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CONSENSUS STATEMENT

Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

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Abstract

Background Weight loss is a milestone in the prevention of chronic diseases associated with high morbility and mortality in industrialized countries. Very-low calorie ketogenic diets (VLCKDs) are increasingly used in clinical practice for weight loss and management of obesity-related comorbidities. Despite evidence on the clinical benefits of VLCKDs is rapidly emerging, some concern still exists about their potential risks and their use in the long-term, due to paucity of clinical studies. Notably, there is an important lack of guidelines on this topic, and the use and implementation of VLCKDs occurs vastly in the absence of clear evidence-based indications.

Purpose We describe here the biochemistry, benefits and risks of VLCKDs, and provide recommendations on the correct use of this therapeutic approach for weight loss and management of metabolic diseases at different stages of life.

Keywords Obesity · Ketone bodies · Weight loss · Cardiovascular risk · Type 2 diabetes · Cardiovascular rehabilitation

Introduction

Over the last decades, the worldwide prevalence of obesity and type 2 diabetes (T2D) has dramatically risen, resulting in a global epidemic [1–3]. Globalization, economic growth, increase in sedentary lifestyle, use of certain drugs, and nutritional transition to high calorie-low fiber diets and processed foods have contributed to this trend [4–6]. Noteworthy, high carbohydrate intake has been recently related to higher risk of total mortality, whereas total fat and specific types of fat have been associated with lower total mortality [7], thus challenging the definition of a healthy diet [8].

Despite great efforts of the scientific and medical communities, prevalence of obesity, T2D, and cardiometabolic diseases is expected to sharply increase within the next years [9–11]. Treatment of obesity and its related comorbidities has, therefore, become one of the most relevant challenges nowadays. Even though several trials of lifestyle modification, pharmacological intervention, and bariatric surgery have shown that weight loss correlates with reduced morbidity [12], most overweight and obese individuals cannot achieve sufficient weight loss or successful long-term weight-loss maintenance [13, 14]. On the other hand, current anti-obesity medications still have some limitations, including need for long-term use, non-trivial costs, and potential poor efficacy and side effects [13, 15]. Bariatric surgery has been shown to provide the highest body weight loss and remission rates of T2D and metabolic syndrome, but it is not devoid of risks and sequelae and cannot be offered to all obese people due to high costs and restricted indications [16]. In this context, the very-low-calorie ketogenic diet (VLCKD) has recently gained growing interest for

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the management of obesity and its comorbidities [17–24]. Ketogenic diets (KDs) are high-fat, adequate-protein, low-carbohydrate diets and have been primarily used to treat refractory epilepsy in children since the 1920s [25]. In the 1970s, the low-carbohydrate high-fat ketogenic diet "Atkins" reached popularity for weight loss [26]. Then, pioneering studies by George Blackburn introduced the concept of "protein-sparing modified fast" (PSMF), a highly restrictive dietary regimen primarily based on the minimum amount of proteins necessary to preserve lean body mass and aiming at achieving a rapid weight loss [27–30], as well as potential additional benefits on blood pressure and serum glucose and lipid levels [31], forming the basis of VLCKD. In our country, a position paper (2014) by the Italian Association of Dietetics and Clinical Nutrition (ADI) has proposed VLCKD as a therapeutic option in different clinical settings, including severe obesity, obesity associated with comorbidities, non-alcoholic fatty liver disease (NAFLD), drug-resistant epilepsy, as well as a useful tool for weight loss before bariatric surgery [32]. In 2016, VLCKD has also been mentioned with similar indications in the standards of care in obesity released by the Italian Society of Obesity (SIO) and ADI itself [33].

VLCKD represents a nutritional intervention that mimics fasting through a marked restriction of daily carbohydrate intake, usually lower than 30 g/day (≃ 13% of total energy intake), with a relative increase in the proportions of fat (≃ 44%) and protein (≃ 43%) and a total daily energy intake < 800 kcal [17–19, 23, 24], depending on the amount and quality of protein preparations. Nonetheless, VLCKD should not be considered as a high-protein diet, since its daily protein intake is approximately 1.2–1.5 g/kg of ideal body weight [18, 24, 34, 35]. VLCKD is based on protein preparations of high biological value derived from green peas, eggs, soy and whey. Each protein preparation is composed by approximately 18 g protein, 4 g carbohydrate, 3 g fat (mainly high-oleic vegetable oils) and provides approximately 100–150 kcal. Therefore, VLCKD is characterized by a low lipid content, mainly deriving from olive oil (≃ 20 g per day). The weight-loss program is structured in different phases. During the first phase (Phase 1), patients are allowed to eat four to six (depending on ideal body weight) of such protein preparations and low-carbohydrate vegetables. In the next phases, the state of ketosis is still maintained, but one (Phase 2) or two (Phase 3) of the provided meals (lunch or/and dinner) are gradually replaced by natural protein meals (meat/fish/eggs/soy). The ketogenic period (Phases 1–3), providing ≃ 600–800 kcal/day, is variable in time and should be prolonged until 80–85% of the desired weight loss is reached. The average length is 8–12 weeks. In the following phases, 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 [24, 36]. The gradual reintroduction of food items allows for a progressive nutritional education that supports long-term weight-loss maintenance. The goal is to achieve a balanced macronutrient composition in the maintenance diet, with a daily calorie intake between 1500 and 2000 kcal, depending on the characteristics of patients. It is essential, during this process, to start a gradual and personalized reintroduction of physical activity. Indeed, VLCKD requires proper medical supervision [17, 37]. Moreover, patients on VLCKD must be closely and periodically monitored through physical examination (anthropometric measurements, blood pressure, heart rate, etc.) and laboratory analysis (Table 1), to prevent dehydration and vitamin/electrolyte abnormalities, which are potentially due to urinary excretion of ketone bodies and poor intake of micronutrients. Hence, proper water intake (at least 2 L of sugarless fluids daily), vitamin/electrolyte and omega-3 polyunsaturated fatty acids supplementation are mandatory, especially during the first phases [36, 37]. Ketone bodies act as powerful anorexigenic agents, reducing cerebral neuropeptide Y, maintaining cholecystokinin (CCK) meal response and decreasing circulating ghrelin. This results in a general reduction of perceived hunger and food intake [38], which is one of the mechanisms accounting for the effectiveness of VLCKD on weight loss, as well as for its tolerability.

This paper reports the current evidence on cardiometabolic benefits of VLCKD in the management of metabolic diseases. On this basis, a Working Group has been generated by the Cardiovascular Endocrinology Club of the Italian Society of Endocrinology to formulate evidence-based recommendations on the use of VLCKD in different clinical settings. We reported the strength of recommendations and the quality of evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. Recommendations are classified into one of two grades (grade 1: strong recommendation; grade 2: weak recommendation), while the quality of the evidence is classified into one of four categories (ØOOO, very low; ØØOO, low; ØØØO, moderate; ØØØØ, high) [39].

Given that updated guidelines for the use of VLCKD in obesity and metabolic diseases are lacking, we summarize the current evidence and main indications for the use of VLCKD in the management of most relevant metabolic disorders, throughout the entire lifespan (Table 2). Due to the complex biochemical implications of VLCKD and the need for a strict therapeutic compliance, contraindications to its use should also be considered (Table 3).

