



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

M. Caprio^{1,2} · M. Infante³ · E. Moriconi^{1,4} · A. Armani¹ · A. Fabbri³ · G. Mantovani⁵ · S. Mariani⁴ · C. Lubrano⁴ · E. Poggiogalle⁴ · S. Migliaccio⁶ · L. M. Donini⁴ · S. Basciani⁴ · A. Cignarelli⁷ · E. Conte⁷ · G. Ceccarini⁸ · F. Bogazzi⁹ · L. Cimino¹⁰ · R. A. Condorelli¹⁰ · S. La Vignera¹⁰ · A. E. Calogero¹⁰ · A. Gambineri¹¹ · L. Vignozzi¹² · F. Prodam¹³ · G. Aimaretti¹³ · G. Linsalata¹⁴ · S. Buralli¹⁴ · F. Monzani¹⁴ · A. Aversa¹⁵ · R. Vettor¹⁶ · F. Santini⁸ · P. Vitti⁹ · L. Gnessi⁴ · U. Pagotto¹¹ · F. Giorgino⁷ · A. Colao¹⁷ · A. Lenzi⁴ on behalf of the Cardiovascular Endocrinology Club of the Italian Society of Endocrinology

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Abstract

Background Weight loss is a milestone in the prevention of chronic diseases associated with high morbidity 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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✉ M. Caprio
massimiliano.caprio@sanraffaele.it

Extended author information available on the last page of the article

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 ($\approx 13\%$ of total energy intake), with a relative increase in the proportions of fat ($\approx 44\%$) and protein ($\approx 43\%$) 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 ($\emptyset\emptyset\emptyset\emptyset$, very low; $\emptyset\emptyset\emptyset\emptyset$, low; $\emptyset\emptyset\emptyset\emptyset$, moderate; $\emptyset\emptyset\emptyset\emptyset$, 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 $\emptyset\emptyset\emptyset\emptyset$)
Management of severe obesity before bariatric surgery	(1 $\emptyset\emptyset\emptyset\emptyset$)
Sarcopenic obesity	(1 $\emptyset\emptyset\emptyset\emptyset$)
Obesity associated with type 2 diabetes (preserved beta cell function)	(1 $\emptyset\emptyset\emptyset\emptyset$)
Obesity associated with hypertriglyceridemia	(1 $\emptyset\emptyset\emptyset\emptyset$)
Obesity associated with hypertension	(1 $\emptyset\emptyset\emptyset\emptyset$)
Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet	(1 $\emptyset\emptyset\emptyset\emptyset$)
Weak recommendations	
Obesity associated with dysbiosis of the gut microbiota	(2 $\emptyset\emptyset\emptyset\emptyset$)
Obesity associated with high levels of LDL-cholesterol and/or low levels of HDL-cholesterol	(2 $\emptyset\emptyset\emptyset\emptyset$)
Obesity associated with non-alcoholic fatty liver disease (NAFLD)	(2 $\emptyset\emptyset\emptyset\emptyset$)
Obesity associated with heart failure (NYHA I–II)	(2 $\emptyset\emptyset\emptyset\emptyset$)
Obesity associated with atherosclerosis	(2 $\emptyset\emptyset\emptyset\emptyset$)
Male obesity secondary hypogonadism	(2 $\emptyset\emptyset\emptyset\emptyset$)
Obesity associated with polycystic ovary syndrome (PCOS)	(2 $\emptyset\emptyset\emptyset\emptyset$)
Menopausal transition-related obesity	(2 $\emptyset\emptyset\emptyset\emptyset$)
Neurodegenerative disorders associated with sarcopenic obesity	(2 $\emptyset\emptyset\emptyset\emptyset$)

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, heart 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

