$, $p = 0.340$
≥ 40.0 kg/m^2	6 (7.2%)	9 (10.5%)	10 (10.6%)	$\chi^2 = 0.73$, $p = 0.693$
Waist circumference (cm)	− 4.4 ± 5.7	− 7.3 ± 5.4[a]	− 8.1 ± 4.9[a]	**< 0.001**
R (Ω)	6.1 ± 36.4	8.9 ± 30.7	− 1.1 ± 49.5	0.227
Xc (Ω)	2.8 ± 6.4	3.8 ± 5.4	5.0 ± 6.7	0.059
FM (%)	− 2.5 ± 2.7	− 3.7 ± 2.6[a]	− 5.1 ± 3.8[a,b]	**< 0.001**
Muscle mass (%)	1.1 ± 2.1	1.8 ± 1.9	2.7 ± 2.6[a,b]	**< 0.001**

Data are expressed as mean ± SD

A *p*-value in bold type denotes a significant difference ($p < 0.05$)

VLCKD Very low-calorie ketogenic diet, *MCTs* Medium chain fatty acids, *BMI* body mass index, *R* resistance, *Xc* reactance, *FM* fat mass

[a] $p < 0.05$ *vs* control; one-way ANOVA and post hoc test for multiple comparisons (Bonferroni)

[b] $p < 0.05$ *vs* VLCKD + MCTs; one-way ANOVA and post hoc test for multiple comparisons (Bonferroni).

decreased the prevalence of higher BMI classes (obesity class III and obesity class III) from baseline to 45 days of VLCKD active phase while lower BMI classes increased (obesity class I, overweight, and normal weight) (Table 2). Although no significant difference was observed ($p = 0.623$), VLCKD + earlyMCTs induced a threefold increase of normal weight participants (n = 6, 6.4%) than the other two dietary interventions (2 participants for both groups) (Table 2).

Inflammatory status was assessed in a subgroup of 207 subjects, being 62 participants in the control group, 67 participants in the VLCKD + MCTs group, and 78 participants in the VLCKD + early MCTs group. Hs-CRP concentrations did not differ among the three groups at baseline (control group: 3.1 ± 2.9 mg/L, VLCKD + MCTs: 2.9 ± 2.6 mg/L, VLCKD + earlyMCTs: 3.7 ± 3.5 mg/L; $p = 0.279$) as well as at 45 days of VLCKD active phase (control group: 1.8 ± 2.3 mg/L, VLCKD + MCTs:

1.5 ± 1.8 mg/L, VLCKD + earlyMCTs: 1.4 ± 1.7 mg/L; $p = 0.530$) (Fig. 1). However, as compared to the control group, CRP concentrations (evaluated as absolute percent change) were significantly lower in both the VLCKD + MCTs group (Δ% = − 22.5 ± 51.2 *vs* − 46.2 ± 25.3; $p = 0.009$), and the VLCKD + earlyMCTs group (Δ% = − 22.5 ± 51.2 *vs* − 45.0 ± 52.4; $p = 0.011$) (Fig. 1).Findings from the logistic regression modeling in the whole population were shown in Table 3.

MCTs supplementation starting at the beginning of the VLCKD active phase (VLCKD + MCTs) did not influence the likelihood to improve BMI classes. As for VLCKD + earlyMCTs intervention, participants presented a high likelihood of improvement of BMI classes

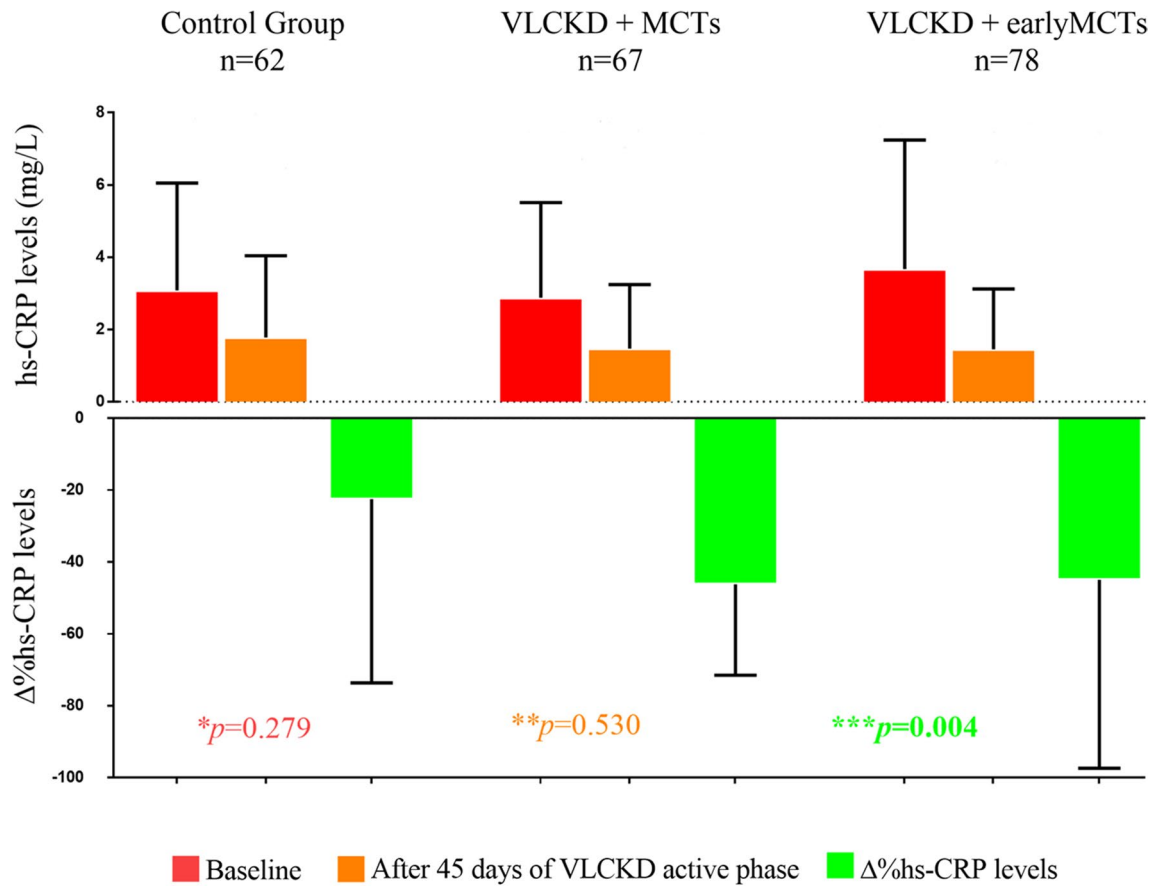


Fig. 1 Changes in hs-CRP concentrations in the three study groups. One-way ANOVA and post hoc test for multiple comparisons (Bonferroni). A *p*-value in bold type denotes a significant difference ($p < 0.05$). * hs-CRP concentrations in the three groups at baseline. ** hs-CRP concentrations in the three groups after 45 days of VLCKD active phase. *** The absolute percent change of hs-CRP concentrations in the three groups

Table 3 Logistic regression analyses on the likelihood of BMI improvement * after MCTs supplementation, adjusted for possible confounders

Intervention	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Control group (no MCTs)	ref	ref	ref	ref
VLCKD + MCTs	1.53 (0.84–2.77) *p*: 0.131	1.59 (0.87–2.91) *p*: 0.162	1.49 (0.83–2.70) *p*: 0.181	1.48 (0.82–2.67) *p*: 0.190
VLCKD + earlyMCTs	1.98 (1.08–3.63) ***p*: 0.028**	1.96 (1.06–3.60) ***p*: 0.031**	1.90 (1.04–3.48) ***p*: 0.037**	1.85 (1.02–3.36) ***p*: 0.043**

*BMI improvement was evaluated as change of BMI classes according to WHO classification after the intervention. Model 1: unadjusted; Model 2: adjusted for age; Model 3: adjusted for age and body weight at baseline; Model 3: adjusted for age, body weight at baseline, and fat mass at baseline

A *p*-value in bold type denotes a significant difference ($p < 0.05$)

VLCK Very low-calorie ketogenic diet, *MCTs* Medium chain fatty acids, *BMI* body mass index, *OR* odds ratios, *CI* confidence interval

(OR: 1.85, 95% CI 1.02–3.36) also after adjusting for the potential confounding factors (age, body weight at baseline, and fat mass at baseline).

Discussion

The present study showed that individuals undergoing a VLCKD with daily MCTs supplementation (20 g/day) obtained a higher body weight loss than individuals supplied with VLCKD alone. Weight loss translated into a significant reduction in BMI, waist circumference, and fat mass. These effects were greater when MCTs supplementation started 5 days before the beginning of the VLCKD active phase than on the first day of the dietary protocol.

Our results are in line with previous studies focusing on supplementation with MCTs during energy-restricted diets [25, 26]. Indeed, two meta-analyses [25, 26] showed that the isoenergetic substitution of LCTs with MCTs during energy-restricted dietary interventions resulted in a small reduction in body weight (− 0.5 to − 0.7 kg) and waist circumference (− 1.5 to − 1.8 cm) in middle-aged individuals with overweight/obesity. However, when considering studies involving very low-calorie diets (< 800 kcal/day) with MCTs supplementation the mean weight reduction was similar to that observed in our study (on average − 8 kg).

As reported above, MCTs are metabolised differently from LCTs, since they can reach the liver after being absorbed in the intestine and are largely oxidized and not stored [23]. In addition, MCTs have been suggested to increase thermogenesis and reduce fat deposition, thus contributing to weight loss [27, 28]. Indeed, Hill and colleagues [49] demonstrated that MCTs s increased thermogenesis by 50% after a 6 day supplementation. Therefore, this mechanism might explain the greater effect on body weight loss that we observed in the group starting MCTs supplementation prior to the VLCKD.