Table 1 Parameters that need to be monitored before, during and at the end of a VLCKD regimen

Parameters	Frequency of monitoring	Rationale of monitoring
Complete blood count	At baseline and at the end of the VLCKD program	To exclude patients with severe alterations of blood count
Creatinine, BUN, uric acid (serum)	At baseline and during the ketogenic phase	Monitoring of kidney function and potential increase in uric acid
Glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (serum)	At baseline and at the end of the VLCKD program	Excluding patients with uncontrolled diabetes, monitoring of lipid profile
ALT, AST, γ-GT, total and direct bilirubin (serum)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring of liver function and cholestatic parameters
Sodium, potassium, calcium, magnesium, inorganic phosphate (serum)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring for potential dehydration and electrolyte abnormalities
β-Hydroxybutyrate (capillary blood or urine)	During the ketogenic phase	Monitoring of ketosis
TSH, FT4 (serum)	At baseline	To exclude thyroid function abnormalities
25-Hydroxyvitamin D (serum)	At baseline	To treat vitamin D deficiency, if present
Complete urinalysis and microalbuminuria (urine)	At baseline, during the ketogenic phase and at the end of the VLCKD program	To exclude any potential kidney damage
Body composition and hydration status (by bioelectrical impedance analysis)	At baseline, during the ketogenic phase and at the end of the VLCKD program	Monitoring of body composition (fat mass, fat-free mass, body cell mass, total body water, extracellular water)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *FT4* free thyroxine, *γ-GT* gamma-glutamyl transferase, *HDL-cholesterol* high-density lipoprotein cholesterol, *LDL* cholesterol, low-density lipoprotein cholesterol, *TSH* thyroid-stimulating hormone, *VLCKD* very-low-calorie ketogenic diet

Table 2 Indications for the use of VLCKD in metabolic diseases

Strong recommendations	Strength of recommendations and quality of evidence according to GRADE system
Severe obesity	(1 ØØØO)
Management of severe obesity before bariatric surgery	(1 ØØØO)
Sarcopenic obesity	(1 ØØØO)
Obesity associated with type 2 diabetes (preserved beta cell function)	(1 ØØØO)
Obesity associated with hypertriglyceridemia	(1 ØØØO)
Obesity associated with hypertension	(1 ØØØO)
Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet	(1 ØØØO)
Weak recommendations	
Obesity associated with dysbiosis of the gut microbiota	(2 ØØØO)
Obesity associated with high levels of LDL-cholesterol and/or low levels of HDL-cholesterol	(2 ØØØO)
Obesity associated with non-alcoholic fatty liver disease (NAFLD)	(2 ØØØO)
Obesity associated with heart failure (NYHA I–II)	(2 ØOOO)
Obesity associated with atherosclerosis	(2 ØOOO)
Male obesity secondary hypogonadism	(2 ØØØO)
Obesity associated with polycystic ovary syndrome (PCOS)	(2 ØOOO)
Menopausal transition-related obesity	(2 ØOOO)
Neurodegenerative disorders associated with sarcopenic obesity	(2 ØOOO)

Table 3 Absolute contraindications to the use of VLCKD

Absolute contraindications
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 (< 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

Biochemistry of ketone bodies

Ketogenesis

Ketogenesis occurs in hepatocyte mitochondria [40], leading to the production of a group of small, water-soluble organic compounds collectively known as ketone bodies. *D*-3-β-Hydroxybutyrate is the most abundant ketone body in the blood, followed by acetoacetate and acetone [41]. Acetoacetate and *D*-3-β-hydroxybutyrate are organic acids able to diffuse through cell membranes; they dissociate at physiological pH and are filtered/reabsorbed in the kidney. Acetone is a highly fat-soluble, volatile compound slowly excreted via the lungs [42]. Although ketone bodies are produced at a low extent in healthy individuals (daily production is up to 185 g/day), ketogenesis substantially increases under conditions of reduced glucose availability, including fasting, intensive physical activity and VLCKD. Under those circumstances, ketone bodies transfer lipid-derived energy from liver to extrahepatic organs (e.g., heart, kidney, skeletal muscle, central nervous system), acting as an alternative fuel source for peripheral tissues [43, 44]. At a molecular level, ketogenesis is regulated by the availability of acetyl-CoA, a thioester considered as the gatekeeper of mammalian metabolism. Indeed, acetyl-CoA represents the critical link to the tricarboxylic acid (TCA) cycle following glycolysis or β-oxidation of fatty acids. Under physiological conditions, acetyl-CoA condenses with oxaloacetate, a metabolic intermediate derived from pyruvate during glycolysis, thus entering the TCA cycle. However, if blood glucose levels are too low or glycolytic pathway is altered (e.g., fasting, insulin deficiency in diabetes), oxaloacetate is preferentially used for gluconeogenesis [43, 44]. Therefore, acetyl-CoA—primarily derived from β-oxidation of fatty acids, which are transported into mitochondria through carnitine palmitoyltransferase I (CPT1) [41, 45] —cannot enter the TCA cycle and is diverted to ketone bodies formation [43, 44]. β-Ketothiolase catalyzes the condensation of two acetyl-CoA molecules into acetoacetyl-CoA, which is then converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by HMG-CoA synthase in the rate-limiting step of ketogenesis. Importantly, the expression of HMG-CoA synthase is finely regulated by insulin and glucagon in an opposite manner [46]: insulin inhibits its expression through phosphorylation and nuclear export of the transcription factor FOXA2 [47], whereas glucagon stimulates its expression through acetylation of FOXA2 [48]. Hence, adequate production of insulin is important to obtain a fine modulation of physiological ketogenesis. HMG-CoA is then cleaved to acetoacetate by HMG-CoA lyase. Finally, the enzyme *D*-β-hydroxybutyrate dehydrogenase (BDH) catalyzes the reduction of acetoacetate to *D*-3-β-hydroxybutyrate [43, 44]. The remaining fraction of acetoacetate undergoes a spontaneous non-enzymic decarboxylation, forming the third, and least abundant, ketone body acetone [41, 44] (Fig. 1a).

Ketolysis

Ketolysis occurs in the mitochondria of several extrahepatic organs, to provide energy to peripheral tissues through oxidation of ketone bodies. Circulating *D*-3-β-hydroxybutyrate and acetoacetate are absorbed by peripheral tissues through monocarboxylate transporter 1 (MCT1), and then converted to acetoacetyl-CoA by succinyl-CoA-oxoacid transferase (SCOT), which represents the rate-limiting step of ketolysis. Then acetoacetyl-CoA is cleaved by methylacetoacetyl-CoA thiolase (MAT), producing two molecules of acetyl-CoA, which can finally enter the TCA cycle for ATP synthesis [41, 44] (Fig. 1b).

Common concerns related to ketone bodies

A concern that frequently arises with regards to KDs is related to the slight acidification caused by the accumulation