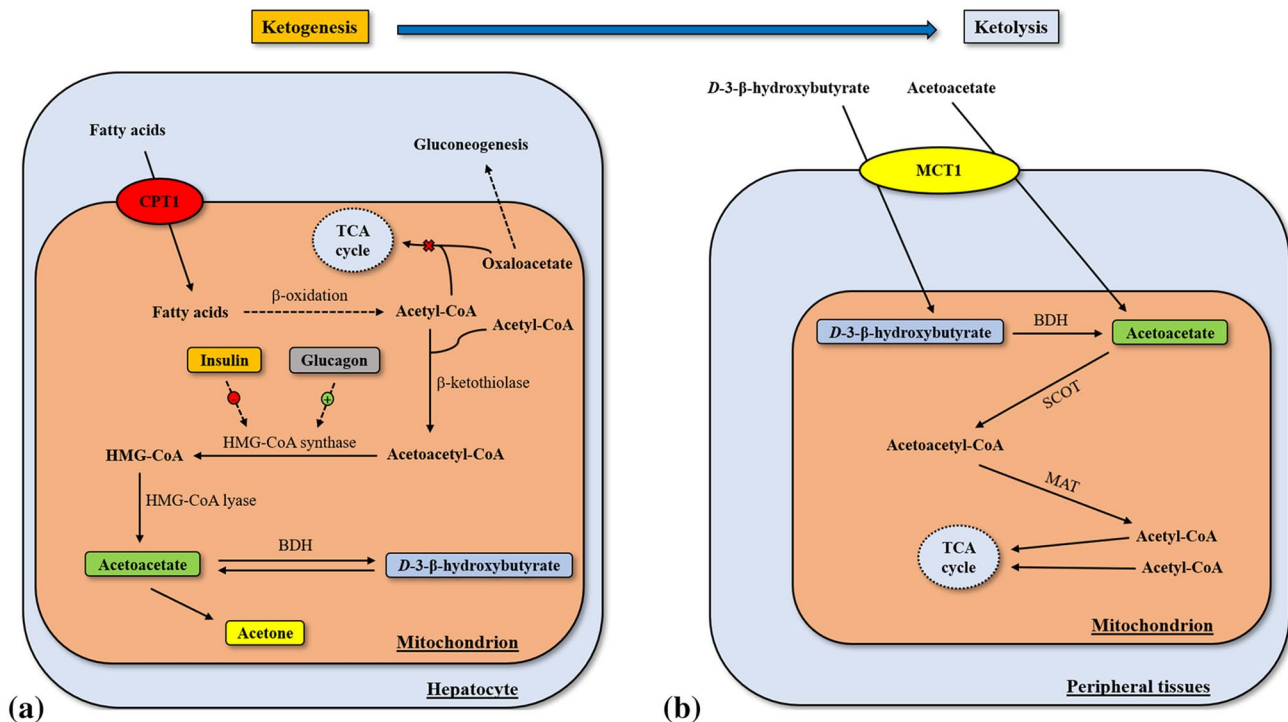


Fig. 1 Molecular basis of ketone body metabolism. **a** Ketogenesis takes place in the mitochondria of hepatocytes. Fatty acids are transported into mitochondria via CPT1, then undergo the β -oxidation process which results in production of acetyl-CoA. Under conditions of reduced glucose availability (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 ØØØØ).
- 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 ØØØØ).
- We suggest the use of a weight-loss program with VLCKD in intermittently combination with low-calorie dietary approaches for severely obese patients (2 ØØØØ).
- We recommend a long-term weight-loss maintenance follow-up after VLCKD in severely obese patients (1 ØØØØ). 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/m²—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 ØØØØ).
- 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 ØØØØ).

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 ØØØØ).
- We suggest the use of VLCKD in the context of severe obesity without relevant concerns for bone health (2 ØØØØ).

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 ØØØØ).
- 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 ØØØØ).

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

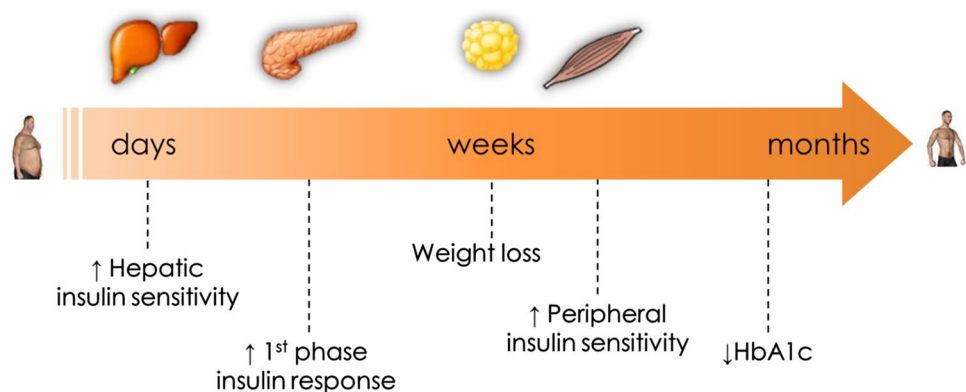
- VLCKD should be considered to obtain an early efficacy on glycemic control, particularly in obese patients with short duration of the disease (1 ØØØØ).
- VLCKD should be considered to reduce the use of glucose-lowering agents, including insulin (1 ØØØØ).

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 ØØØØ).

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 ØØØØ).
- 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 ØØØØ).

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 ØØØØ).
- We recommend VLCKD in obese hypertensive patients, not responsive to standard diets (1 ØØØØ).
- 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 ØØØØ).

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 ØØØØ).
- We suggest a weight-loss program with VLCKD for obese male patients with hypogonadism to improve their sexual function (2 ØØØØ).

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 ∅000).
- 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 ∅000).

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 ØØØØ).

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 flashes 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 ØØØØ).
- 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/m²) 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/m²) 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/m²) 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 ØØØØ).
- We suggest the use of KDs as adjuvant to conventional therapies in selected forms of Alzheimer/Parkinson's disease (2 ØØØØ).
- We suggest the use of VLCKD as a possible approach in selected elderly (65–75 years) with sarcopenic obesity (2 ØØØØ).

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 goals of nutritional therapy, characteristics of the patients, and clinical setting.

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Compliance with ethical standards

Conflict of interest MC. gave talks in symposia sponsored by Therascience, Eli Lilly, Novo Nordisk and New Penta, participated to advisory board for Therascience and Sanofi, and received research grants from Bayer AG; G.M. participated to advisory boards for Novartis and Shire and received honoraria for courses sponsored by Pfizer; S.B. gave talks in symposia sponsored by New Penta; L.C. and R.V. gave talks in symposia sponsored by Therascience; F.P. received grants by Difass International, Nutricia Research Foundation, and Probiotal; G.A. received honoraria from Astra Zeneca and Sanofi. All the other authors have nothing to disclose, related to this publication.

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.