As for the effect on body composition, MCTs supplementation significantly reduce fat mass whereas muscle mass was increased only in the earlyMCTs group as compared to VLCKD alone.

It is known that during nutritional ketosis, ketone bodies can be used as the main energy source thus limiting protein breakdown for energy purposes [50]. On the other hand, high doses of MCTs have been shown to stimulate lipolysis by increasing lipoprotein lipase activity in animal models [51, 52]. Nevertheless, the mechanisms underlying the effect of MCTs on body composition in humans need further clarification.

In the management of obesity and its metabolic comorbidities, VLCKD has been proposed also to reduce systemic inflammation by virtue of its antioxidant and anti-inflammatory effects [53, 54]. Interestingly, in our study all groups undergoing the VLCKD presented a reduction of CRP concentrations, a well-known marker of inflammation. This result confirms those obtained in previous studies demonstrating the anti-inflammatory effects of the VLCKD in the short [36, 54] and -long-term in individuals with obesity [55]. Indeed, VLCKD has shown to reduce inflammation through several mechanisms, i.e.by inhibiting activation of the nuclear factor kappa-light-chain-enhancer of activated B cells, and the inflammatory nucleotide-binding, leucine-rich-containing family, pyrin domain-containing-3, and inhibiting histone deacetylases [56]. Notably, the earlyMCTs group experienced the greatest reduction as compared to the other groups, likely due to the overflow of ketone bodies [57]. Unfortunately, we did not perform a quantitative measurement of ketone bodies and we were not able to test this hypothesis.

Our study has some strengths and limitations. To the best of our knowledge, this is the first study evaluating the effect of MCTs supplementation in addition to VLCKD in individuals with overweight/obesity. In addition, this study was performed in a large population in a real-life setting.

Weaknesses included the single-centre recruitment with potential selection bias. Nevertheless, to increase the homogeneity of the study population, we included only women to avoid potential gender differences in body composition and CRP concentrations. In addition, we did not evaluate the long-term effect of MCTs supplementation. However, the short study duration increased participants' compliance to the treatment. Finally, we did not analyse other inflammatory markers, but CRP is a reliable inflammatory biomarker in different clinical settings [58].

Another limitation might be the transferability of these results to other populations. Our study focused on young adult women with overweight/obesity. Previous studies reported that MCTs supplementation did not increase ketone bodies in middle-aged and elderly subjects [59]. Therefore, further studies of the ketogenic effect of MCTs in different populations are warranted.

Conclusion

The results of the present study demonstrated for the first time that MCTs supplementation (20 g/day) during the active stage of the VLCKD may be a useful tool to enhance the beneficial effect of VLCKD on the reduction of body weight and fat mass, as well as the improvement of the inflammatory state. In particular, MCTs supplementation 5 days before the beginning of the VLCKD active phase might facilitate the transition into ketosis thus contributing to the effectiveness of the nutritional intervention and enhancing its beneficial effects (Fig. 2). However, further studies extending the observations to

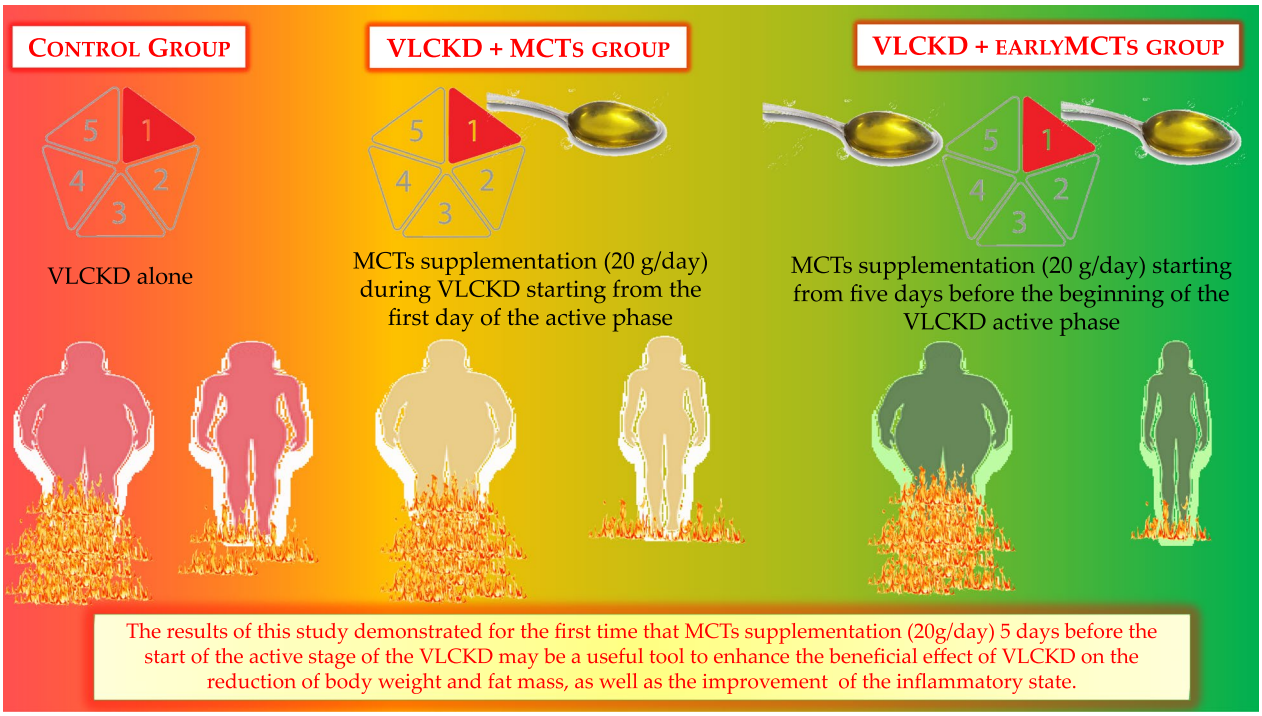


Fig. 2 MCTs supplementation during the active stage of the VLCKD. The MCTs supplementation (20 g/day) 5 days before the beginning of the VLCKD active phase might facilitate the transition into ketosis thus contributing to the effectiveness of the nutritional intervention enhancing its beneficial effects on weight loss, body composition modulation and inflammatory status

subsequent stages of the VLCKD are mandatory. In addition, VLCKD with early MCTs supplementation (5 days before the onset of the active phase) should be compared with other hypocaloric dietary programs to confirm its role in the enhancement of weight loss and reduced inflammation by virtue of the increase of ketosis. Finally, this study underlines the pivotal role of the nutritionist in the management and correct planning of the VLCKD.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
LCTs	Long-chain fatty acids
MCTs	Medium-chain fatty acids
OR	Odds ratio
T2D	Type 2 diabetes mellitus
VLCKD	Very low-calorie ketogenic diet

Acknowledgements
The authors thank the study participants.

Author contributions
LB designed the study. CV and LV provided data collection. CV performed the statistical analysis. CV and LV wrote the manuscript. SS, AC, GM, and LB revised the paper. All authors read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Kanso Company contributed to the payment of open access publication charges for this manuscript. There are no other conflicts of interest to declare.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
The study has been approved by the Local Ethical Committee (n.50/20) and carried out in accordance with the Declaration of Helsinki for experiments that involved humans. The aim of the study was clearly explained to all the study participants and a written informed consent was obtained.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Dipartimento Di Scienze Umanistiche, Centro Direzionale, Università Telematica Pegaso, Via Porzio, Isola F2, 80143 Naples, Italy. [2]Centro Italiano per la cura e il Benessere del paziente con Obesità (C.I.B.O), University of Naples "Federico II", Via Sergio Pansini 5, 80131 Naples, Italy. [3]Department of Clinical Medicine and Surgery, Endocrinology Unit, University of Naples "Federico II", Via Sergio Pansini 5, 80131 Naples, Italy. [4]UNESCO Chair "Education for Health and Sustainable Development", University of Naples "Federico II", Naples, Italy.

Received: 10 November 2022 Accepted: 8 January 2023
Published online: 16 January 2023