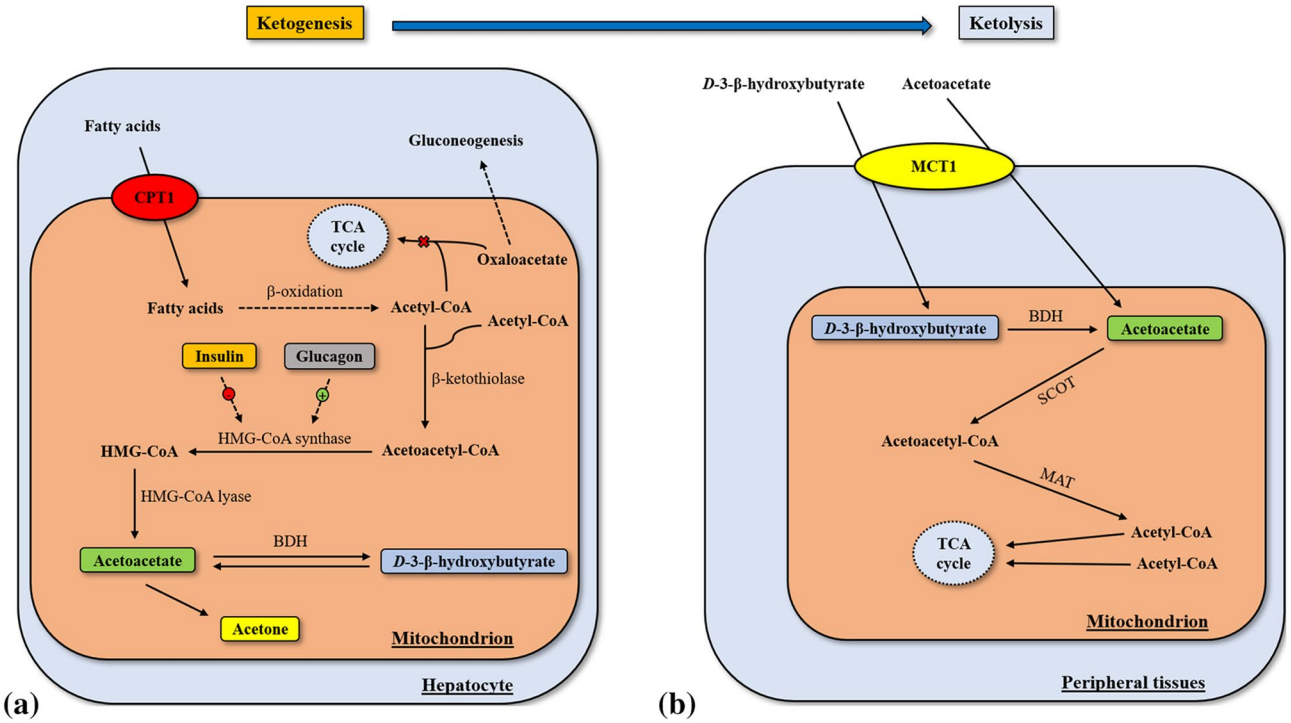

Fig. 1 Molecular basis of ketone body metabolism. **a** Ketogenesis takes place in the mitochondria of hepatocytes. Fatty acids are transported into mitochondria via CPT1, then undergo the β-oxidation process which results in production of acetyl-CoA. Under conditions of reduced glucose availability (e.g., fasting, VLCKD), acetyl-CoA cannot condense with oxaloacetate (preferentially used for gluconeogenesis) and enter the TCA cycle. Therefore, β-ketothiolase mediates the reaction of two molecules of acetyl-CoA to form acetoacetyl-CoA, which is subsequently converted to HMG-CoA by HMG-CoA synthase. The expression of HMG-CoA synthase is finely regulated by insulin and glucagon in an opposite manner: insulin inhibits its expression, whereas glucagon plays a stimulatory role. In the next step, HMG-CoA is cleaved to acetoacetate via HMG-CoA lyase. Then, acetoacetate is mostly converted to *D*-3-β-hydroxybutyrate by BDH, whereas the remaining fraction undergoes a spontaneous non-enzymic decarboxylation forming the third and least abundant ketone body acetone. **b** Ketolysis takes place in the mitochondria of extrahepatic tissues, where it is aimed at providing energy through oxidation of ketone bodies. In particular, MCT1 mediates the transport of circulating *D*-3-β-hydroxybutyrate and acetoacetate into peripheral tissues. At the level of mitochondria, BDH catalyzes the conversion of *D*-3-β-hydroxybutyrate to acetoacetate, which is then transformed into acetoacetyl-CoA by SCOT. Acetoacetyl-CoA is cleaved by MAT, thus forming two molecules of acetyl-CoA which can finally enter the TCA cycle for ATP synthesis. *BDH D*-β-hydroxybutyrate dehydrogenase, *CPT1* carnitine palmitoyltransferase I, *HMG-CoA* 3-hydroxy-3-methylglutaryl-CoA, *MAT* methylacetoacetyl-CoA thiolase, *MCT1* monocarboxylate transporter 1, *SCOT* succinyl-CoA-oxoacid transferase, *TCA cycle* tricarboxylic acid cycle

of ketone bodies in the bloodstream. However, nutritional ketosis occurring during VLCKD represents a physiological mechanism, completely different from the pathological condition known as diabetic ketoacidosis (DKA) [17, 23, 49]. During physiological ketosis, blood pH remains normal since circulating ketone bodies rarely achieve maximum levels of 3 mmol/L. This is due to the fact that central nervous system can efficiently use ketone bodies as an alternative fuel source in addition to glucose [23]. Moreover, blood glucose levels tend to decrease, although remaining within the physiological range due to glucogenic sources (glucogenic amino acids and lipolysis-derived glycerol) [50]. Differently, in DKA the condition of insulin deficiency leads to severe hyperglycemia (blood glucose levels > 300 mg/dL) and ketone bodies concentrations can exceed 20 mmol/L, with a concomitant blood pH drop usually below the normal range [23]. In non-diabetic individuals, there are two feedback loops to prevent runaway ketoacidosis from occurring. When ketone bodies reach high circulating levels (approximately 4–6 mmol/L), they stimulate insulin secretion. In turn, insulin reduces the release of free fatty acids (FFA) from adipocytes, leading to a decreased rate of ketogenesis in the liver, along with an increased urinary excretion of ketones [51]. Importantly, Urbain et al. showed that blood β-hydroxybutyrate concentrations do not usually exceed 0.70 mmol/L during a KD [52], which are well below the blood levels indicative of DKA in adults (3.8 mmol/L) [53]. Despite some studies have documented the safety of VLCKD in the long-term period [17, 20, 54, 55], it is important to reiterate that VLCKD requires proper medical supervision [17, 37], along with the routine measurement of urine and/or blood ketones according to clinical judgment (Table 1).

VLCKD in severe obesity

Recommendations

- We recommend a maximum 12-week weight-loss program with VLCKD as part of a multidisciplinary weight management strategy to adult severely (class 2 or higher) obese patients not responsive to standardized diet as a second line option (1 ØØØO).
- We recommend a maximum 12-week VLCKD treatment as part of a multidisciplinary weight management strategy for obese patients who have a clinically assessed need to lose weight rapidly (1 ØØØO).
- We suggest the use of a weight-loss program with VLCKD in intermittently combination with low-calorie dietary approaches for severely obese patients (2 ØOOO).
- We recommend a long-term weight-loss maintenance follow-up after VLCKD in severely obese patients (1 ØØØO). Weight maintenance or additional weight-loss strategies, if weight-loss target is not achieved, are recommended.

Evidence

VLCKD is a dietary strategy to assist patients affected by obesity in losing weight more rapidly than would otherwise be possible. Guidelines by the US NIH and the AHA/ACC/TOS, ENDO, ASBP, AACE, and the United Kingdom's NICE emphasize weight management as a pathway to prevention and management of obesity-associated comorbidities, and include VLCKD as a therapeutic option for patients with obesity, who have reached a plateau in weight loss after a conventional dietary approach [12, 56]. VLCKD is suggested for a maximum of 12 weeks, continuously or intermittently, in a context of multidisciplinary intervention associated with lifestyle modifications (including mild physical activity) and psychological counseling [56–58]. Anti-obesity drugs are not allowed during the period of adherence to this dietary regimen. VLCKD displays important anorexigenic effects that improve compliance and motivational spur to treatment [59]. This feature makes severe obesity—as defined by body mass index (BMI) > 35 kg/m^2—a major indication for VLCKD.

Reported evidence shows that intervention with VLCKD is effective in terms of weight loss, visceral fat reduction, and improvement of metabolic parameters and inflammation markers. It rapidly fulfills the recommended 5–10% weight loss within 6 months to produce clinically relevant health benefits [17, 23, 60–62]. Generally, the conspicuous weight loss results in amelioration of most weight-related comorbidities, together with beneficial changes in body composition, which occur with sparing of lean mass compared to fat, thus preserving muscle mass and strength [61, 63, 64].

Most of the studies on the efficacy of VLCKD on severe obesity are short term. Some case reports, although poor from a methodological point of view, are suggestive of VLCKD safety and effectiveness in the long term [65, 66]. A recent meta-analysis of randomized controlled trials (RCTs) showed that VLCKD may be an effective tool against obesity in the long-term, well tolerated and associated to few adverse events [67]. To date, strong confirmation by high-quality long-term studies is required.

Despite the gradual nutritional rehabilitation is critical after a VLCKD, there are essentially poor scientific references on how to get the patient out of ketosis. The controlled transition to the reintegration of carbohydrate intake allows the body to slowly get used to the glucose consumption, and influences the weight regain avoiding spikes of insulin. A significant weight-loss maintenance after 2-year VLCKD follow-up with limited carbohydrate refeeding was shown in one longitudinal retrospective study [68]. However, although gradual carbohydrate reintroduction and long-term follow-up after VLCKD appear crucial to maintain weight reduction, further studies are needed to attribute a stronger level of evidence to these approaches.