References

- Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C et al (2014) 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* 384(9945):766–781
- Gregg EW, Shaw JE (2017) Global health effects of overweight and obesity. *N Engl J Med* 377(1):80–81
- (NCD-RisC) NRFC (2016) Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*. 387(10027):1513–1530
- Hruby A, Hu FB (2015) The epidemiology of obesity: a big picture. *Pharmacoeconomics* 33(7):673–689
- Verhaegen AA, Van Gaal LF (2017) Drug-induced obesity and its metabolic consequences: a review with a focus on mechanisms and possible therapeutic options. *J Endocrinol Invest* 40(11):1165–1174
- Piaggi P, Vinales KL, Basolo A, Santini F, Krakoff J (2018) Energy expenditure in the etiology of human obesity: spendthrift and thrifty metabolic phenotypes and energy-sensing mechanisms. *J Endocrinol Invest* 41(1):83–89
- Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V et al (2017) Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet* 390(10107):2050–2062
- Ramsden CE, Domenichiello AF (2017) PURE study challenges the definition of a healthy diet: but key questions remain. *Lancet* 390(10107):2018–2019

9. (NCD-RisC) NRFC (2016) Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet*. 387(10026):1377–1396
10. Scherer PE, Hill JA (2016) Obesity, diabetes, and cardiovascular diseases: a compendium. *Circ Res* 118(11):1703–1705
11. Saklayen MG (2018) The global epidemic of the metabolic syndrome. *Curr Hypertens Rep* 20(2):12
12. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA et al (2014) 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. *J Am Coll Cardiol*. 63(25 Pt B):2985–3023
13. Siraj ES, Williams KJ (2015) Another agent for obesity—will this time be different? *N Engl J Med* 373(1):82–83
14. Montesi L, El Ghoch M, Brodosi L, Calugi S, Marchesini G, Dalle Grave R (2016) Long-term weight loss maintenance for obesity: a multidisciplinary approach. *Diabetes Metab Syndr* 9:37–46
15. Patel DK, Stanford FC (2018) Safety and tolerability of new-generation anti-obesity medications: a narrative review. *Postgrad Med* 130(2):173–182
16. Pories WJ (2008) Bariatric surgery: risks and rewards. *J Clin Endocrinol Metab* 93(11 Suppl 1):S89–S96
17. Abbasi J (2018) Interest in the ketogenic diet grows for weight loss and type 2 diabetes. *JAMA* 319(3):215–217
18. Merra G, Miranda R, Barrucco S, Gualtieri P, Mazza M, Moriconi E et al (2016) 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* 20(12):2613–2621
19. Merra G, Gratteri S, De Lorenzo A, Barrucco S, Perrone MA, Avolio E et al (2017) 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* 21(2):329–345
20. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T (2013) Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr* 110(7):1178–1187
21. Westman EC, Yancy WS, Mavropoulos JC, Marquart M, McDuffie JR (2008) 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)* 5:36
22. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM (2012) Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition* 28(10):1016–1021
23. Paoli A, Rubini A, Volek JS, Grimaldi KA (2013) Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur J Clin Nutr* 67(8):789–796
24. Cicero AF, Benelli M, Brancaleoni M, Dainelli G, Merlini D, Negri R (2015) Middle and long-term impact of a very low-carbohydrate ketogenic diet on cardiometabolic factors: a multi-center, cross-sectional, clinical study. *High Blood Press Cardiovasc Prev*. 22(4):389–394
25. Wilder RM (1921) The effects of ketonemia on the course of epilepsy. *Mayo Clin Proc* 2:307–308