References

1. Jastrebof AM, Kotz CM, Kahan S, Kelly AS, Heymsfeld SB. Obesity as a disease: the obesity society 2018 position statement. Obesity. 2019;27:7–9.
2. De Lorenzo A, Gratteri S, Gualtieri P, Cammarano A, Bertucci P, Di Renzo L. Why primary obesity is a disease? J Transl Med. 2019;17:169.
3. Dai H, Alsalhe TA, Chalghaf N, Riccò M, Bragazzi NL, Wu J. The global burden of disease attributable to high body mass index in 195 countries and territories, 1990–2017: an analysis of the global burden of disease study. PLoS Med. 2020;17(7):e1003198. https://doi.org/10.1371/journal.pmed.1003198.
4. Muscogiuri G, Barrea L, Aprano S, Framondi L, Di Matteo R, Laudisio D, Pugliese G, Savastano S, Colao A. On behalf of the opera prevention project sleep quality in obesity: does adherence to the mediterranean diet matter? Nutrients. 2020;12(5):1364. https://doi.org/10.3390/nu12051364.
5. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Ärnlöv J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Fürst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirrakhimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JI, Singh JA, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13–27. https://doi.org/10.1056/NEJMoa1614362.
6. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet. 2020;396(10258):1223–49. https://doi.org/10.1016/S0140-6736(20)30752-2.
7. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380:2095–128. https://doi.org/10.1016/S0140-6736(12)61728-0.
8. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2019;393:1958–72. https://doi.org/10.1016/S0140-6736(19)30041-8.
9. Muscogiuri G, El Ghoch M, Colao A, Hassapidou M, Yumuk V, Busetto L. Obesity management task force (OMTF) of the european association for the study of obesity (EASO) european guidelines for obesity management in adults with a very low-calorie ketogenic diet: a systematic review and meta-analysis. Obes Facts. 2021;14(2):222–45. https://doi.org/10.1159/000515381.
10. Caprio M, Infante M, Moriconi E, Armani A, Fabbri A, Mantovani G, Mariani S, Lubrano C, Poggiogalle E, Migliaccio S, Donini LM, Basciani S, Cignarelli A, Conte E, Ceccarini G, Bogazzi F, Cimino L, Condorelli RA, La Vignera S, Calogero AE, Gambineri A, Vignozzi L, Prodam F, Aimaretti G, Linsalata G, Buralli S, Monzani F, Aversa A, Vettor R, Santini F, Vitti P, Gnessi L, Pagotto U, Giorgino F, Colao A, Lenzi A. Cardiovascular endocrinology club of the Italian society of endocrinology very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian society of endocrinology (SIE). J Endocrinol Invest. 2019;42(11):1365–86. https://doi.org/10.1007/s40618-019-01061-2.
11. Mohammadifard N, Haghighatdoost F, Rahimlou M, Rodrigues APS, Gaskarei MK, Okhovat P, de Oliveira C, Silveira EA, Sarrafzadegan N. The effect of ketogenic diet on shared risk factors of cardiovascular disease and cancer. Nutrients. 2022;14(17):3499. https://doi.org/10.3390/nu14173499.
12. Muscogiuri G, Barrea L, Laudisio D, Pugliese G, Salzano C, Savastano S, Colao A. The management of very low-calorie ketogenic diet in obesity outpatient clinic: a practical guide. J Transl Med. 2019;17(1):356. https://doi.org/10.1186/s12967-019-2104-z.
13. Harvey CJDC, Schofield GM, Williden M. The use of nutritional supplements to induce ketosis and reduce symptoms associated with keto-induction: a narrative review. PeerJ. 2018;6:e4488. https://doi.org/10.7717/peerj.4488.
14. Sukkar SG, Muscaritoli M. A clinical perspective of low carbohydrate ketogenic diets: a narrative review. Front Nutr. 2021;8:642628. https://doi.org/10.3389/fnut.2021.642628.
15. Khabbush A, Orford M, Tsai YC, Rutherford T, O'Donnell M, Eaton S, Heales SJR. Neuronal decanoic acid oxidation is markedly lower than that of octanoic acid: a mechanistic insight into the medium-chain triglyceride ketogenic diet. Epilepsia. 2017;58(8):1423–9. https://doi.org/10.1111/epi.13833.
16. Lin TY, Liu HW, Hung TM. The ketogenic effect of medium-chain triacylglycerides. Front Nutr. 2021;8:747284. https://doi.org/10.3389/fnut.2021.747284.
17. Norgren J, Sindi S, Sandebring-Matton A, Kåreholt I, Daniilidou M, Akenine U, Nordin K, Rosenborg S, Ngandu T, Kivipelto M. Ketosis after intake of coconut oil and caprylic acid-with and without glucose: a cross-over study in healthy older adults. Front Nutr. 2020;15(7):40. https://doi.org/10.3389/fnut.2020.00040.
18. Clegg ME, Golsorkhi M, Henry CJ. Combined medium-chain triglyceride and chilli feeding increases diet-induced thermogenesis in normal-weight humans. Eur J Nutr. 2013;52(6):1579–85. https://doi.org/10.1007/s00394-012-0463-9.
19. Lee YY, Tang TK, Lai OM. Health benefits, enzymatic production, and application of medium-and long-chain triacylglycerol (MLCT) in food industries: a review. J Food Sci. 2012;77(8):R137–44. https://doi.org/10.1111/j.1750-3841.2012.02793.x.
20. Rego Costa AC, Rosado EL, Soares-Mota M. Influence of the dietary intake of medium chain triglycerides on body composition, energy expenditure and satiety: a systematic review. Nutr Hosp. 2012;27(1):103–8. https://doi.org/10.1590/S0212-16112012000100011.
21. Wanten GJ, Naber AH. Cellular and physiological effects of medium-chain triglycerides. Mini Rev Med Chem. 2004;4(8):847–57. https://doi.org/10.2174/1389557043403503.
22. St-Onge MP, Ross R, Parsons WD, Jones PJ. Medium-chain triglycerides increase energy expenditure and decrease adiposity in overweight men. Obes Res. 2003;11(3):395–402. https://doi.org/10.1038/oby.2003.53.
23. Krotkiewski M. Value of VLCD supplementation with medium chain triglycerides. Int J Obes Relat Metab Disord. 2001;25(9):1393–400. https://doi.org/10.1038/sj.ijo.0801682.
24. Harvey CJ, Schofield GM, Williden M, McQuillan JA. The effect of medium chain triglycerides on time to nutritional ketosis and symptoms of keto-induction in healthy adults: a randomised controlled clinical trial. J Nutr Metab. 2018;2018:2630565. https://doi.org/10.1155/2018/2630565.
25. Bueno NB, de Melo IV, Florêncio TT, Sawaya AL. Dietary medium-chain triacylglycerols versus long-chain triacylglycerols for body composition in adults: systematic review and meta-analysis of randomized controlled trials. J Am Coll Nutr. 2015;34(2):175–83. https://doi.org/10.1080/07315724.2013.879844.
26. Mumme K, Stonehouse W. Effects of medium-chain triglycerides on weight loss and body composition: a meta-analysis of randomized controlled trials. J Acad Nutr Diet. 2015;115(2):249–63. https://doi.org/10.1016/j.jand.2014.10.022.
27. Hara T, Kashihara D, Ichimura A, Kimura I, Tsujimoto G, Hirasawa A. Role of free fatty acid receptors in the regulation of energy metabolism. Biochim Biophys Acta. 2014;1841(9):1292–300. https://doi.org/10.1016/j.bbalip.2014.06.002.
28. Swarnamali H, Ranasinghe P, Hills AP, Jayawardena R. Coconut oil consumption and bodyweight reduction: a systematic review and meta-analysis. Minerva Endocrinol. 2021. https://doi.org/10.23736/S2724-6507.21.03654-X.