The use of VLCKD in combination with other dietary approaches represents an intriguing point [69]. Modulating the introduction of carbohydrates up to a balanced and healthy diet with the aim of a long-term diet management is of interest. Hypocaloric Mediterranean diet, with undisputed benefit on health, remains the most prescribed first-choice diet in Italy, penalized, however, by the high incidence of dropouts due to the difficulty in controlling hunger. The development of a controlled ketosis, which effectively inhibits subjective hunger and increases satiation and satiety, makes VLCKD a valuable option for intermittent treatments in combination with other diets.

Value

The available scientific evidence suggests that a weight-loss program with VLCKD is beneficial for severe obesity, provided that a multidisciplinary weight management strategy and a long-term weight-loss maintenance follow-up (≥ 1 year) is carried out under specialized supervision.

Remarks

There is evidence that the efficacy derived from the use of VLCKD is substantial in the short term. The evidence of a long-term intervention with VLCKD for severe obesity is

sporadic. Lifestyle intervention and VLCKD approach used together for the management of severe obesity are more successful than interventions used alone and without specialized supervision.

VLCKD and bariatric surgery

Recommendations

- We recommend a 2- to 4-week preoperative weight-loss program with VLCKD for patients who are candidate to bariatric surgery to induce a weight loss of approximately 5% and a reduction in liver volume of at least 10% (1 ØØØO).
- We suggest a 2- to 6-week preoperative weight-loss program with VLCKD for patients who are candidate to bariatric surgery to reduce visceral adipose tissue (2 ØOOO).

Evidence

To date, bariatric surgery (BS) appears to be the most effective and durable therapeutic option for obesity treatment and it is performed laparoscopically in almost all cases. However, BS carries potential complications ranging from 5 to 20% [70]. Consequently, current guidelines [70, 71] support an intentional preoperative weight loss to reduce liver volume, and consequently the risk of transitioning to an open procedure, as well as the risk of perioperative complications [72]. Several diet protocols have reported decreased weight and liver volume in patients candidate to BS. A total weight loss of at least 5% has been shown to achieve the general liver volume reduction target of approximately 10%. There is a significant heterogeneity in the type of energy-restricted dietary regimes being prescribed. VLCKD has been consistently described as safe and effective in reducing body weight, visceral adipose tissue (VAT) and liver volume in patients scheduled for BS [73–75]. A 3-week VLCKD preoperative regimen before laparoscopic sleeve gastrectomy was associated with a significantly better absolute weight loss compared to VLCD alone. Importantly, when compared to VLCD, VLCKD showed better surgical outcomes, lowering hematic drainage output and increasing post-operative hemoglobin levels [76]. A 4-week preoperative VLCKD with micronutrient supplementation also resulted in improved blood glucose and hypertension, along with a 19.8% reduction of the baseline volume of the left hepatic lobe [77]. Given the early reduction in liver volume and the decrease in VAT occurring more slowly, a previous study [78] indicates that the minimum duration for a preoperative VLCKD should be 2 weeks up to 6 weeks.

Value

The quality of the evidence strongly supports a weight-loss program with VLCKD before bariatric surgery with a minimum duration of 2 weeks to reduce body weight and liver volume, while minimizing perioperative complications risks.

Remarks

Although intentional preoperative weight loss should be encouraged as it improves perioperative outcomes, the limited number of trials available does not allow any definitive evidence-based conclusions about safety and optimal duration of VLCKD in patients candidate to BS.

VLCKD, skeletal muscle and bone health

Recommendations

- We recommend the use of VLCKD in the context of sarcopenic obesity without relevant concerns for loss of lean body mass (1 ØØØO).
- We suggest the use of VLCKD in the context of severe obesity without relevant concerns for bone health (2 ØØØO).

Evidence

It is well established that energy restriction typically leads to a loss of lean mass in the absence of resistance training. Indeed, protein intake, particularly during the first weeks of a KD, will prevent muscle loss by supplying the amino acids for gluconeogenesis without affecting the lean mass [30]. In the following weeks, under conditions of low glucose availability, glucose requirements decrease, due to the increase in alternative energetic fuels, such as FFA and ketones, and the need for enhancing gluconeogenesis from protein also decreases.

Only a few data on long-term effects of KD on body composition are available. The results of a small case series suggest that maintaining a KD for more than 5 years does not pose any major negative effects on body composition and bone mineral density in adults with glucose transporter-1 (GLUT-1) deficiency syndrome [79]. A pilot study conducted on 25 subjects for 3 weeks with a VLCKD showed that this diet was highly effective in terms of body weight reduction without inducing lean body mass loss, thus preventing the risk of sarcopenia [18]. A small study involving six cancer patients undergoing radiotherapy and concurrently consuming a KD regimen, indicated that the KD-induced weight loss was mainly due to fat mass

loss with concurrent preservation of muscle mass [80]. A 21-day RCT comparing VLCKD with different sources of protein did not find any detrimental effect on nutritional status including sarcopenia [81]. A recent study confirmed a rapid and marked loss of fat mass induced by a VLCKD, without the expected decrease in resting metabolic rate (RMR). Interestingly, the absent reduction in RMR was not due to increased sympathetic tone, but was probably related to the preservation of lean mass [82]. This aspect could represent a major determinant for the lack of short-time weight regain after a VLCKD.

Of note, most of the studies considering KD are based on a sustained caloric deficit and do not implement an exercise intervention that could have potentially helped retain muscle mass during weight loss. The addition of a structured resistance training program to a KD may favor further improvement in body composition [83, 84].

Although no studies are available on VLCKD and skeletal metabolism, it is well known that chronic metabolic acidosis increases urine calcium excretion without increasing intestinal calcium absorption, leading to bone calcium loss in an acute manner by physico-chemical dissolution, and chronically by increasing bone resorption [85, 86]. This effect is independent of the nature of the metabolic acidosis. KDs leading to metabolic acidosis might, therefore, have an adverse effect on bone mineral content (BMC) [87]. However, VLCKD does not lead to metabolic acidosis and no studies have been conducted so far with the aim of evaluating its effects on bone health. Data on the effects of VLCKD on phosphorus metabolism are very limited, while vitamin D metabolism during the consumption of these diets has not been investigated.

Studies in children with refractory epilepsy have shown that a prolonged KD can induce a progressive loss of BMC associated with poor bone health status [88, 89]. Furthermore, studies based on animal models suggest that low-calorie diets (LCDs) can lead to poor bone quality, probably due to poor gastrointestinal calcium absorption [90].

However, many studies investigating the adverse metabolic consequences of VLCKD had in most cases a duration of less than 3 months. Of note, studies investigating critical endpoints, such as the effect of total diet replacements for weight control on calcium loss and bone health, have not been conducted for periods longer than 8 weeks. The available evidence does not raise any concern with respect to bone health in adults when these diets are consumed for a single period of up to 8 weeks, even though data on the impact of increased calcium loss on bone health when these diets are used over prolonged periods of time or repeatedly for short periods are scarce [87].

A study published by Carter et al. showed that patients on a LCD had a significantly higher weight loss, without alteration of bone turnover markers (urinary N-telopeptide, uNTx; bone-specific alkaline phosphatase, BSAP) [90]. A 21-day RCT comparing VLCKDs with different sources of protein found no negative effect on nutritional status, including BMC, lipid profile, as well as hepatic and renal function [81].

Remarks

Due to the lack of data regarding the effects of long-term VLCKDs on bone health, further studies are needed to fully characterize any potential bone side effects.

Effects of VLCKD on gut microbiota

Recommendations

- We suggest the use of VLCKD in obesity as an important tool to modify the gut microbiota towards a lean phenotype (2 ØØØO).
- In the context of a VLCKD, we recommend the use of whey and vegetal proteins, since these are more efficient than animal protein, in terms of healthy modification of gut microbiota (1 ØØOO).