26. Nagy R (1974) Dr. Atkins' diet revolution: a review. *Va Med Mon* 101(5):383–385
27. Blackburn GL, Flatt JP, Clowes GH, O'Donnell TF, Hensle TE (1973) Protein sparing therapy during periods of starvation with sepsis of trauma. *Ann Surg* 177(5):588–594
28. Bistrian BR, Blackburn GL, Flatt JP, Sizer J, Scrimshaw NS, Sherman M (1976) Nitrogen metabolism and insulin requirements in obese diabetic adults on a protein-sparing modified fast. *Diabetes* 25(6):494–504
29. Bistrian BR (1978) Clinical use of a protein-sparing modified fast. *JAMA* 240(21):2299–2302
30. Palgi A, Read JL, Greenberg I, Hofer MA, Bistrian BR, Blackburn GL (1985) Multidisciplinary treatment of obesity with a protein-sparing modified fast: results in 668 outpatients. *Am J Public Health* 75(10):1190–1194
31. Walters JK, Hoogwerf BJ, Reddy SS (1997) The protein-sparing modified fast for obesity-related medical problems. *Cleve Clin J Med* 64(5):242–244
32. Pezzana A, Amerio ML, Fatati G, Caregaro Negrin L, Muratori F, Rovera GM et al (2014) La dieta chetogenica—fondazione ADI: position Paper. *ADI* 6:38–43
33. 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)
34. Paoli A (2014) Ketogenic diet for obesity: friend or foe? *Int J Environ Res Public Health* 11(2):2092–2107
35. Antonio J, Ellerbroek A, Silver T, Vargas L, Tamayo A, Buehn R et al (2016) A high protein diet has no harmful effects: a one-year crossover study in resistance-trained males. *J Nutr Metab* 2016:9104792
36. Bakhach M, Shah V, Harwood T, Lappe S, Bhesania N, Mansoor S et al (2016) The protein-sparing modified fast diet: an effective and safe approach to induce rapid weight loss in severely obese adolescents. *Glob Pediatr Health*. 3:2333794X15623245
37. Atkinson RL, Dietz WH, Foreyt JP, Goodwin NJ, Hill JO, Hirsch J et al (1993) Very low-calorie diets. National task force on the prevention and treatment of obesity. National Institutes of Health. *JAMA* 270(8):967–974
38. Paoli A, Bosco G, Camporesi EM, Mangar D (2015) Ketosis, ketogenic diet and food intake control: a complex relationship. *Front Psychol* 6:27
39. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH et al (2008) A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 93(3):666–673
40. Fukao T, Lopaschuk GD, Mitchell GA (2004) Pathways and control of ketone body metabolism: on the fringe of lipid biochemistry. *Prostaglandins Leukot Essent Fatty Acids* 70(3):243–251
41. Grabacka M, Pierzchalska M, Dean M, Reiss K (2016) Regulation of ketone body metabolism and the role of PPAR α . *Int J Mol Sci* 17(12):2093
42. Mitchell GA, Kassovska-Bratinova S, Boukaftane Y, Robert MF, Wang SP, Ashmarina L et al (1995) Medical aspects of ketone body metabolism. *Clin Invest Med* 18(3):193–216
43. Laffel L (1999) Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes Metab Res Rev*. 15(6):412–426
44. McPherson PA, McEneny J (2012) The biochemistry of ketogenesis and its role in weight management, neurological disease and oxidative stress. *J Physiol Biochem*. 68(1):141–151
45. Garber AJ, Menzel PH, Boden G, Owen OE (1974) Hepatic ketogenesis and gluconeogenesis in humans. *J Clin Invest* 54(4):981–989
46. Newman JC, Verdin E (2014) Ketone bodies as signaling metabolites. *Trends Endocrinol Metab* 25(1):42–52
47. Wolfrum C, Besser D, Luca E, Stoffel M (2003) Insulin regulates the activity of forkhead transcription factor Hnf-3 β /Foxa-2 by Akt-mediated phosphorylation and nuclear/cytosolic localization. *Proc Natl Acad Sci USA* 100(20):11624–11629