29. St-Onge MP, Jones PJ. Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. J Nutr. 2002;132(3):329–32. https://doi.org/10.1093/jn/132.3.329.
30. Deemer SE, Plaisance EP, Martins C. Impact of ketosis on appetite regulation-a review. Nutr Res. 2020;77:1–11. https://doi.org/10.1016/j.nutres.2020.02.010.
31. Maher T, Clegg ME. Dietary lipids with potential to affect satiety: mechanisms and evidence. Crit Rev Food Sci Nutr. 2019;59(10):1619–44. https://doi.org/10.1080/10408398.2017.1423277.
32. Courchesne-Loyer A, Fortier M, Tremblay-Mercier J, Chouinard-Watkins R, Roy M, Nugent S, Castellano CA, Cunnane SC. Stimulation of mild, sustained ketonemia by medium-chain triacylglycerols in healthy humans: estimated potential contribution to brain energy metabolism. Nutrition. 2013;29(4):635–40. https://doi.org/10.1016/j.nut.2012.09.009.
33. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE initiative the strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X.
34. Barrea L, Verde L, Vetrani C, Marino F, Aprano S, Savastano S, Colao A, Muscogiuri G. VLCKD: a real time safety study in obesity. J Transl Med. 2022;20(1):23. https://doi.org/10.1186/s12967-021-03221-6.
35. Barrea L, de Alteriis G, Muscogiuri G, Vetrani C, Verde L, Camajani E, Aprano S, Colao A, Savastano S. Impact of a very low-calorie ketogenic diet (VLCKD) on changes in handgrip strength in women with obesity. Nutrients. 2022;14(19):4213. https://doi.org/10.3390/nu14194213.
36. Barrea L, Muscogiuri G, Aprano S, Vetrani C, de Alteriis G, Varcamonti L, Verde L, Colao A, Savastano S. Phase angle as an easy diagnostic tool for the nutritionist in the evaluation of inflammatory changes during the active stage of a very low-calorie ketogenic diet. Int J Obes. 2022;46(9):1591–7. https://doi.org/10.1038/s41366-022-01152-w.
37. Barrea L, Tarantino G, Somma CD, Muscogiuri G, Macchia PE, Falco A, Colao A, Savastano S. Adherence to the mediterranean diet and circulating levels of sirtuin 4 in obese patients: a novel association. Oxid Med Cell Longev. 2017;2017:6101254. https://doi.org/10.1155/2017/6101254.
38. Muscogiuri G, Barrea L, Aprano S, Framondi L, Di Matteo R, Laudisio D, Pugliese G, Savastano S, Colao A. On behalf of the opera prevention project. chronotype and adherence to the mediterranean diet in obesity: results from the opera prevention project. Nutrients. 2020;12(5):1354. https://doi.org/10.3390/nu12051354.
39. Vetrani C, Barrea L, Verde L, Docimo A, Aprano S, Savastano S, Colao A, Muscogiuri G. Vitamin D and chronotype: is there any relationship in individuals with obesity? J Endocrinol Invest. 2022. https://doi.org/10.1007/s40618-022-01973-6.
40. Barrea L, Vetrani C, Altieri B, Verde L, Savastano S, Colao A, Muscogiuri G. The importance of being a 'lark' in post-menopausal women with obesity: a ploy to prevent type 2 diabetes mellitus? Nutrients. 2021;13(11):3762. https://doi.org/10.3390/nu13113762.
41. Barrea L, Verde L, Vetrani C, Savastano S, Colao A, Muscogiuri G. Chronotype: a tool to screen eating habits in polycystic ovary syndrome? Nutrients. 2022;14(5):955. https://doi.org/10.3390/nu14050955.
42. Madden AM, Smith S. Body composition and morphological assessment of nutritional status in adults: a review of anthropometric variables. J Hum Nutr Diet. 2016;29:7–25. https://doi.org/10.1111/jhn.12278.
43. WHO | World Health Organization. Body mass index—BMI n.d. https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi (Accessed July 15 2022).
44. Bioelectrical impedance analysis in body composition measurement. National institutes of health technology assessment conference statement. Am J Clin Nutr. 1996;64(3 Suppl):524S-532S. https://doi.org/10.1093/ajcn/64.3.524S.
45. Bera TK. Bioelectrical impedance methods for noninvasive health monitoring: a review. J Med Eng. 2014;2014:381251. https://doi.org/10.1155/2014/381251.
46. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gómez JM, et al. Bioelectrical impedance analysis—part II: utilization in clinical practice. Clin Nutr. 2004;23(6):1430–53. https://doi.org/10.1016/j.clnu.2004.09.012.
47. Barrea L, Muscogiuri G, Laudisio D, Di Somma C, Salzano C, Pugliese G, de Alteriis G, Colao A, Savastano S. Phase angle: a possible biomarker to quantify inflammation in subjects with obesity and 25(OH)D deficiency. Nutrients. 2019;11(8):1747. https://doi.org/10.3390/nu11081747.
48. Barrea L, Macchia PE, Di Somma C, Napolitano M, Balato A, Falco A, Savanelli MC, Balato N, Colao A, Savastano S. Bioelectrical phase angle and psoriasis: a novel association with psoriasis severity, quality of life and metabolic syndrome. J Transl Med. 2016;14(1):130. https://doi.org/10.1186/s12967-016-0889-6.
49. Hill JO, Peters JC, Yang D, Sharp T, Kaler M, Abumrad NN, Greene HL. Thermogenesis in humans during overfeeding with medium-chain triglycerides. Metabolism. 1989;38(7):641–8. https://doi.org/10.1016/0026-0495(89)90101-7.
50. Manninen AH. Very-low-carbohydrate diets and preservation of muscle mass. Nutr Metab. 2006;3:9. https://doi.org/10.1186/1743-7075-3-9.
51. Miller WC, Bryce GR, Conlee RK. Adaptations to a high-fat diet that increase exercise endurance in male rats. J Appl Physiol Respir Environ Exerc Physiol. 1984;56(1):78–83. https://doi.org/10.1152/jappl.1984.56.1.78.
52. Miyamoto J, Ohue-Kitano R, Mukouyama H, Nishida A, Watanabe K, Igarashi M, Irie J, Tsujimoto G, Satoh-Asahara N, Itoh H, Kimura I. Ketone body receptor GPR43 regulates lipid metabolism under ketogenic conditions. Proc Natl Acad Sci USA. 2019;116(47):23813–21. https://doi.org/10.1073/pnas.1912573116.
53. Forsythe CE, Phinney SD, Fernandez ML, Quann EE, Wood RJ, Bibus DM, Kraemer WJ, Feinman RD, Volek JS. Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. Lipids. 2008;43(1):65–77. https://doi.org/10.1007/s11745-007-3132-7.
54. Monda V, Polito R, Lovino A, Finaldi A, Valenzano A, Nigro E, et al. Short-term physiological effects of a very low-calorie ketogenic diet: effects on adiponectin levels and inflammatory states. Int J Mol Sci. 2020;21(9):3228. https://doi.org/10.3390/ijms21093228.
55. Moreno B, Bellido D, Sajoux I, Goday A, Saavedra D, Crujeiras AB, Casanueva FF. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. Endocrine. 2014;47(3):793–805. https://doi.org/10.1007/s12020-014-0192-3.
56. Barrea L, Caprio M, Watanabe M, Cammarata G, Feraco A, Muscogiuri G, Verde L, Colao A, Savastano S. Could very low-calorie ketogenic diets turn off low grade inflammation in obesity? emerging evidence. Crit Rev Food Sci Nutr. 2022;4:1–17. https://doi.org/10.1080/10408398.2022.2054935.
57. Qi J, Gan L, Fang J, Zhang J, Yu X, Guo H, Cai D, Cui H, Gou L, Deng J, Wang Z, Zuo Z. Beta-hydroxybutyrate: a dual function molecular and immunological barrier function regulator. Front Immunol. 2022;13:805881. https://doi.org/10.3389/fimmu.2022.805881.
58. Nimptsch K, Konigorski S, Pischon T. Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine. Metabolism. 2019;92:61–70. https://doi.org/10.1016/j.metabol.2018.12.006.
59. Freemantle E, Vandal M, Tremblay Mercier J, Plourde M, Poirier J, Cunnane SC. Metabolic response to a ketogenic breakfast in the healthy elderly. J Nutr Health Aging. 2009;13(4):293–8. https://doi.org/10.1007/s12603-009-0026-9.

Publisher's Note

Current Nutrition Reports
https://doi.org/10.1007/s13668-019-00297-x

GASTROENTEROLOGY, CRITICAL CARE, AND LIFESTYLE MEDICINE (SA MCCLAVE, SECTION EDITOR)

Ketogenic Diet: an Endocrinologist Perspective

Aravind Reddy Kuchkuntla[1] · Meera Shah[2] · Saketh Velapati[2] · Victoria M. Gershuni[3] · Tamim Rajjo[1] · Sanjeev Nanda[4] · Ryan T. Hurt[2,4,5] · Manpreet S. Mundi[2]

Abstract

Purpose of Review Obesity and its related comorbidities make up a large part of healthcare expenditures. Despite a wide array of options for treatment of obesity, rates of sustained weight loss continue to be low, leading patients to seek alternative treatment options. Although the first medically utilized ketogenic diet was described nearly 100 years ago, it has made a resurgence as a treatment option for obesity. Despite increased popularity in the lay public and increased use of ketogenic dietary strategies for metabolic therapy, we are still beginning to unravel the metabolic impact of long-term dietary ketosis.

Recent Findings There are a number of recent trials that have highlighted the short- and long-term benefits of ketogenic diet on weight, glycemic control, and other endocrine functions including reproductive hormones.

Summary This review is a summary of available data on the effectiveness and durability of the ketogenic diet when compared to conventional interventions. Ketogenic dietary strategies may play a role in short-term improvement of important metabolic parameters with potential for long-term benefit. However, response may vary due to inter-individual ability to maintain long-term carbohydrate restriction.

Keywords Obesity · Diabetes · Ketogenic diet · Weight loss

Introduction

Obesity is directly associated with multiple co-morbidities, adversely affects disease outcomes, and results in substantially increased health care spending [1, 2]. The global prevalence of obesity has doubled in the last two decades, and recent estimates suggest that over two thirds of the US adult population is overweight (BMI > 25 kg/m2), including the more than one third of Americans that are obese (BMI > 30 kg/m2) [3••, 4].

The pathogenesis of obesity is multifactorial with significant impact from genetic, environmental, and life style factors that contribute to development of a state of neuroendocrine dysregulation in many patients [5–8]. Long-term positive energy balance increases fat storage in adipose tissue and has the potential to elicit a pro-inflammatory physiologic state affecting insulin signaling, thereby creating a state of insulin resistance [9, 10]. Insulin resistance over time leads to changes in metabolic parameters, including increased plasma free fatty acids (FFA), elevated plasma triglycerides, and inflammatory cytokines, as well as atherogenic dyslipidemia (high triglycerides, high LDL-C, and low HDL-C), which contribute to an increased risk of cardiovascular disease and other obesity-related comorbidities [11].

Optimal management of obesity requires a multidisciplinary approach to promote weight loss which can reduce its detrimental health effects [11]. Currently, there are several weight loss approaches available—including commercially available dietary regimens, cognitive behavioral interventions, pharmacological therapies, endoscopic procedures, and surgical interventions [12]. Despite this range of weight loss strategies, less than 20% of individuals who try to lose

✉ Manpreet S. Mundi
Mundi.manpreet@mayo.edu

[1] Department of Family Medicine, Mayo Clinic, Rochester, MN, USA

[2] Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA

[3] Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

[4] Division of General Internal Medicine, Mayo Clinic, Rochester, MN, USA

[5] Division of Gastroenterology, Mayo Clinic, Rochester, MN, USA

Published online: 08 November 2019

weight are able to achieve and maintain a 10% reduction over a year, with the majority gaining it back within 3–5 years [13]. As individuals regain weight, many of the associated comorbidities have the potential to return, leading to a great deal of frustration and feelings of hopelessness. Each of these strategies has different strengths and potential weaknesses; however, it often requires a combination of these approaches to achieve sustained weight reduction. This article will focus on the ketogenic diet as one of these strategies, due to the renewed interest in utilizing a ketogenic dietary approach with its rapid initial weight loss and theoretical potential for improving insulin resistance and metabolic health.

History of Ketogenic Diets

Ketogenic diets (KD) have been used as metabolic therapy for over a hundred years. One of the earliest applications of KD was for the treatment of children with intractable epilepsy; through the production of circulating blood ketones ("ketosis"), a ketogenic diet is able to induce a state similar to prolonged fasting, which leads to a reduction in seizure activity. Initially in 1921, Woodyatt et al. noted that ketone bodies developed either through starvation or a diet containing high ratio of fat to carbohydrates [14]. Building upon previous research, Wilder and Winter reported that a ratio of at least 2:1 of "ketogenic" to glucose molecules was needed to produce significant ketosis and coined the term "ketogenic diet". Their initial paper in 1922 (the year exogenous insulin was first used for treatment of diabetes mellitus (DM)) reported outcomes from 16 patients (3 with epilepsy and 13 with DM) who were placed on a very low carbohydrate diet (average 23.88 g of carbohydrates per day) in a controlled setting with serum and urinary acetone being measured after 3 days. Significant ketogenesis was observed in a majority of the patients [15]. Based on this initial paper, subsequent research observed that the ketogenic diet was as effective as fasting in producing ketosis and could be maintained for a longer period of time.