Evidence

Emerging evidence suggests an essential role of microbiota in human health and disease, including digestion, energy and glucose metabolism, as well as immunomodulation and brain function [91]. On the other hand, several factors (e.g., host genetics, diet, environment, antibiotic use, and age) greatly influence the development and composition of the human gut microbiome. In particular, several data show that diet and changes in the intake of main macronutrients can rapidly and reproducibly alter the human gut microbiota. A reduced relative abundance of *Bacteroidetes*, increased *Firmicutes*, as well as a reduced bacterial diversity, have been demonstrated in obese patients [92]. Interestingly, whey and pea proteins are known to increase gut-commensal *Bifidobacterium* and *Lactobacillus*, whereas pea proteins increase intestinal short-chain fatty acids levels, which contribute to the maintenance of the mucosal barrier [93, 94].

It has been shown that non-ketogenic VLCD positively alters gut microbiota diversity and metabolism in obese individuals and is able to modulate gut permeability and decrease markers of inflammation. According to recent studies, these activities seem to be connected to the acute and marked caloric restriction and to the nutritional

components, rather than to the decrease in body weight [95].

KD has also been recently shown to act on gut microbiota. Initial experiments investigating the effects of acute electrically induced seizures in mice have shown that KDs are able to alter gut microbiota, inducing the increase in *Akkermansia Muciniphila* and *Parabacteroides*, which is required for protection against seizures. In fact, mice treated with antibiotics or germ-free are resistant to KD-mediated seizure protection. The subsequent treatment with KD-associated *Akkermansia* and *Parabacteroides* restores seizure protection. These results strengthen the fact that the composition of the KD-induced gut microbiota rebalance has a pivotal role in the activity of KDs themselves [96].

Remarks

VLCKDs represent an important approach to caloric restriction in obese patients. However, there are still very few data that evaluate the impact of these diets on gut microbiota. Therefore, studies evaluating the ability of VLCKDs to modify intestinal bacteria are warranted.

VLCKD, insulin resistance and type 2 diabetes

Recommendations

- VLCKD should be considered to obtain an early efficacy on glycemic control, particularly in obese patients with short duration of the disease (1 ØØØO).
- VLCKD should be considered to reduce the use of glucose-lowering agents, including insulin (1 ØØØO).

Evidence

In obese non-diabetic patients, the effect of VLCKD is powerful in reducing plasma insulin levels; consequently, HOMA-IR and HOMA-beta, which represent markers of insulin resistance and beta-cell function, respectively, display significant improvements after this type of dietetic intervention [97, 98]. Of relevance, an important benefit of VLCKD to improve insulin resistance is evident in youth obesity [99–102].

In obese patients with T2D, exposure to VLCKD for 1 week resulted in a significant improvement of beta-cell function not fully explained by the marginal weight loss achieved. The reduction in carbohydrate intake was associated with an early and significant decrease in hepatic triacylglycerol content; consequently, higher suppression of hepatic glucose production was observed as a consequence of improved hepatic insulin sensitivity [103]. Higher hepatic insulin sensitivity was also associated with lower fasting plasma glucose and plasma insulin levels. However, changes in peripheral insulin sensitivity only partly explain the effects of VLCKD in the short term [104]. On the other hand, a remarkable increase in skeletal muscle glucose uptake was observed only after a significant weight loss, which requires longer exposure to VLCKD regimen and follow-up [105]. An enhanced insulin response to arginine—an index of beta-cell function—has also been observed after a short period of VLCKD [103]. Specifically, after 1 week of VLCKD, obese patients with T2D in good glycemic control displayed a recovery of the acute insulin response assessed during hyperglycemic clamp, as well as of the second phase of insulin secretion [104]. VLCKD leads to recovery of the first phase of insulin secretion in 40% of participants at the end of a longer program (8 weeks) involving a heterogeneous group of patients with T2D [106]. Moreover, a higher disposition index was also observed [104]. Interestingly, VLCKD has been demonstrated to be as effective as the Roux-en-Y gastric bypass on insulin sensitivity and beta-cell function in patients with T2D in the short term [107].

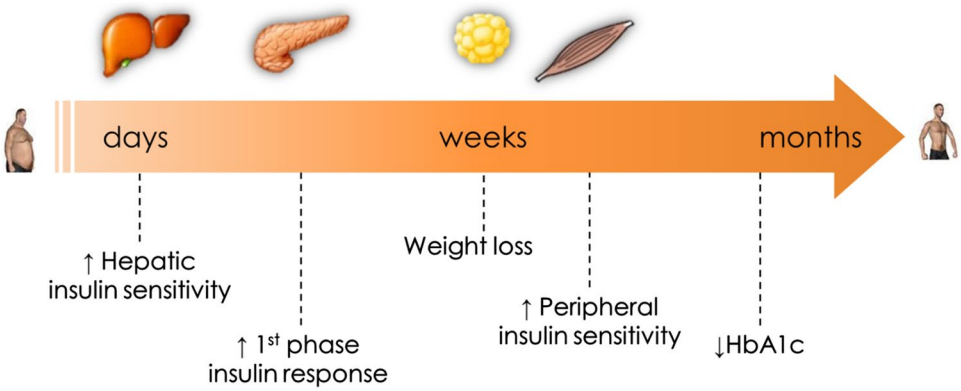

Fig. 2 Effects of VLCKD on glucose homeostasis and metabolic parameters in obese subjects with or without type 2 diabetes

Beyond the documented short-term efficacy, the assessment of the effects of VLCKD on insulin resistance and beta-cell function in the long term and the comparison with those of a standard diet is still lacking.

VLCKD has been shown rapidly efficacious on metabolic control in patients with T2D. Treatment with VLCKD was associated with a greater reduction of glycated hemoglobin (HbA1c) after 3 months as compared to a standard LCD [108, 109]. Significant improvements in fasting plasma glucose, acute insulin response, fasting plasma insulin and C-peptide levels have also been observed during the first days of VLCKD [103, 104, 110]. These early effects are associated with improvement in beta-cell function [104], while the contribution from weight loss ensues later, after a substantial VAT reduction [103] (Fig. 2). Noteworthy, VLCKD provides comparable weight loss in obese patients with T2D and obese patients without T2D, even though the reduction of fat mass seems to be lower in patients with T2D, due to a greater loss of body water in the diabetic group [111].

The effects of VLCKD on beta-cell function may be responsible for the significant percentage of patients showing remission of T2D. Indeed, remission of diabetes may be expected in a relevant percentage of patients with early diagnosis of the disease after 3 months of VLCKD [103, 109]. A longer observation reveals a persistent remission in almost half of the patients [103, 106], despite weight regain [103]. Long-lasting remission was frequently observed in patients with lower fasting plasma glucose, younger age and a shorter duration of diabetes [106]. Improvements in glycemic control during intervention with VLCKD have been found, despite discontinuation of anti-diabetes therapy [106, 112].

Continuous [107, 108, 110] or intermittent use [111] of VLCKD has been associated with a dramatic reduction in insulin and oral glucose-lowering medication requirements.

Remarks

Current studies provide information mostly on short-term follow-up with VLCKD, albeit persistent lower fasting plasma glucose and HbA1c are observed even after 18 months of intervention [112]. Potential effects of VLCKD on long-lasting metabolic memory should also be adequately investigated. Finally, VLCKD promotes a metabolic improvement beyond the extent of weight loss; therefore, it should be considered in lifestyle intervention programs in patients with obesity and T2D.

VLCKD and dyslipidemia

Recommendations

- We recommend VLCKD to decrease serum triglycerides in hypertriglyceridemic obese patients (1 ØØØO).

Evidence

The effects of VLCKD on plasma lipoproteins in obese patients have been investigated since long time: a fall in plasma triglycerides, an increase in low-density lipoprotein (LDL)-cholesterol and a neutral effect on high-density lipoprotein (HDL)-cholesterol were initially described by some short-term, small-size, non-randomized studies. Randomized trials of VLCKD based on an initial daily consumption of carbohydrate < 20 g/day have documented favorable effects on triglycerides [113–117]. The amount of weight lost was an independent predictor of improvement in triglyceride levels [114].