48. von Meyenn F, Porstmann T, Gasser E, Selevsek N, Schmidt A, Aebersold R et al (2013) Glucagon-induced acetylation of Foxa2 regulates hepatic lipid metabolism. *Cell Metab* 17(3):436–447
49. Krebs HA (1966) The regulation of the release of ketone bodies by the liver. *Adv Enzyme Regul* 4:339–354
50. Veldhorst MA, Westerterp-Plantenga MS, Westerterp KR (2009) Gluconeogenesis and energy expenditure after a high-protein, carbohydrate-free diet. *Am J Clin Nutr* 90(3):519–526
51. McDonald L (1998) The basics of fuel utilization. In: *The Ketogenic diet: a complete guide for the dieter and practitioner*, Chapter 3, 1st edn. Morris Publishing, pp 18–27. ISBN: 0967145600
52. Urbain P, Bertz H (2016) Monitoring for compliance with a ketogenic diet: what is the best time of day to test for urinary ketosis? *Nutr Metab (Lond)*. 13:77
53. Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D et al (2016) American association of clinical endocrinologists and American College of endocrinology position statement on the association of sglt-2 inhibitors and diabetic ketoacidosis. *Endocr Pract* 22(6):753–762
54. Dashti HM, Mathew TC, Hussein T, Asfar SK, Behbahani A, Khourshed MA et al (2004) Long-term effects of a ketogenic diet in obese patients. *Exp Clin Cardiol* 9(3):200–205
55. Dashti HM, Mathew TC, Khadada M, Al-Mousawi M, Talib H, Asfar SK et al (2007) Beneficial effects of ketogenic diet in obese diabetic subjects. *Mol Cell Biochem* 302(1–2):249–256
56. Ryan DH (2016) Guidelines for Obesity Management. *Endocrinol Metab Clin N Am* 45(3):501–510
57. Stegenga H, Haines A, Jones K, Wilding J, Group GD (2014) Identification, assessment, and management of overweight and obesity: summary of updated NICE guidance. *BMJ*. 349:g6608
58. Raynor HA, Champagne CM (2016) Position of the academy of nutrition and dietetics: interventions for the treatment of overweight and obesity in adults. *J Acad Nutr Diet* 116(1):129–147
59. Gibson AA, Seimon RV, Lee CM, Ayre J, Franklin J, Markovic TP et al (2015) Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. *Obes Rev* 16(1):64–76
60. Pilone V, Tramontano S, Renzulli M, Romano M, Cobellis L, Berselli T et al (2018) Metabolic effects, safety, and acceptability of very low-calorie ketogenic dietetic scheme on candidates for bariatric surgery. *Surg Obes Relat Dis*. 14(7):1013–1019
61. Gershuni VM, Yan SL, Medici V (2018) Nutritional Ketosis for Weight Management and Reversal of Metabolic Syndrome. *Curr Nutr Rep*. 7(3):97–106
62. Bhanpuri NH, Hallberg SJ, Williams PT, McKenzie AL, Ballard KD, Campbell WW et al (2018) 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* 17(1):56
63. Moreno B, Crujeiras AB, Bellido D, Sajoux I, Casanueva FF (2016) Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. *Endocrine* 54(3):681–690
64. Gomez-Arbelaes D, Bellido D, Castro AI, Ordoñez-Mayan L, Carreira J, Galban C et al (2017) Body composition changes after very-low-calorie ketogenic diet in obesity evaluated by 3 standardized methods. *J Clin Endocrinol Metab* 102(2):488–498
65. Temmerman JC, Friedman AN (2013) Very low calorie ketogenic weight reduction diet in patients with cirrhosis: a case series. *Nutr Diabetes*. 3:e95
66. Sumithran P, Proietto J (2008) Safe year-long use of a very-low-calorie diet for the treatment of severe obesity. *Med J Aust* 188(6):366–368
67. Parretti HM, Jebb SA, Johns DJ, Lewis AL, Christian-Brown AM, Aveyard P (2016) Clinical effectiveness of very-low-energy diets in the management of weight loss: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev* 17(3):225–234
68. Chang JJ, Bena J, Kannan S, Kim J, Burguera B, Kashyap SR (2017) Limited carbohydrate refeeding instruction for long-term weight maintenance following a ketogenic, very-low-calorie meal plan. *Endocr Pract*. 23(6):649–656
69. Paoli A, Bianco A, Grimaldi KA, Lodi A, Bosco G (2013) Long term successful weight loss with a combination biphasic ketogenic Mediterranean diet and Mediterranean diet maintenance protocol. *Nutrients* 5(12):5205–5217
70. Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L (2017) American society for metabolic and bariatric surgery integrated health nutritional guidelines for the surgical weight loss patient 2016 update: micronutrients. *Surg Obes Relat Dis* 13(5):727–741
71. Mechanick JI, Youdim A, Jones DB, Timothy Garvey W, Hurley DL, Molly McMahon M et al (2013) Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Surg Obes Relat Dis* 9(2):159–191
72. Naseer F, Shabbir A, Livingstone B, Price R, Syn NL, Flannery O (2018) The efficacy of energy-restricted diets in achieving preoperative weight loss for bariatric patients: a systematic review. *Obes Surg* 28(11):3678–3690
73. Schiavo L, Scalera G, Sergio R, De Sena G, Pilone V, Barbarisi A (2015) 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* 11(5):1164–1170
74. Ross LJ, Wallin S, Osland EJ, Memon MA (2016) Commercial very low energy meal replacements for preoperative weight loss in obese patients: a systematic review. *Obes Surg* 26(6):1343–1351
75. Leonetti F, Campanile FC, Coccia F, Capoccia D, Alessandrini L, Puzziello A et al (2015) Very low-carbohydrate ketogenic diet before bariatric surgery: prospective evaluation of a sequential diet. *Obes Surg* 25(1):64–71
76. Albanese A, Prevedello L, Markovich M, Busetto L, Vettor R, Foletto M (2018) Pre-operative very low calorie ketogenic diet (VLCKD) vs. very low calorie diet (VLCD): surgical impact. *Obes Surg*. 29:292–296
77. Schiavo L, Pilone V, Rossetti G, Barbarisi A, Cesaretti M, Iannelli A (2018) 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* 28(8):2215–2224
78. Colles SL, Dixon JB, Marks P, Strauss BJ, O'Brien PE (2006) Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging. *Am J Clin Nutr* 84(2):304–311
79. Bertoli S, Trentani C, Ferraris C, De Giorgis V, Veggiotti P, Tagliabue A (2014) Long-term effects of a ketogenic diet on body composition and bone mineralization in GLUT-1 deficiency syndrome: a case series. *Nutrition* 30(6):726–728
80. Klement RJ, Sweeney RA (2016) Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients. *BMC Res Notes*. 9:143
81. Colica C, Merra G, Gasbarrini A, De Lorenzo A, Cioccoloni G, Gualtieri P et al (2017) Efficacy and safety of very-low-calorie