Following the initial work with ketogenic diet and DM, Wilder and colleagues at the Mayo Clinic began to explore the possibility of its use in intractable epilepsy. They determined that over half the patients had clinical benefit from the diet and three patients who had at least monthly epileptic events had between 8 and 24 months of no seizures. These observations were similar to the pediatric study of 144 children with intractable seizures treated with a ketogenic diet. An estimated 54% of children had seizure activity improved while on the diet. As with adults, dietary compliance in the children was the main cited reason for failure [16].

In 1925, Peterman et al. further defined the original adult 1922 ketogenic diet as being composed of 1 g of protein per kilogram of body weight in children along with 10–15 g of carbohydrates per day [17]. The remainder of the calories were provided as fat. They showed that with good education of patients and caregivers, this diet could be successfully implemented in the outpatient setting. In the early 1900s, prior to the advent of insulin, a very low carbohydrate diet was the preferred therapeutic approach for diabetes in order to keep blood glucose levels low and insulin sensitivity optimized [18]. Although the ketogenic diet continued to be utilized in the 1920s and 1930s for both DM and seizures, the discovery of insulin in 1922 and safe anti-epileptic medications such as phenytoin (1938) decreased the routine clinical use of the ketogenic diet. From the 1960s onwards, very low carbohydrate ketogenic diets (VLCKD) became more commonly known as methods for obesity treatment.

In 1972, Dr. Atkins popularized ketogenic diet with the lay population and described a very low-carbohydrate diet for weight loss based on the principle of promoting ketogenesis. Ketones, predominantly acetoacetate (AcAc) and beta-hydoxybutyrate (BHB), are generated in response to fat oxidation and are able to be utilized as a primary source of fuel rather than glucose [19]. There are several variations of KD described in the literature; a "very-low carbohydrate ketogenic diet" (VLCKD) recommends 20 to 50 g per day or 10% of a 2000 kcal/day diet to achieve a ketogenic state [20]. This is in contrast to the current US dietary guideline recommendation of 45 to 65% of kilocalorie from carbohydrates per day [21, 22]. A "low carbohydrate diet" is defined as < 130 g carbohydrate per day and falls somewhere between the two extremes. The effectiveness of KD for weight loss and other metabolic disorders, including polycystic ovarian disease, diabetes mellitus, and neurologic disorders (epilepsy, Alzheimer's disease, glioblastoma multiforme, etc.), are multifactorial, but appear to be related to the macronutrient composition of the diet that results in induction of circulating ketones with resultant changes in metabolism, the gut microbiome, inflammatory pathways, and cell signaling [23–27].

Despite multiple studies showing benefits of KD for the management of metabolic disorders, there is ongoing debate over the mechanism of weight loss and safety of long-term carbohydrate restriction. We have previously described the evidence behind the Atkins diet [28]. In this review, we will focus on the endocrinological impact of KD, specifically outlining physiologic endocrine changes that may explain its effectiveness and subsequently implications on clinical practice.

Understanding the Ketogenic State

Glucose homeostasis under most circumstances is maintained by the counter-regulatory actions of insulin and glucagon on glucose, amino acid, and fatty acid metabolism. In normal fed conditions, glucose is the primary fuel utilized by tissues, and

a post-prandial rise in glucose stimulates the β-cells of the pancreas to release insulin that mediates cellular uptake of glucose to normalize blood glucose levels and allow glucose to be converted into cellular energy. Once in the cell, glucose can undergo glycolysis for immediate generation of pyruvate and adenosine triphosphate (ATP) [29, 30]. Pyruvate in the presence of oxygen then is transported into the mitochondria and converted into acetyl-CoA, which is able to enter the citric acid cycle for oxidative phosphorylation and generation of ATP via the electron transport chain. During periods of short-term fasting (1–3 days), blood glucose is maintained through the stimulatory actions of glucagon on glycogenolysis (glycogen breakdown) and de novo gluconeogenesis (production of endogenous glucose) [31].

In states of prolonged fasting (> 3 days), the counter-regulatory actions of glucagon, epinephrine, and cortisol stimulate mobilization of FFA from the stored triglycerides in adipose tissue by their actions on lipoprotein lipase. These FFAs released into circulation undergo β-oxidation in the liver to form acetyl coenzyme A (CoA), which is then able to enter the citric acid cycle for complete metabolism via oxidative phosphorylation [32]. Each 2C fragment released as acetyl-CoA from a fatty acid chain during beta-oxidation is able to be utilized for ATP production. When insulin is low and intracellular ATP is sufficient, these acetyl groups can be converted to ketone bodies (BHB, AcAc, and acetone) for export from the liver [33, 34]. In normal circumstances, ketone bodies are produced in the liver at about 180 g/day providing energy for 2–6% of body needs [35]. Their production increases in response to physiological conditions (2–20 fold normal) such as prolonged fast, exercise, low levels of insulin, pregnancy, and consumption of a very low carbohydrate diet and also in pathological states (> 50-fold normal) such as diabetic ketoacidosis, toxic ketoacidosis, and inborn metabolic errors promoting insulin resistance [35–39]. Ketones produce 31% more energy than glucose per carbon unit and provide up to 30–40% of energy required for body functioning after 3 days of fasting [23, 37].

What Constitutes a Ketogenic Diet?

While a therapeutic level of ketones is essential for increasing seizure threshold in epileptics, it is not essential for KD as a weight loss tool. The plan proposed by Dr. Atkins modified from the 4:1 ratio and focused more on an induction phase with 20 g of carbohydrate to promote ketosis. Once weight loss is achieved, Dr. Atkins recommended increasing carbohydrates by 5 g per day to a maximum of 100 g per day during the maintenance phase. There is inter-individual variation in the ability to maintain ketosis, so the individual dieter needs to monitor their ketones to determine the ultimate carbohydrate threshold that works for maintenance of ketosis in their body [40, 41]. However, other versions of KD limit the threshold to a maximum of 50 g of carbohydrate per day to induce and maintain ketosis. Others recommend a "low-carbohydrate" diet containing between 50 and 150 g per day of carbohydrate, with limited starches and sugar [42]. Protein recommendations remain between 1 and 1.5 g/kg per day to maintain positive nitrogen balance and lean muscle mass [43, 44]. Of note, certain amino acids can be used as a precursor for de novo gluconeogenesis, so some people may have difficulty maintaining ketosis if their protein levels exceed these recommendations. The protein recommendations of KD are in accordance with the US dietary guidelines of 0.8–1.2 g/kg per day.

Mechanisms for Effectiveness of Ketogenic Diet

The carbohydrate-insulin model of obesity proposes that in states of excess carbohydrate consumption with subsequent elevations in insulin levels, glucose and fatty acids are driven towards storage rather than utilization, which can result in "internal starvation" indicated by excessive hunger with adaptive lowering of energy expenditure and increased weight gain [45]. This concept of excess energy storage as lipid is supported by increased expression of fatty acid synthase in rats fed high glycemic index foods [46]. The traditional dogma attributed greater weight loss with greater reduction in the number of calories consumed; however, not all dietary calories induce the same metabolic effect, which questions this viewpoint, and a VLCKD is associated with calorie-independent mechanisms that produce a metabolic advantage compared to the standard "calories in, calories out" approach [47, 48]. VLCKD results in a glucagon-dominant physiological state, similar to a state of fasting with high glucagon to insulin ratio that favors glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis [49]. This results in a shift from a glucose-dependent (glucocentric) to a ketone-dependent state (ketocentric) where the primary energy is derived from beta-oxidation of dietary and endogenous fatty acids and ketogenesis/ketolysis [50–52].

Dr. Atkins was the first to postulate the hypothesis of a "metabolic advantage" in which a VLCKD breaks the vicious cycle of glucose dependence and shifts metabolism toward a keto-centric state. He also postulated that significant amounts of fats could be consumed without much weight gain as long as insulin levels remain low in accordance with low carbohydrate consumption [40, 53]. The proposed mechanism on the effectiveness of KD is maintenance of resting energy expenditure and lean muscle mass, high fat mass loss, and increased fat oxidation rate compared to iso-caloric high carbohydrate diets [54]. Consistent with this hypothesis, small controlled feeding and metabolic chamber studies in humans have reported increased resting energy expenditures and higher

sleeping energy expenditure in patients on a very low carb, high-fat diet compared to iso-caloric high carbohydrate, low-fat diets [48, 55].

Based on the available evidence, a recent randomized trial was conducted in 164 individuals with a BMI greater than 25 kg/m^2 to evaluate the changes in energy expenditure on low carbohydrate diet [56••]. After an initial phase with a 60% calorie-restricted diet (45% CHO, 30% fat, and 25% protein) that resulted in 12% weight loss, individuals were randomized to one of three isonitrogenous intervention arms stratified by carbohydrate content (60% vs 40% vs 20%). The diets were kept iso-caloric with reductions in carbohydrates balanced by increasing calories from fat. After 20 weeks on the assigned diet, total energy expenditure increased significantly (52 kcal/day; 95% CI 23 to 82 kcal/day) with every 10% reduction in carbohydrate intake. They have also reported significant reductions in ghrelin and leptin on high-fat diet compared to moderate- and low-fat diets.

Effect of Ketogenic Diet on Insulin

Insulin primarily acts via two signaling pathways: the phosphatidylinositol-3-OH kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathway. Activation of PI3K pathway increases the glucose uptake by translocating the GLUT 4 transporter to the cell surface, inhibiting lipolysis and promoting glycogen synthesis in the muscle and liver, and inhibiting gluconeogenesis (by reducing production of hepatic acetyl CoA). The MAPK pathway primarily promotes differentiation of pre-adipocytes to adipocytes in the adipose tissue to store triglyceride as fat droplets. Therefore, defects in any of the described cellular pathways results in impaired glucose disposal resulting in insulin resistance. It is important to understand the role of increased adipose tissue and insulin resistance to comprehend the effectiveness of KD [57, 58].