Variable results on total, LDL- and HDL-cholesterol were reported by different studies, likely due to differences in diet composition (intake from fat ranges from 40 to 50% of the total caloric daily intake), genetic background and physical activity of the study groups. After 6 months of very low carbohydrate diets, total, LDL- and HDL-cholesterol were unchanged [113, 114, 117], while in other randomized trials HDL-cholesterol improved up to 12 months [115, 116].

In a study conducted in Kuwaiti obese patients, VLCKD improved total cholesterol, LDL-cholesterol, triglycerides, and increased HDL-cholesterol both in normo- or hypercholesterolemic obese patients independently of their sex [118]. The normalization of cholesterol and triglyceride levels occurred earlier (8 weeks) than the normalization of BMI [118].

Remarks

Randomized trials available in obese patients indicate that weight-loss programs based on VLCKD are usually accompanied by a better outcome of triglyceride levels when compared to conventional diets. Unfortunately, longer studies (> 1 year) are not available for overweight and normal-weight subjects with metabolic syndrome, and for obese patients.

VLCKD and non-alcoholic fatty liver disease

Recommendations

- In overweight/obese patients with non-alcoholic fatty liver disease (NAFLD), a 7–10% weight loss is the target of most lifestyle interventions. In this context, we recommend energy restriction and exclusion of NAFLD-promoting components (1 ØØØO).
- We suggest the use of VLCKD in the management of obese patients with NAFLD, for a rapid reduction in liver volume and intrahepatic triglyceride content (2 ØØØO).

NAFLD is the most common liver disorder in Western industrialized countries, where obesity and T2DM are the major risk conditions for this disease and for its progression towards non-alcoholic steatohepatitis (NASH) and liver cirrhosis or hepatocellular carcinoma. NAFLD is characterized by the presence of steatosis in > 5% of hepatocytes at histology or by an intrahepatic triglyceride level > 5.6% at magnetic resonance spectroscopy when no other causes for secondary hepatic fat accumulation are present.

Given the tight association of NAFLD with obesity, even modest weight loss significantly reduces liver fat while improving hepatic insulin resistance [119, 120]. Weight loss obtained with dietary intervention resulted in the resolution of NASH and reduction of NAFLD Activity Score (NAS), which paralleled body weight reduction. Moreover, 7% weight loss was associated with positive histological outcomes [121]. Similarly, in a large, uncontrolled 12-month cohort study, an even higher weight loss (> 10%) induced by lifestyle changes, was associated with improvement in steatohepatitis and fibrosis [122]. No data are available on their long-term effects on the natural history of NAFLD [121]. Mediterranean diet is considered as the most appropriate approach to improve liver function and histological features in patients with NAFLD, but this statement is based on a few cross-sectional and longitudinal studies [123]. The current recommendation of the American Association for the Study of Liver Diseases for weight reduction in clinical practice is based on a low-calorie, low-fat diet, designed to produce modest weight loss [124].

At present, there are no RCTs allowing drawing any conclusions about the clinical impact of VLCKD on NAFLD/NASH and its efficacy to reduce or ameliorate the major outcomes. Moreover, long-term studies of adequate statistical power are missing.

In humans, 2 weeks of dietary intervention with a VLCKD reduced hepatic triglycerides in subjects with NAFLD; importantly, reductions were significantly greater with VLCKD than with standard caloric restriction [125]. A similar study showed that liver total volume was rapidly decreased by a short-term (6 days) VLCKD, probably due to glycogen depletion, and such decrease was higher than with a standard (7 months) hypocaloric diet [126].

Although several observational and experimental studies have examined the effects of low-carbohydrate diets on NAFLD, there are considerable inconsistencies among studies. In a recent meta-analysis, low carbohydrate consumption in subjects with NAFLD led to a significant reduction in intrahepatic lipid content, but did not affect the concentration of liver enzymes [127].

Importantly, intrahepatic triglyceride (IHTG) content is highly dependent on dietary protein intake in the short-term period [128–130]. Indeed, a 2-year study recently reported that increasing the amount of protein in the diet may reduce liver fat content and lower the risk of T2D in people with NAFLD. In particular, more than half of the participants, who were previously diagnosed with NAFLD, no longer had fatty liver [131].

A 12-week intervention study showed that IHTG content is lower after a high protein-low carbohydrate diet than a low protein-high carbohydrate diet [132]. This suggests that high protein-low carbohydrate diets may limit IHTG in healthy humans. High-protein intake stimulates hepatic lipid oxidation due to the high energetic demand for amino acid catabolism and ketogenesis [133]. Protein-induced glucagon secretion inhibits de novo lipogenesis and stimulates hepatic ketogenesis [134]. High-protein intake may blunt the increase of very-low-density lipoprotein (VLDL)-cholesterol and triglyceride concentrations induced by carbohydrate intake [135]. High VLDL and triglyceride concentrations may increase hepatic triglycerides, and subsequently IHTG content [136].

Remarks

Lack of RTCs and the poor quality in the diagnosis and follow-up due to rough measures of liver outcomes—as defined by the international guidelines—limit the validation of VLCKD use in patients with NAFLD.

VLCKD, cardiovascular risk factors and diseases

Recommendations

- We recommend VLCKD for a rapid reduction of cardiovascular risk factors in obese patients, not responsive to standard diets (1 ØØØO).
- We recommend VLCKD in obese hypertensive patients, not responsive to standard diets (1 ØØØO).
- We suggest VLCKD as an option for rapid reduction in body weight and cardiac overload in obese patients with

heart failure (NYHA I-II), upon careful examination of cardiac function and fluid balance (2 ØOOO).

Evidence

Obesity is strictly associated with shorter longevity and significantly increased risk of cardiovascular morbidity and mortality [137]. Of note, overweight status—despite similar longevity compared to normal BMI—has also been found significantly associated with increased risk of developing cardiovascular disease (CVD) at an earlier age [138]. It is well known that an excess fat mass worsens most of CVD risk factors, such as dyslipidemia, hypertension, insulin resistance, and systemic inflammation [139]. The rapid impact of VLCKD in reducing visceral fat displays beneficial effects on the pivotal risk factors for CVD. In this context, VLCKD could be part of a multidisciplinary strategy for cardiovascular rehabilitation in obese patients. Pioneering studies by Blackburn showed marked pleiotropic effects of VLCKD in the reduction of body weight, systolic and diastolic blood pressure, fasting plasma glucose and triglyceride levels [30]. Similar data were reproduced by other authors [24], and have already been discussed. Noteworthy, VLCKD has been found to be more effective in blood pressure lowering than a combined intervention based on LCD plus orlistat [140], probably due to the increased natriuresis associated with ketone bodies urinary excretion.

It is well established that obesity is associated with an increased left ventricular stroke volume and cardiac output. These changes result in ventricular hypertrophy and enlargement, which predispose to heart failure [137]. Notably, prolonged caloric restriction in obese patients leads to a significant improvement in diastolic heart function, along with decreased myocardial triglyceride content and marked reduction of BMI [141]. A similar study in obese T2D patients showed that a VLCD (450 kcal/day, 50–60 g carbohydrates) improves diastolic function after 14-month follow-up, regardless of weight regain [142]. Importantly, the failing heart shifts to ketone bodies as main fuel source for ATP production [143]. Pharmacological inhibition of the renal sodium/glucose cotransporter 2 (SGLT2)—a therapy used to lower blood glucose through increased glycosuria and natriuresis—increases ketone bodies [144] and determines a 38% reduction in cardiovascular mortality, that cannot be explained only on the basis of the improvement in cardiovascular risk factors [145]. Since the average urinary glucose excretion during SGLT2-inhibition therapy in normal glucose-tolerant individuals is approximately 70 g/day [146], increased ketone bodies may represent one of the causal mechanisms for cardiac protection derived from the use of SGLT2 inhibitors [144]. Importantly, β-hydroxybutyrate has been shown to suppress sympathetic nervous system activity and to reduce heart rate and total energy expenditure by inhibiting short chain fatty acid signaling through G protein-coupled receptor 41 (GPR41) [147]. Furthermore, the anti-inflammatory effects of VLCKD could also play an important cardioprotective role. In fact, 12-week-long VLCKD has been reported to significantly reduce the levels of pro-inflammatory cytokines (tumor necrosis factor alpha, TNF-α; interleukin 6, IL-6; interleukin 8, IL-8; monocyte chemoattractant protein 1, MCP-1; E-selectin; intercellular adhesion molecule 1, ICAM-1; plasminogen activator inhibitor 1, PAI-1) [148]. Accordingly, pre-clinical studies demonstrated that β-hydroxybutyrate blocks NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome [149], thus supporting a direct anti-inflammatory role of VLCKD beyond its beneficial effects on metabolic parameters [150].