- ketogenic diet: a double blind randomized crossover study. *Eur Rev Med Pharmacol Sci*. 21(9):2274–2289
82. Gomez-Arbelaez D, Crujeiras AB, Castro AI, Martinez-Olmos MA, Canton A, Ordoñez-Mayan L et al (2018) Resting metabolic rate of obese patients under very low calorie ketogenic diet. *Nutr Metab (Lond)*. 15:18
 83. Tinsley GM, Willoughby DS (2016) Fat-free mass changes during ketogenic diets and the potential role of resistance training. *Int J Sport Nutr Exerc Metab* 26(1):78–92
 84. Vargas S, Romance R, Petro JL, Bonilla DA, Galancho I, Espinar S et al (2018) Efficacy of ketogenic diet on body composition during resistance training in trained men: a randomized controlled trial. *J Int Soc Sports Nutr* 15(1):31
 85. Carnauba RA, Baptistella AB, Paschoal V, Hübscher GH (2017) Diet-induced low-grade metabolic acidosis and clinical outcomes: a review. *Nutrients* 9(6):538
 86. Yuan FL, Xu MH, Li X, Xinlong H, Fang W, Dong J (2016) The roles of acidosis in osteoclast biology. *Front Physiol* 7:222
 87. European Food Safety Authority (EFSA) (2015) Scientific Opinion on the essential composition of total diet replacements for weight control. *EFSA J* 13(1):3957
 88. Gissel T, Poulsen CS, Vestergaard P (2007) Adverse effects of antiepileptic drugs on bone mineral density in children. *Expert Opin Drug Saf* 6(3):267–278
 89. Bergqvist AG, Schall JI, Stallings VA, Zemel BS (2008) Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. *Am J Clin Nutr* 88(6):1678–1684
 90. Carter JD, Vasey FB, Valeriano J (2006) The effect of a low-carbohydrate diet on bone turnover. *Osteoporos Int* 17(9):1398–1403
 91. Barengolts E (2016) Gut microbiota, prebiotics, probiotics, and synbiotics in management of obesity and prediabetes: review of randomized controlled trials. *Endocr Pract* 22(10):1224–1234
 92. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE et al (2014) Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505(7484):559–563
 93. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K et al (2017) Influence of diet on the gut microbiome and implications for human health. *J Transl Med* 15(1):73
 94. McAllan L, Skuse P, Cotter PD, O'Connor P, Cryan JF, Ross RP et al (2014) Protein quality and the protein to carbohydrate ratio within a high fat diet influences energy balance and the gut microbiota in C57BL/6J mice. *PLoS One* 9(2):e88904
 95. Heinsen FA, Fangmann D, Müller N, Schulte DM, Rühlemann MC, Türk K et al (2016) Beneficial effects of a dietary weight loss intervention on human gut microbiome diversity and metabolism are not sustained during weight maintenance. *Obes Facts* 9(6):379–391
 96. Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY (2018) The gut microbiota mediates the anti-seizure effects of the ketogenic diet. *Cell* 173(7):1728–41.e13
 97. Gu Y, Yu H, Li Y, Ma X, Lu J, Yu W et al (2013) Beneficial effects of an 8-week, very low carbohydrate diet intervention on obese subjects. *Evid Based Complement Alternat Med* 2013:760804
 98. Svendsen PF, Jensen FK, Holst JJ, Haugaard SB, Nilas L, Madsbad S (2012) The effect of a very low calorie diet on insulin sensitivity, beta cell function, insulin clearance, incretin hormone secretion, androgen levels and body composition in obese young women. *Scand J Clin Lab Invest* 72(5):410–419
 99. Demol S, Yacobovitch-Gavan M, Shalitin S, Nagelberg N, Gillon-Keren M, Phillip M (2009) Low-carbohydrate (low & high-fat) versus high-carbohydrate low-fat diets in the treatment of obesity in adolescents. *Acta Paediatr* 98(2):346–351
 100. Kirk S, Brehm B, Saelens BE, Woo JG, Kissel E, D'Alessio D et al (2012) Role of carbohydrate modification in weight management among obese children: a randomized clinical trial. *J Pediatr* 161(2):320–327.e1
 101. Krebs NF, Gao D, Gralla J, Collins JS, Johnson SL (2010) Efficacy and safety of a high protein, low carbohydrate diet for weight loss in severely obese adolescents. *J Pediatr* 157(2):252–258
 102. Partsalaki I, Karvela A, Spiliotis BE (2012) Metabolic impact of a ketogenic diet compared to a hypocaloric diet in obese children and adolescents. *J Pediatr Endocrinol Metab* 25(7–8):697–704
 103. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R (2011) Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 54(10):2506–2514
 104. Malandrucchio I, Pasqualetti P, Giordani I, Manfellotto D, De Marco F, Alegiani F et al (2012) Very-low-calorie diet: a quick therapeutic tool to improve β cell function in morbidly obese patients with type 2 diabetes. *Am J Clin Nutr* 95(3):609–613
 105. Viljanen AP, Lautamäki R, Järvisalo M, Parkkola R, Huupponen R, Lehtimäki T et al (2009) Effects of weight loss on visceral and abdominal subcutaneous adipose tissue blood-flow and insulin-mediated glucose uptake in healthy obese subjects. *Ann Med* 41(2):152–160
 106. Steven S, Hollingsworth KG, Al-Mrabeh A, Avery L, Aribisala B, Caslake M et al (2016) Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. *Diabetes Care* 39(5):808–815
 107. Jackness C, Karmally W, Febres G, Conwell IM, Ahmed L, Bessler M et al (2013) Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and β -cell Function in type 2 diabetic patients. *Diabetes* 62(9):3027–3032
 108. Goday A, Bellido D, Sajoux I, Crujeiras AB, Burguera B, García-Luna PP et al (2016) 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* 6(9):e230
 109. Rothberg AE, McEwen LN, Kraftson AT, Fowler CE, Herman WH (2014) Very-low-energy diet for type 2 diabetes: an underutilized therapy? *J Diabetes Complic* 28(4):506–510
 110. Capstick F, Brooks BA, Burns CM, Zilkens RR, Steinbeck KS, Yue DK (1997) Very low calorie diet (VLCD): a useful alternative in the treatment of the obese NIDDM patient. *Diabetes Res Clin Pract* 36(2):105–111
 111. Baker ST, Jerums G, Prendergast LA, Panagiotopoulos S, Strauss BJ, Proietto J (2012) Less fat reduction per unit weight loss in type 2 diabetic compared with nondiabetic obese individuals completing a very-low-calorie diet program. *Metabolism* 61(6):873–882
 112. Jazet IM, de Craen AJ, van Schie EM, Meinders AE (2007) Sustained beneficial metabolic effects 18 months after a 30-day very low calorie diet in severely obese, insulin-treated patients with type 2 diabetes. *Diabetes Res Clin Pract* 77(1):70–76
 113. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA (2003) 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* 88(4):1617–1623
 114. Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J et al (2003) A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 348(21):2074–2081
 115. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS et al (2003) A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 348(21):2082–2090
 116. Yancy WS, Olsen MK, Guyton JR, Bakst RP, Westman EC (2004) A low-carbohydrate, ketogenic diet versus a low-fat diet