Metabolic changes contributing to the development of insulin resistance is complex, and a complete review of the topic is beyond the scope of this paper. In brief, increased adipose tissue results in excess amounts of FFA due to a combination of poor responsiveness of adipose tissue to anti-lipolytic action of insulin and reduced utilization of fatty acids in the peripheral tissues as a result of poor lipoprotein lipase expression. The increased FFAs released from adipose tissue along with increased myo-cellular adipose deposition promote insulin resistance by (1) affecting cellular uptake of glucose; (2) preventing cellular utilization of glucose and fatty acids [59, 60]; (3) reducing glycogen synthesis by serial inhibition of hexokinase II, pyruvate dehydrogenase, and phosphofructokinase [61]; and (4) increasing expression of enzymes involved in gluconeogenesis [62]. Excess FFA levels are seen especially in individuals with central obesity as visceral adipose tissue is less responsive to anti-lipolytic activity of insulin releasing large amounts of FFA into the portal circulation, which results in insulin resistance in the liver followed by resistance in the peripheral tissues [63–65]. Adipose tissue is also a very active endocrine organ with adipocytes secreting several chemical mediators ("adipokines") that regulate energy homeostasis and inflammation. Increases in adipose tissue may result in excess pro-inflammatory chemokines and cytokines that increase recruitment of macrophages into the adipose tissue promoting inflammation, thereby causing insulin resistance and also increase expression of enzymes coding for gluconeogenesis causing hyperglycemia [66]. KD not only decreases postprandial insulin secretion, but it also reverses insulin resistance by inducing weight loss and fat mass loss thereby helping restore the functionality of insulin.

Changes in Short-Term Insulin Release

The reduction of fasting insulin levels is profound in the early phases of KD initiation; in addition to decreased insulin requirements in response to VLCKD, changes in insulin are also related to weight loss. In a 6-week study evaluating the effects of low carbohydrate diets in healthy volunteers, 12 were transitioned to a KD and 8 continued on the regular diet as controls. At the end of 12-week period, there was significant reduction in body mass and fat mass from baseline at 3 weeks and 6 weeks in the KD arm compared to the control. On comparing the fasting hormonal levels from baseline, there was a significant reduction in the insulin concentration from baseline to 3 weeks (− 19.4%) and 6 weeks (− 34.2%). The changes in insulin concentration were directly co-related to the changes in body composition and more specifically to the reduction in total fat mass and percent fat mass. The authors concluded that the endocrine adaption to low carbohydrate diet especially the significant reduction in insulin mediated the accelerated short-term weight and fat loss with KD [67••].

In a subsequent 12-week study of 178 men evaluated for effects of carbohydrate restriction on atherogenic dyslipidemia, the low carbohydrate group (26% of total energy from carbohydrates with low saturated fat) demonstrated significant improvements ApoB and improved LDL particle peak diameter with reduction in small dense LDL (that increase risk of residual cardiovascular risk) [68]. The benefits are associated with the weight loss from carbohydrate restriction and are lost with subsequent weight regain after dietary carbohydrate intake increases. Like all dietary regimens, the biggest challenge with maintaining metabolic improvements is long-term adherence to the diet.

Ketogenic Diet and Long-Term Glycemic Control

Over the last few years, there has been an increasing emphasis on investigating diets with different macro-nutrient

composition for sustainable weight loss. Atkins diet, Zone diet, Dean Ornish diet, and Mediterranean diet have been compared head to head in several clinical RCTs. Clinical trials and meta-analysis have reported a greater weight loss with KD on comparing other diets that were iso-caloric but differed in the macronutrient composition [69]. Weight loss has been shown to reduce insulin levels and improve insulin resistance. In a clinical trial comparing KD vs low-fat diet (LFD) in 132 severely obese patients, weight loss was significantly greater with KD at 6 months along with a reduction in triglycerides [70••]. The mean fasting glucose levels reduced significantly by − 9 ± 19% with KD compared to the other groups, and the reduction was greater in diabetic patients. Insulin sensitivity in non-diabetic patients was significantly greater in the KD group compared to LFD (6 ± 9% vs − 3 ± 8%; $P = 0.01$).

In a 1-year study that compared four diets ($n = 160$; 40 participants per group) (Atkins diet, Zone diet, Dean Ornish diet, and Mediterranean diet), mean weight loss was greater with KD (2.1 ± 4.8 kg) and the effects were more profound in those who completed the trial [71••]. In this study, insulin levels in all four groups were significantly reduced at 2 months (− 6.5 ± 15μIU/mL), but the reductions were not sustained at 6 months nor at 1 year suggesting that the change in insulin is correlated to the amount of weight loss. In another 48-month randomized controlled trial by Shai et al. in 322 moderately obese individuals, mean weight loss was greater in the KD group (4.7 kg) compared to Mediterranean (4.4 kg) and low-fat diet (2.9 kg) with greater reductions in completers [72••]. At 48 months, insulin levels significantly reduced in all the 3 groups in both diabetic and non-diabetic individuals from the baseline, but the reduction in HbA1c from baseline in diabetics was significant only within the KD group (0.9 ± 0.8%; $P < 0.05$). Interestingly, a significant improvement in insulin resistance that was reported as reduction in HOMA-IR at 24 months was observed in the Mediterranean diet group. The findings from the study suggest a short-term improvement in insulin levels and insulin resistance, but the weight regain associated with poor compliance of KD attenuates the beneficial effects in the long term [72••].

Glycemic Control with Ketogenic diet in Type 2 Diabetes Mellitus

KD results in improvement in insulin sensitivity with reduced insulin levels needed for improved glycemic control as observed in lowering of HbA1c levels [73]. In a 24-week randomized controlled study of 84 obese diabetic individuals, KD showed greater improvement in the HbA1c (− 1.5% vs − 0.5%, $P = 0.03$) along with a reduction/elimination in the use of diabetic medications (20 out of 21 individuals) compared to a calorie-restricted moderate carbohydrate diet (40–50% carbohydrates) [74]. Within the KD group, significant improvements in metabolic parameters were also reported; however, the differences did not reach significance when compared between the groups. In a 24-week study comparing KD ($n = 220$) vs low-calorie diet (LCD) (2200 calories/day) ($n = 143$), 75 participants (35.5%) in KD and 24 in LCD (16.8%) had type 2 diabetes mellitus (T2DM). On comparing the effectiveness of KD on blood glucose and HbA1c in individuals with T2DM, the reductions were significant in the KD group [75]. Yancy et al. reported similar reductions in a 16-week pilot study of 28 overweight individuals [76]. HbA1c was reduced by 16% in the KD group from baseline (7.5 ± 1.4% to 6.3 ± 1.0% ($P < 0.001$)) concurrent with a significant reduction in the use of diabetic medications with complete discontinuation of hypoglycemics in 7 participants along with dose reductions in 10 other participants. Importantly, this study highlighted that the reduction in weight from baseline was not a predictor or entirely necessary for improvement in glycemic status.

These short-term trials showing the potential for KD to improve glycemic control were analyzed in a meta-analysis of 9 randomized controlled trials with a follow-up range between 2 and 24 months. A significant reduction in HbA1c was observed in the KD group [77••]. In a subsequent meta-analysis that included 18 studies with a patient population of 2204 individuals, 7 studies were included that evaluated for the effect of KD on HbA1c change [78]. They have reported a significant reduction in HbA1c at 1 year with estimated effect of − 0.28% (95% CI − 0.53 to − 0.02, $P = 0.03$). The HbA1c reduction was correlated to dietary adherence; however, the authors note that 15 out of 18 studies had high risk of bias.

The effectiveness of KD to improve glycemic control has been consistent in the short-term, but its effectiveness for long-term use has been inconsistent. In a 1-year RCT of 105 diabetic patients comparing KD vs low-fat diet, there was no significant reduction in HbA1c at 1 year [79••]. A reduction was observed during the initial 3 months of the study, and it was positively correlated to the baseline HbA1c values. However, the reduction in the HbA1c was not sustained in the long term due to poor adherence. Similar observations of initial short-term success followed by long-term failure was demonstrated in a non-blinded randomized trial comparing KD vs low-fat diet in 61 diabetic individuals. The reductions in HbA1c in the KD group at 6 months were greater compared to baseline (− 4.8 ± 8.3 mmol/mol, $P = 0.004$), but the change at 12 months was not sustained and insignificant at the end of the study period comparing to baseline (− 2.2 ± 7.7 mmol/mol, $P = 0.12$) [80]. KD use in diabetic patients can be beneficial; however, the factor limiting the KDs potential is poor adherence with individuals reverting to consuming food with high carbohydrate content. Also, other concerns for KD use in patients with diabetes are the need for dose adjustment of hypoglycemic medications immediately after initiation of KD, potential for hypoglycemia if medications are not titrated appropriately, life-threatening ketoacidosis, and KD effects on renal function [81–83].

Effect of Ketogenic Diet on Reproductive Hormones

Being obese or overweight may negatively impact reproductive health in women by predisposing them to developing of polycystic ovarian syndrome (PCOS) or infertility. In addition, obesity in pregnant women is an independent risk factor for obstetric and neonatal complications as well. Weight loss has been proven to improve fertility, increase probability of ovulation, improve success of assisted reproductive techniques, and reduce complications of pregnancy [84, 85]. A meta-analysis of 7 studies evaluating the effect of low carbohydrate diet (not typical KD) in infertile women reported that energy restriction and the resultant weight loss reduces the levels of testosterone and resets the hormonal equilibrium thereby enhancing the chances of ovulation and pregnancy [86].