Remarks

Complex and pleiotropic mechanisms induced by VLCKDs significantly reduce cardiovascular risk factors. However, a general recommendation of the VLCKD for prevention and treatment of CVD associated with obesity is still not straightforward due to the lack of long-term studies evaluating the impact of this regimen on major cardiovascular outcomes.

VLCKD and obesity-related hypogonadism in men

Recommendations

- We suggest a weight-loss program with VLCKD for obese male patients with hypogonadism to increase plasma androgen levels (2 ØØØO).
- We suggest a weight-loss program with VLCKD for obese male patients with hypogonadism to improve their sexual function (2 ØØOO).

Evidence

Mild hypogonadism, defined by low levels of serum total testosterone, is a clinical consequence of abdominal obesity and appears to independently predict the development of insulin resistance and diabetes mellitus [151–154]. Few studies have evaluated the effects of rapid weight loss on plasma total testosterone and other sex hormone levels in obese hypogonadal patients. Two RCTs described the effects of 10-week VLCKD, respectively on 19 and 51 obese hypogonadal patients [155, 156]. The studies showed a significant increase of total testosterone, sex hormone-binding globulin (SHBG), HDL-cholesterol [155, 156], as well as a significant decrease of insulin [155], leptin [155] and triglycerides

[156]. There were no significant changes in LH levels [156] and in the questionnaire scores on sexual function [155]. Similar to the results of these two RCTs, other two observational studies [157, 158] reported a significant increase of total testosterone concentrations, SHBG and calculated free testosterone levels [157, 158] after caloric restriction. Dehydroepiandrosterone sulfate (DHEA-S) concentrations did not significantly change during the VLCKD [157]. There was also a significantly greater increase in the mean of the abridged five-item version of the International Index of Erectile Function (IIEF-5) and the Sexual Desire Inventory (SDI) scores, as well as significant reductions in mean of the International Prostate Symptom Scale (IPSS) scores [158]. No studies on the effects of VLCKD on male fertility have been performed so far.

Value

The quality of the evidence suggests a weight-loss program with VLCKD for obese hypogonadal patients to increase plasma androgen levels and to improve their sexual function. There is currently no evidence on the impact of VLCKD on male fertility.

Remarks

In consideration of the limited evidence provided by the few available studies, it is advisable to suggest to obese hypogonadal patients to undergo a weight-loss program with VLCKD to improve sex hormone plasma concentrations and sexual function. No study ever evaluated the effects of VLCKD on sperm parameters, although the negative role of obesity on sperm parameters has clearly been documented [159].

VLCKD and polycystic ovary syndrome in women

Recommendations

- We suggest a weight-loss program with VLCKD for overweight/obese patients with polycystic ovary syndrome (PCOS) not responsive to multicomponent standardized diet to improve insulin resistance (2 ØOOO).
- We suggest a weight-loss program with VLCKD for overweight/obese patients with PCOS not responsive to multicomponent standardized diet to improve ovulatory dysfunctions and hyperandrogenemia (2 ØOOO).

Evidence

Overweight/obese women with PCOS have a worse phenotype with respect to the normal-weight counterparts in terms of menses abnormalities, anovulation, infertility and metabolic alterations [160]. Particularly evident is the impact of obesity on insulin resistance, as it affects 94% of obese PCOS women against 78% and 59% of overweight and normal-weight PCOS women, respectively [161]. Insulin resistance exerts a fundamental role in promoting or aggravating hyperandrogenism, ovulatory dysfunctions, as well as the metabolic disorders that frequently complicate the obese PCOS phenotype [160]. In addition, obese PCOS women are frequently characterized by a state of low-grade inflammation that aggravates insulin resistance and hyperandrogenism, thus participating in the pathophysiology of the syndrome and its metabolic complications [162]. There is a high quality of evidence that diet-induced weight loss of at least 5% improves hyperandrogenism, anovulatory infertility and metabolic alterations in obese PCOS women [160]. However, a great inter-individual variability in the response to weight loss obtained from standardized diet programs has been reported and predictive factors are still largely under evaluation [163]. In addition, there is no or limited evidence that any specific energy equivalent diet type is better than another in PCOS [164]. However, it is of interest that only low-carbohydrate diets lead to significant decrease in insulin resistance [165, 166] and in circulating markers of inflammation in most of overweight/obese-treated PCOS women [165]. Little but positive experience has been reported on VLCKD in obese PCOS women. Indeed, only a pilot uncontrolled study has been performed so far, where a VLCKD has been administered to 11 overweight/obese PCOS women for a 24-week period, but only five subjects ended the study [167]. In these five subjects evaluated at 24 weeks, VLCKD produced a significant reduction in body weight (− 12% from baseline in mean), free testosterone (− 30% from baseline in mean), LH to FSH ratio (− 36% from baseline in mean), and, importantly, fasting insulin (− 54% from baseline in mean). In addition, two women became pregnant despite previous infertility problems.

Remarks

Although we only have preliminary evidence of the positive effects of VLCKD in overweight/obese PCOS women, there are clear mechanisms consistent with the plausibility of such dietary therapy. However, in consideration of the limited evidence provided, it is advisable to suggest a weight loss program with VLCKD to obese patients with PCOS not responsive to multicomponent standardized diet. Further adequate controlled studies are needed to confirm the

beneficial effects of VLCKD on the various clinical aspects of PCOS and to establish if these effects are attributable to weight loss or to the specific dietary approach.

VLCKD and obesity after the menopausal transition in women

Recommendations

- We suggest the use of VLCKD in obese women after menopausal transition, in consideration of the increased cardiometabolic risk characterizing this phase of life (2 ØOOO).

Evidence

Menopause is defined as a clinical status after the final menstrual period, and should be diagnosed retrospectively after cessation of menses for 12 months in a previously cycling woman; it reflects complete—or nearly complete—permanent cessation of ovarian function [168]. Menopausal transition precedes the menopause and is characterized by variations in menstrual cycle length and bleeding pattern [168].

In women, the risk for CVD significantly increases after menopause. Indeed, menopause transition is marked by adverse changes in body fat deposition, lipid and lipoprotein levels, vascular remodeling and inflammation, involved in the atherosclerotic process [169]. Emerging findings have pointed out new potential cardiovascular risk markers relevant to postmenopausal women, namely: epicardial fat and higher HDL-cholesterol levels, which do not appear cardioprotective in this population [169]. Moreover, vasomotor symptoms have been considered as directly involved in the pathophysiology of CVD, representing a marker of endothelial dysfunction and arterial stiffness [170]. Adiposity was initially theorized to be protective against vasomotor symptoms due to increased peripheral aromatization. However, recent investigations indicated that BMI and waist circumference were positively related to incident hot flushes in early menopause and negatively related in late menopause [171]. Ultimately, the direction of relations between body fat and vasomotor symptoms may change over time, with obesity being a risk factor early in the transition (when adipose tissue insulates against the heat dissipating action of hot flashes), and protective in the postmenopausal phase, when ovarian estrogen production significantly ceases [172].

Remarks

Data on weight loss and vasomotor symptoms are very limited. In a recent pilot-controlled study, women randomized to weight loss showed greater reductions in questionnaire-reported hot flashes than controls [172]. The literature lacks studies on the effect of VLCKD on weight loss, vasomotor symptoms and cardiovascular risk in menopause. The rationale of using VLCKD in this population might stem on the effect of ketone bodies in reducing adrenergic tone [147] and promoting metabolic benefit [30]. This is an area of interest that should be further explored.