- to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med* 140(10):769–777
117. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGroy J et al (2004) 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* 140(10):778–785
 118. Dashti HM, Al-Zaid NS, Mathew TC, Al-Mousawi M, Talib H, Asfar SK et al (2006) Long term effects of ketogenic diet in obese subjects with high cholesterol level. *Mol Cell Biochem* 286(1–2):1–9
 119. Zelber-Sagi S, Ratziu V, Oren R (2011) Nutrition and physical activity in NAFLD: an overview of the epidemiological evidence. *World J Gastroenterol* 17(29):3377–3389
 120. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI (2005) Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 54(3):603–608
 121. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO) (2016) Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. 64(6):1388–1402
 122. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L et al (2015) Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 149(2):367–378.e5 (**quiz e14-5**)
 123. Anania C, Perla FM, Olivero F, Pacifico L, Chiesa C (2018) Mediterranean diet and nonalcoholic fatty liver disease. *World J Gastroenterol* 24(19):2083–2094
 124. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M et al (2018) The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 67(1):328–357
 125. Browning JD, Baker JA, Rogers T, Davis J, Satapati S, Burgess SC (2011) Short-term weight loss and hepatic triglyceride reduction: evidence of a metabolic advantage with dietary carbohydrate restriction. *Am J Clin Nutr* 93(5):1048–1052
 126. Bian H, Hakkarainen A, Lundbom N, Yki-Järvinen H (2014) Effects of dietary interventions on liver volume in humans. *Obesity (Silver Spring)*. 22(4):989–995
 127. Haghighatdoost F, Salehi-Abargouei A, Surkan PJ, Azadbakht L (2016) The effects of low carbohydrate diets on liver function tests in nonalcoholic fatty liver disease: a systematic review and meta-analysis of clinical trials. *J Res Med Sci* 21:53
 128. Bortolotti M, Kreis R, Debard C, Cariou B, Faeh D, Chetiveaux M et al (2009) High protein intake reduces intrahepatocellular lipid deposition in humans. *Am J Clin Nutr* 90(4):1002–1010
 129. Bortolotti M, Maiolo E, Corazza M, Van Dijke E, Schneiter P, Boss A et al (2011) Effects of a whey protein supplementation on intrahepatocellular lipids in obese female patients. *Clin Nutr* 30(4):494–498
 130. Theytaz F, Noguchi Y, Egli L, Campos V, Buehler T, Hodson L et al (2012) Effects of supplementation with essential amino acids on intrahepatic lipid concentrations during fructose overfeeding in humans. *Am J Clin Nutr* 96(5):1008–1016
 131. Drummen M, Dorenbos E, Vreugdenhil AC, Raben A, Fogelholm M, Westerterp-Plantenga MS et al (2018) Long-term effects of increased protein intake after weight loss on intrahepatic lipid content and implications for insulin sensitivity—a preview study. *Am J Physiol Endocrinol Metab* 315:E885–E891
 132. Drummen M, Tischmann L, Gatta-Cherifi B, Adam T, Westerterp-Plantenga M (2018) Dietary protein and energy balance in relation to obesity and co-morbidities. *Front Endocrinol (Lausanne)*. 9:443
 133. Westerterp-Plantenga MS, Lemmens SG, Westerterp KR (2012) Dietary protein—its role in satiety, energetics, weight loss and health. *Br J Nutr* 108(Suppl 2):S105–S112
 134. Torres N, Tovar AR (2007) The role of dietary protein on lipotoxicity. *Nutr Rev* 65(6 Pt 2):S64–S68
 135. Hudgins LC, Hellerstein MK, Seidman CE, Neese RA, Tremaroli JD, Hirsch J (2000) Relationship between carbohydrate-induced hypertriglyceridemia and fatty acid synthesis in lean and obese subjects. *J Lipid Res* 41(4):595–604
 136. Schwarz JM, Neese RA, Turner S, Dare D, Hellerstein MK (1995) Short-term alterations in carbohydrate energy intake in humans. Striking effects on hepatic glucose production, de novo lipogenesis, lipolysis, and whole-body fuel selection. *J Clin Invest* 96(6):2735–2743
 137. Ortega FB, Lavie CJ, Blair SN (2016) Obesity and cardiovascular disease. *Circ Res* 118(11):1752–1770
 138. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD et al (2018) Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. *JAMA Cardiol* 3(4):280–287
 139. Armani A, Berry A, Cirulli F, Caprio M (2017) Molecular mechanisms underlying metabolic syndrome: the expanding role of the adipocyte. *FASEB J* 31(10):4240–4255
 140. Yancy WS, Westman EC, McDuffie JR, Grambow SC, Jeffreys AS, Bolton J et al (2010) A randomized trial of a low-carbohydrate diet vs orlistat plus a low-fat diet for weight loss. *Arch Intern Med* 170(2):136–145
 141. Hammer S, Snel M, Lamb HJ, Jazet IM, van der Meer RW, Pijl H et al (2008) Prolonged caloric restriction in obese patients with type 2 diabetes mellitus decreases myocardial triglyceride content and improves myocardial function. *J Am Coll Cardiol* 52(12):1006–1012
 142. Jonker JT, Snel M, Hammer S, Jazet IM, van der Meer RW, Pijl H et al (2014) Sustained cardiac remodeling after a short-term very low calorie diet in type 2 diabetes mellitus patients. *Int J Cardiovasc Imaging* 30(1):121–127
 143. Aubert G, Martin OJ, Horton JL, Lai L, Vega RB, Leone TC et al (2016) The failing heart relies on ketone bodies as a fuel. *Circulation* 133(8):698–705
 144. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R et al (2016) Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. *Diabetes* 65(5):1190–1195
 145. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 373(22):2117–2128
 146. Abdul-Ghani MA, Norton L, DeFronzo RA (2015) Renal sodium-glucose cotransporter inhibition in the management of type 2 diabetes mellitus. *Am J Physiol Renal Physiol* 309(11):F889–F900
 147. Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S et al (2011) Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proc Natl Acad Sci USA* 108(19):8030–8035
 148. Forsythe CE, Phinney SD, Fernandez ML, Quann EE, Wood RJ, Bibus DM et al (2008) Comparison of low fat and low carbohydrate diets on circulating fatty acid composition and markers of inflammation. *Lipids* 43(1):65–77
 149. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D et al (2015) The ketone metabolite β -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med* 21(3):263–269
 150. Prattichizzo F, De Nigris V, Micheloni S, La Sala L, Ceriello A (2018) Increases in circulating levels of ketone bodies and cardiovascular protection with SGLT2 inhibitors: is low-grade