PCOS is common in young women and is generally associated with obesity, hyperinsulinemia, and insulin resistance [87]. Insulin resistance and hyperinsulinemia increase free androgen as a result of increased androgen secretion from the ovary and a reduced circulating sex hormone-binding globulin. In such patients, dietary modification and weight loss are recommended as the first line of treatment. KD's potential to induce weight loss and insulin resistance and lowering androgen levels may result in clinical improvement [88]. In a 24-week pilot study of 11 women diagnosed with PCOS, KD has shown significant improvement of the endocrine changes associated with PCOS. In the women who completed the 24-week study period, significant improvements from baseline were seen in the levels of free testosterone (mean percent change = − 30%, $P = 0.04$) and LH/FSH ratio (mean percent change (− 36%, $P = 0.03$) suggesting a reversal of increased androgen secretion and endocrine normalization respectively [89]. A significant reduction in fasting serum glucose and insulin were reported in these patients suggestive of improved insulin resistance. Along with improvements in the biochemistry profile, significant clinical improvement in hirsutism, infertility, and menstruation was also reported.

Effect on Testosterone

Apart from the study of weight loss and other therapeutic applications in obesity and diabetes, the role of KD in the performance and body composition changes has been investigated in athletes, endurance trainers, and cyclists. The results from the studies are inconsistent; however, the benefits could be possibly from keto adaption and an increased rate of fat β-oxidation in muscle mitochondria [90–92]. As testosterone is synthesized from cholesterol, it can be assumed that KD could increase total testosterone levels due to its higher cholesterol content compared to a typical western diet. The only study conducted in recent times reported the hormonal effect of KD on testosterone in resistance training males [93]. In this study, 25 men were assigned to either KD or western diet for 10 weeks followed by a week of carbohydrate re-introduction. At the end of the study, significant improvements in lean body mass and fat mass were reported in both the groups. In terms of total testosterone levels, significant increase in total testosterone from baseline was observed in the KD group compared to the western diet group (118 ng/dL vs − 36 ng/dL) possibly explaining the effects in testosterone due to increased cholesterol intake. However, this evidence is inconclusive leaving several questions to be addressed [94]. In another study of 12 healthy volunteers, low carbohydrate diet did not show any significant changes in testosterone or sex hormone-binding globulin suggesting that KD might have a minimal effect on testosterone [67••].

Effect of Ketogenic Diet on Thyroid Hormones

As described earlier, KD diet mimics a state of starvation changing the metabolism from an anabolic state that is insulin dominant to a catabolic state favoring a predominant glucagon state. This switch affects the thyroid hormone status as its functioning correlates with body weight, lean mass, and dietary carbohydrate content [95]. In general, high carbohydrate diets are associated with higher serum T3 concentrations compared to diet low in carbohydrate content. KD, similar to fasting, significantly reduces the levels of serum T3 levels along with a concomitant increase in reverse-T3, and these changes are correlated to the presence of ketone bodies [96–98]. In a 56-week study of 12 healthy volunteers on low carbohydrate diet, significant increases in total T4 (59.2 ± 11.2 nmol/L vs 66.4 ± 12.2 nmol/L) and free T4 index (19.2 ± 3.4 vs 21.6 ± 4.6) were reported compared to the baseline. Caution should be taken when interpreting the increased T4 as the investigators did not measure free fractions of T3 and T4 [67••]. KD is also a long-term therapeutic option for pediatric patients with intractable drug-resistant epilepsy, and in such patients, due to the lower peripheral conversion of T4 to T3, it predisposes children to develop hypothyroidism. A study reported the risk of hypothyroidism in such patients with long-term use of KD. Hypothyroidism was diagnosed in 20/120 patients during the first year of treatment requiring levothyroxine supplementation [99••]. The literature investigating the effects of KD on thyroid function status are limited; however, there is an ongoing randomized trial evaluating the effects of KD and high carbohydrate diet on sleep and thyroid function which will provide a better insight into thyroid hormone changes with KD [100].

Conclusions

The physiology behind a diet that induces ketosis is compelling and has led to much interest in the use of a ketogenic diet in weight loss, management of diabetes, and treatment of other endocrine disorders. Although almost always favorable initially, improvements in metabolic parameters are difficult to sustain in the long term because of challenges in adhering to such a restricted diet. The long-term safety of such diets is also unknown. In conclusion, the ketogenic diet has shown short-term benefit for weight loss and improvements in diabetes control when done under supervised conditions, and may be an appropriate strategy for some patients.

Author Contributions Manpreet Mundi and Ryan Hurt formulated an outline of the manuscript. Aravind Kuchkuntla created the first draft. Manpreet Mundi, Meera Shah, Aravind Kuchkuntla, Saketh Velapati, Victoria Gershuni, Tamim Rajjo, Sanjeev Nanda, and Ryan Hurt critically revised the manuscript. All authors agree to be responsible for its content.

Compliance with Ethical Standards

Conflict of Interest Aravind Reddy Kuchkuntla declares that he has no conflict of interest.

Meera Shah declares that she has no conflict of interest.

Saketh Velapati declares that he has no conflict of interest.

Victoria M. Gershuni declares that she has no conflict of interest.

Tamim Rajjo declares that he has no conflict of interest.

Sanjeev Nanda declares that he has no conflict of interest.

Ryan T. Hurt has served as a consultant for Nestlé.

Manpreet S. Mundi has received research funding from Fresenius Kabi, Nestlé, and Real Food Blends.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Biener, A., J. Cawley, and C. Meyerhoefer, The high and rising costs of obesity to the US health care system. 2017, Springer.
2. Ng M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766–81.
3. •• Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13–27 **(A global study showing the impact of obesity in the last 2 decades, reported a two fold increase in obesity from the 1980s)**.
4. Flegal KM, et al. Trends in Obesity Among Adults in the United States, 2005 to 2014. Jama. 2016;315(21):2284–91.
5. Bray MS, et al. NIH working group report-using genomic information to guide weight management: from universal to precision treatment. Obesity (Silver Spring). 2016;24(1):14–22.
6. van der Klaauw AA, Farooqi IS. The hunger genes: pathways to obesity. Cell. 2015;161(1):119–32.
7. Church TS, et al. Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. PLoS One. 2011;6(5):e19657.
8. McAllister EJ, et al. Ten putative contributors to the obesity epidemic. Crit Rev Food Sci Nutr. 2009;49(10):868–913.
9. Tchkonia T, et al. Mechanisms and metabolic implications of regional differences among fat depots. Cell Metab. 2013;17(5):644–56.
10. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860.
11. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med. 2017;376(3):254–66.
12. Ryan DH. Guidelines for obesity management. Endocrinol Metab Clin N Am. 2016;45(3):501–10.
13. Velapati SR, et al. Weight regain after bariatric surgery: prevalence, etiology, and treatment. Curr Nutr Rep. 2018;7(4):329–34.
14. Wheless JW. History of the ketogenic diet. Epilepsia. 2008;49(Suppl 8):3–5.
15. Wilder RM, Winter MD. The threshold of ketogenesis. J Biol Chem. 1922;52(2):393–401.
16. HELMHOLZ HF. The treatment of epilepsy in childhood: five years' experience with the ketogenic diet. JAMA. 1927;88(26):2028–32.
17. Peterman M. The ketogenic diet in epilepsy. J Am Med Assoc. 1925;84(26):1979–83.
18. Westman EC, Yancy WS, Humphreys M. Dietary treatment of diabetes mellitus in the pre-insulin era (1914-1922). Perspect Biol Med. 2006;49(1):77–83 https://muse.jhu.edu/ (accessed June 30, 2019).
19. Atkins RD. *Dr.* Government Institutes: Atkins' new diet revolution; 2002.
20. Feinman RD, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition. 2015;31(1):1–13.
21. Kossoff EH, Dorward JL. The modified Atkins diet. Epilepsia. 2008;49(Suppl 8):37–41.
22. Westman EC, et al. Low-carbohydrate nutrition and metabolism. Am J Clin Nutr. 2007;86(2):276–84.
23. Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. Prostaglandins Leukot Essent Fat Acids. 2004;70(3):309–19.
24. Thomsen HH, et al. Effects of 3-hydroxybutyrate and free fatty acids on muscle protein kinetics and signaling during LPS-induced inflammation in humans: anticatabolic impact of ketone bodies. Am J Clin Nutr. 2018;108(4):857–67.
25. Koppel SJ, Swerdlow RH. Neuroketotherapeutics: a modern review of a century-old therapy. Neurochem Int. 2018;117:114–25.
26. Crawford P. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. Biophys J. 2019;116(3, Supplement 1):2a.
27. Ma D, et al. Ketogenic diet enhances neurovascular function with altered gut microbiome in young healthy mice. Sci Rep. 2018;8(1):6670.
28. Kuchkuntla AR, et al. Fad diets: hype or hope? Curr Nutr Rep. 2018;7(4):310–23.
29. Newsholme EA, Dimitriadis G. Integration of biochemical and physiologic effects of insulin on glucose metabolism. Exp Clin Endocrinol Diabetes. 2001;109(Suppl 2):S122–34.