VLCKD in pediatric obesity

Recommendations

- VLCKD should be considered in epileptic obese children who have increased dramatically weight due to concomitant treatments (1 ØØØØ).
- A 12-week VLCKD should be considered in pediatric severely obese patients with a high level of insulin resistance and/or comorbidities and not responsive to standardized diet, as a second line option (1 ØØØO).
- We recommend a long-term follow-up on weight-loss maintenance, growth, bone accrual and cardiovascular risk factors after VLCKD in pediatric severely obese patients (1 ØØØØ).

Paradoxically, KDs in classical or modified modalities have been widely used over the past decades for the management of several pediatric diseases, i.e., refractory epilepsy and GLUT-1 deficiency. Adverse events and main short- and long-term complications have been first reported in children. KD is effective and well tolerated also in epileptic infants younger than 2 years, although this population is at higher risk for nutritional deficiencies. Particular attention should be paid to impairment or retardation of growth and bone accrual, mainly in the youngest. Differently, intima-media thickness, and more generally cardiovascular risk, did not increase in studies conducted over a 10-year follow-up period [173]. In these diseases, VLCKD should be suggested in children who had dramatically increased weight due to concomitant treatments [174, 175].

Although KD is a well-known diet regimen for pediatricians, VLCKD has not been considered yet as a treatment option for pediatric obesity. Also, recent guidelines on the management of pediatric obesity do not mention VLCKD [176]. Published papers investigating the role of VLCKD in pediatric obesity or T2D are scarce. However, most of them were open-label RCTs [177, 178]. The trials showed a greater reduction in weight and BMI (from − 2.5 to − 5.6 kg/m^2) after 10 or 16 weeks of treatment than a hypocaloric low-fat diet in approximately 100 subjects (7–17 years) [179, 180]. The difference between the two regimens persisted for 6 months, but not for 12 months [179]. Other three studies

used Atkins KD without energy restriction for fats and proteins in comparison to standard hypocaloric diets. A greater reduction in weight and BMI (from − 3.7 to − 3.3 kg/m^2) was observed after 8, 12 or 24 weeks of KD diet in approximately 300 children and adolescents (6–18 years) [102, 181, 182]. The VLCKD was administered to 20 adolescents with T2D and was efficacious in reducing body weight and BMI (− 3.2 kg/m^2) durably for 2 years [183].

All these studies showed improvements in blood pressure, lipid profile, fasting insulin and glucose, and insulin sensitivity. HbA1c dropped down (− 1.4%), and antidiabetic medications were permanently interrupted in obese adolescents with T2D [102, 179–183]. No severe adverse events were reported, and the adherence was high. No data on growth are available.

Remarks

Due to the short-term follow-up of these studies, along with the different KD modalities and the relative paucity of treated patients, strong evidence is lacking. However, KD seems to be efficacious and safe in the short term to help losing body weight.

Ketogenic diet in ageing and neurodegenerative disorders

Recommendations

- We suggest the use of KDs as possible treatment in neurodegenerative disorders associated with sarcopenic obesity and refractory epilepsy in the elderly (2 ØOOO).
- We suggest the use of KDs as adjuvant to conventional therapies in selected forms of Alzheimer/Parkinson's disease (2 ØOOO).
- We suggest the use of VLCKD as a possible approach in selected elderly (65–75 years) with sarcopenic obesity (2 ØØØO).

Evidence

Epidemiological observations indicate that oral intake of a ketogenic medium-chain triglyceride diet improves cognitive function in patients with Alzheimer's disease (AD) [184].

It is widely recognized that brain energy deficit is an important pre-symptomatic feature of AD, which precedes progression of cognitive decline associated with the disease. In fact, regional brain glucose uptake is impaired in AD and in mild cognitive impairment (MCI) [185].

Several studies showed that the blood–brain barrier in AD is impaired and the result is an altered expression of some transporters, including down-regulation of glucose transporter. Ketone bodies represent the alternative energy source to glucose for the brain, since their brain uptake is still normal in MCI and in early AD [186]. In the last few years, chronic inflammation and oxidative stress are considered two key factors in the development of AD [187]. The beneficial effects of KD in AD are described as an improvement of cellular metabolism and mitochondrial function, inducing a shift in energy metabolism, and are also associated with decreased oxidative damage and modulation of inflammatory status through several mechanisms of neuroprotection [188]. These observations help explain why ketogenic interventions improve some cognitive outcomes in MCI and in AD [189]. Various problems have been encountered in patients adhering to this diet; indeed, long-term 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. Previous studies have also reported adverse short-term events associated with KD, including nausea, vomiting, diarrhea, fatigue, dehydration, gastroesophageal reflux and abdominal pain [189]. However, recent data suggest that VLCKD is highly effective in body weight reduction of young adults (18–65 years), preserving muscle mass during weight loss and preventing the risk of sarcopenia [18]. Thus, once confirmed in not age-limited randomized studies, VLCKD might become an interesting therapeutic strategy for sarcopenic obesity of older people (65–75 years).

Value

Recent exciting studies in mice indicate that low-carbohydrate ketogenic diets (LCKDs) prevent age-related cognitive decline and extend lifespan through the increase in circulating ketone bodies [190, 191]. LCKD significantly increased median lifespan and survival compared to controls diet, with preservation of physiological function [190]. The other authors showed that cyclic LCKD, alternated weekly with a control diet, slowed age-related cognitive and memory decline and reduced midlife mortality in mice [191]. Interestingly, the increase in ketone bodies could improve central nervous system insulin resistance, with important perspectives for the prevention of cognitive decline in patients with T2D [192]. However, there is still not enough evidence to recommend the use of KDs for the treatment of MCI and/or AD and other dementias.

Remarks

Although KD may find a field of application in delaying the onset or the progression of MCI and AD in older people (> 65 years), it is not recommended in frail older AD patients with comorbidities, sarcopenia and severe

impairment of activities of daily living, since no data exist for these patients. Specific concern should be taken for some symptoms of late AD, such as dysphagia and multiorgan dysfunction. Thus, further studies are needed to design KDs specifically indicated for single-brain diseases, and to improve the balance between beneficial and adverse effects in aged individuals.

Conclusions and perspectives

Despite the short- and middle-term benefits of VLCKD in terms of weight loss and reduction in cardiovascular risk factors are widely documented [18, 19, 23, 34], some concerns exist about its use in the long-term period due to the paucity of studies. Long-term studies are indeed needed to explore the potential benefit of VLCKD on specific endpoints such as cardiovascular and neurodegenerative diseases. A few studies have previously demonstrated that VLCKD is safe and effective in the long term [17, 20, 54, 55], although there is need for additional clinical trials. Major difficulties in planning such studies may depend on the poor adherence to a highly restrictive dietary regimen over a long-term period. However, VLCKD is a highly effective therapeutic tool in patients who need a rapid weight loss over a short-term period, such as individuals with moderate to severe obesity and cardiovascular risk factors. The potential of VLCKD in determining remission of T2D, particularly in obese patients with short disease duration [103], should be also taken into consideration. Once an ideal body weight is achieved, VLCKD should be necessarily followed by a long-term multifactorial strategy aimed at weight-loss maintenance, highlighting the importance of a comprehensive program of lifestyle modification which includes behavior therapy, nutritional counseling and physical activity [12, 14, 37], along with specific protocols for reintroduction of carbohydrates.

One of the open questions is related to the ideal duration and frequency of use of VLCKDs. In the past, the use of VLCKDs without proper medical supervision generated therapeutic failures and side effects that led to their default for many years. It should be emphasized that the use of VLCKD requires a clear clinical indication under strict medical supervision. If the results are unsatisfactory or a new cycle of VLCKD is needed, it is mandatory to investigate the causes of the previous failure. Furthermore, it is likely that specific protocols for VLCKD implementation will need to be defined according to the specific hols of nutritional therapy, characteristics of the patients, and clinical setting.

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Compliance with ethical standards

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Research involving human or animals participants This consensus statement does not contain any study with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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