30. Plum L, Belgardt BF, Brüning JC. Central insulin action in energy and glucose homeostasis. J Clin Invest. 2006;116(7):1761–6.
31. Taborsky GJ Jr. The physiology of glucagon. SAGE Publications. 2010;4(6):1338–44.
32. Xiong J. Fatty acid oxidation in cell fate determination. Trends Biochem Sci. 2018;43(11):854–7.
33. Rui L. Energy metabolism in the liver. Compr Physiol. 2011;4(1): 177–97.
34. Cahill G, et al. Hormone-fuel interrelationships during fasting. J Clin Invest. 1966;45(11):1751–69.
35. VanItallie TB, Nufert TH. Ketones: metabolism's ugly duckling. Nutr Rev. 2003;61(10):327–41.
36. Gupta L, et al. Ketogenic diet in endocrine disorders: current perspectives. J Postgrad Med. 2017;63(4):242–51.
37. Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev. 1999;15(6):412–26.
38. Reichard G, et al. Ketone-body production and oxidation in fasting obese humans. J Clin Invest. 1974;53(2):508–15.
39. Owen OE, et al. Comparative measurements of glucose, beta-hydroxybutyrate, acetoacetate, and insulin in blood and cerebrospinal fluid during starvation. Metabolism. 1974;23(1):7–14.
40. Atkins RC, D.A.D. Revolution. The high calorie way to stay thin forever. New York: McKay Co.; 1972.
41. Atkins, R.C., Dr. Atkins' diet revolution. 1981: Bantam Books New York.
42. Heinbecker P. Studies on the metabolism. J Biol Chem. 1928;80: 461–75.
43. Jungas RL, Halperin ML, Brosnan JT. Quantitative analysis of amino acid oxidation and related gluconeogenesis in humans. Physiol Rev. 1992;72(2):419–48.
44. Volek JS, et al. Body composition and hormonal responses to a carbohydrate-restricted diet. Metab-Clin Exp. 2002;51(7):864–70.
45. Ludwig DS, Friedman MI. Increasing adiposity: consequence or cause of overeating? Jama. 2014;311(21):2167–8.
46. Kabir M, et al. A high glycemic index starch diet affects lipid storage–related enzymes in normal and to a lesser extent in diabetic rats. J Nutr. 1998;128(11):1878–83.
47. Hall KD. A review of the carbohydrate-insulin model of obesity. Eur J Clin Nutr. 2017;71(3):323–6.
48. Howell S, Kones R. "Calories in, calories out" and macronutrient intake: the hope, hype, and science of calories. Am J Physiol Endocrinol Metab. 2017;313(5):E608–e612.
49. Klein S, Wolfe RR. Carbohydrate restriction regulates the adaptive response to fasting. Am J Phys. 1992;262(5 Pt 1):E631–6.
50. Cox PJ, et al. Nutritional ketosis alters fuel preference and thereby endurance performance in athletes. Cell Metab. 2016;24(2):256–68.
51. Goedecke JH, et al. Metabolic adaptations to a high-fat diet in endurance cyclists. Metabolism. 1999;48(12):1509–17.
52. Westman EC, et al. A review of low-carbohydrate ketogenic diets. Curr Atheroscler Rep. 2003;5(6):476–83.
53. Kuchkuntla AR, et al. Fad diets: hype or hope? Current nutrition reports. 2018;7(4):310–23.
54. Ebbeling CB, et al. Effects of dietary composition on energy expenditure during weight-loss maintenance. Jama. 2012;307(24): 2627–34.
55. Hall KD, et al. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men, 2. Am J Clin Nutr. 2016;104(2):324–33.
56.•• Ebbeling CB, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. BMJ. 2018;363:k4583 **(An important study evaluating the physiological changes with weight loss on Ketogenic diet focussing on energy expenditure).**
57. Cheatham B, Kahn CR. Insulin action and the insulin signaling network*. Endocr Rev. 1995;16(2):117–42.
58. Smith U, et al. Insulin signaling and action in fat cells: associations with insulin resistance and type 2 diabetes. Ann N Y Acad Sci. 1999;892(1):119–26.
59. Kelley DE, et al. The effect of non-insulin-dependent diabetes mellitus and obesity on glucose transport and phosphorylation in skeletal muscle. J Clin Invest. 1996;97(12):2705–13.
60. Rothman DL, et al. Decreased muscle glucose transport/phosphorylation is an early defect in the pathogenesis of non-insulin-dependent diabetes mellitus. Proc Natl Acad Sci. 1995;92(4):983–7.
61. Shulman GI, et al. Quantitation of muscle glycogen synthesis in normal subjects and subjects with non-insulin-dependent diabetes by 13C nuclear magnetic resonance spectroscopy. N Engl J Med. 1990;322(4):223–8.
62. Yang Q, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature. 2005;436(7049):356.
63. Perseghin G, et al. Intramyocellular triglyceride content is a determinant of in vivo insulin resistance in humans: a 1H-13C nuclear magnetic resonance spectroscopy assessment in offspring of type 2 diabetic parents. Diabetes. 1999;48(8):1600–6.
64. Roden M, et al. Mechanism of free fatty acid-induced insulin resistance in humans. J Clin Invest. 1996;97(12):2859–65.
65. Carey DG, et al. Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. Diabetes. 1996;45(5):633–8.
66. Jung U, Choi M-S. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014;15(4):6184–223.
67.•• Volek JS, et al. Body composition and hormonal responses to a carbohydrate-restricted diet. Metabolism. 2002;51(7):864–70 (A key study that evaluated the effects of KD on endocrine changes).
68. Krauss RM, et al. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr. 2006;83(5):1025–31 quiz 1205.
69. Hu T, et al. Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. Am J Epidemiol. 2012;176(Suppl 7):S44–54.
70.•• Samaha FF, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med. 2003;348(21):2074–81 **(One of the earliest RCTs comparing the KD vs Low fat diet, showing the weight loss potential of KD).**
71.•• Dansinger ML, et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. JAMA. 2005;293(1):43–53 **(A key landmark study comparing the metabolic effects and weight loss potentials of different diets).**
72.•• Shai I, et al. Weight loss with a low-carbohydrate, mediterranean, or low-fat diet. N Engl J Med. 2008;359(3):229–41 **(One of the long term RCTs comparing the effectiveness of different diets and their implications into clinical practice).**
73. Abbasi J. Interest in the ketogenic diet grows for weight loss and type 2 diabetes. Jama. 2018;319(3):215–7.
74. Westman EC, et al. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr Metab. 2008;5(1):36.
75. Hussain TA, et al. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Nutrition. 2012;28(10):1016–21.
76. Yancy WS, et al. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. Nutr Metab. 2005;2(1):34.

77.•• Meng Y, et al. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: a systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract. 2017;131:124–31 **(Systematic review of 7 RCTs evaluating the effectiveness of KD in T2DM).**
78. Huntriss R, Campbell M, Bedwell C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr. 2018;72(3):311–25.
79.•• Davis NJ, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. Diabetes Care. 2009;32(7):1147–52 **(An important RCT showing the short-term benefits of KD in glycemic control).**
80. Guldbrand H, et al. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. Diabetologia. 2012;55(8):2118–27.
81. Oyabu C, et al. Impact of low-carbohydrate diet on renal function: a meta-analysis of over 1000 individuals from nine randomised controlled trials. Br J Nutr. 2016;116(4):632–8.
82. Bonikowska K, Magnusson P, Sjoholm A. Life-threatening ketoacidosis in patients with type 2 diabetes on LCHF diet. Lakartidningen. 2018;115:E4AD.
83. Clifton PM, Condo D, Keogh JB. Long term weight maintenance after advice to consume low carbohydrate, higher protein diets–a systematic review and meta analysis. Nutr Metab Cardiovasc Dis. 2014;24(3):224–35.
84. Sim KA, et al. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. Clin Obes. 2014;4(2):61–8.
85. Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. Obes Rev. 2014;15(10):839–50.
86. McGrice M, Porter J. The effect of low carbohydrate diets on fertility hormones and outcomes in overweight and obese women: a systematic review. Nutrients. 2017;9(3):204.
87. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med. 2005;352(12):1223–36.
88. Moran LJ, et al. Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. J Acad Nutr Diet. 2013;113(4):520–45.
89. Mavropoulos JC, et al. The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. Nutr Metab. 2005;2(1):35.
90. Volek JS, et al. Metabolic characteristics of keto-adapted ultra-endurance runners. Metabolism. 2016;65(3):100–10.
91. Urbain P, et al. Impact of a 6-week non-energy-restricted ketogenic diet on physical fitness, body composition and biochemical parameters in healthy adults. Nutr Metab. 2017;14(1):17.
92. Paoli A, et al. Ketogenic diet does not affect strength performance in elite artistic gymnasts. J Int Soc Sports Nutr. 2012;9(1):34.
93. Wilson JM, et al., The effects of ketogenic dieting on body composition, strength, power, and hormonal profiles in resistance training males. J Strength Cond Res, 2017.
94. Santos HO. Ketogenic diet and testosterone increase: is the increased cholesterol intake responsible? To what extent and under what circumstances can there be benefits? Hormones (Athens). 2017;16(3):266–70.
95. Kopp W. Nutrition, evolution and thyroid hormone levels - a link to iodine deficiency disorders? Med Hypotheses. 2004;62(6):871–5.
96. Pasquali R, et al. Relationships between iodothyronine peripheral metabolism and ketone bodies during hypocaloric dietary manipulations. J Endocrinol Investig. 1983;6(2):81–9.
97. Reinhardt W, et al. Effect of small doses of iodine on thyroid function during caloric restriction in normal subjects. Horm Res. 1993;39(3-4):132–7.
98. Serog P, et al. Effects of slimming and composition of diets on VO2 and thyroid hormones in healthy subjects. Am J Clin Nutr. 1982;35(1):24–35.
99.•• Kose E, et al. Changes of thyroid hormonal status in patients receiving ketogenic diet due to intractable epilepsy. J Pediatr Endocrinol Metab. 2017;30(4):411–6 **(Pediatric study that has reported a risk of hypothyroidism with long-term use of KD).**
100. Iacovides S, Meiring RM. The effect of a ketogenic diet versus a high-carbohydrate, low-fat diet on sleep, cognition, thyroid function, and cardiovascular health independent of weight loss: study protocol for a randomized controlled trial. Trials. 2018;19(1):62.