- inflammation the neglected component? *Diabetes Obes Metab* 20(11):2515–2522
151. Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L (1996) Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple risk factor intervention trial. *Am J Epidemiol* 143(9):889–897
 152. Haffner SM (2000) Sex hormones, obesity, fat distribution, type 2 diabetes and insulin resistance: epidemiological and clinical correlation. *Int J Obes Relat Metab Disord* 24(Suppl 2):S56–S58
 153. Abate N, Haffner SM, Garg A, Peshock RM, Grundy SM (2002) Sex steroid hormones, upper body obesity, and insulin resistance. *J Clin Endocrinol Metab* 87(10):4522–4527
 154. Livingstone C, Collison M (2002) Sex steroids and insulin resistance. *Clin Sci (Lond)*. 102(2):151–166
 155. Kaukua J, Pekkarinen T, Sane T, Mustajoki P (2003) Sex hormones and sexual function in obese men losing weight. *Obes Res* 11(6):689–694
 156. Ng Tang Fui M, Prendergast LA, Dupuis P, Raval M, Strauss BJ, Zajac JD et al (2016) Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet: a randomised controlled trial. *BMC Med* 14(1):153
 157. Niskanen L, Laaksonen DE, Punnonen K, Mustajoki P, Kaukua J, Rissanen A (2004) Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome. *Diabetes Obes Metab* 6(3):208–215
 158. Khoo J, Piantadosi C, Worthley S, Wittert GA (2010) Effects of a low-energy diet on sexual function and lower urinary tract symptoms in obese men. *Int J Obes (Lond)*. 34(9):1396–1403
 159. La Vignera S, Condorelli RA, Vicari E, Calogero AE (2012) Negative effect of increased body weight on sperm conventional and nonconventional flow cytometric sperm parameters. *J Androl* 33(1):53–58
 160. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A et al (2014) The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. *Eur J Endocrinol* 171(4):P1–P29
 161. Tosi F, Bonora E, Moghetti P (2017) Insulin resistance in a large cohort of women with polycystic ovary syndrome: a comparison between euglycaemic-hyperinsulinaemic clamp and surrogate indexes. *Hum Reprod* 32(12):2515–2521
 162. Repaci A, Gambineri A, Pasquali R (2011) The role of low-grade inflammation in the polycystic ovary syndrome. *Mol Cell Endocrinol* 335(1):30–41
 163. Pasquali R, Gambineri A, Cavazza C, Ibarra Gasparini D, Ciampaglia W, Cognigni GE et al (2011) Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. *Eur J Endocrinol* 164(1):53–60
 164. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L et al (2018) Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril* 110(3):364–379
 165. Mehrabani HH, Salehpour S, Amiri Z, Farahani SJ, Meyer BJ, Tahbaz F (2012) Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. *J Am Coll Nutr* 31(2):117–125
 166. Gower BA, Goss AM (2015) A lower-carbohydrate, higher-fat diet reduces abdominal and intermuscular fat and increases insulin sensitivity in adults at risk of type 2 diabetes. *J Nutr* 145(1):177S–183S
 167. Mavropoulos JC, Yancy WS, Hepburn J, Westman EC (2005) The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. *Nutr Metab (Lond)* 2:35
 168. Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV et al (2015) Treatment of symptoms of the menopause: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 100(11):3975–4011
 169. El Khoudary SR, Thurston RC (2018) Cardiovascular implications of the menopause transition: endogenous sex hormones and vasomotor symptoms. *Obstet Gynecol Clin N Am* 45(4):641–661
 170. Thurston RC, Chang Y, Barinas-Mitchell E, Jennings JR, von Känel R, Landsittel DP et al (2017) Physiologically assessed hot flashes and endothelial function among midlife women. *Menopause* 24(8):886–893
 171. Gold EB, Crawford SL, Shelton JF, Tepper PG, Crandall CJ, Greendale GA et al (2017) Longitudinal analysis of changes in weight and waist circumference in relation to incident vasomotor symptoms: the Study of Women’s Health Across the Nation (SWAN). *Menopause* 24(1):9–26
 172. Thurston RC, Ewing LJ, Low CA, Christie AJ, Levine MD (2015) Behavioral weight loss for the management of menopausal hot flashes: a pilot study. *Menopause* 22(1):59–65
 173. Heussinger N, Della Marina A, Beyerlein A, Leiendecker B, Hermann-Alves S, Dalla Pozza R et al (2018) 10 patients, 10 years—long term follow-up of cardiovascular risk factors in Glut1 deficiency treated with ketogenic diet therapies: a prospective, multicenter case series. *Clin Nutr* 37(6 Pt A):2246–2251
 174. van der Louw E, van den Hurk D, Neal E, Leiendecker B, Fitzsimmon G, Dority L et al (2016) Ketogenic diet guidelines for infants with refractory epilepsy. *Eur J Paediatr Neurol* 20(6):798–809
 175. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R et al (2018) Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open* 3(2):175–192
 176. Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH et al (2017) Pediatric obesity-assessment, treatment, and prevention: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 102(3):709–757
 177. Gibson LJ, Peto J, Warren JM, dos Santos Silva I (2006) Lack of evidence on diets for obesity for children: a systematic review. *Int J Epidemiol* 35(6):1544–1552
 178. Gow ML, Garnett SP, Baur LA, Lister NB (2016) The effectiveness of different diet strategies to reduce type 2 diabetes risk in youth. *Nutrients* 8(8):486
 179. Figueroa-Colon R, von Almen TK, Franklin FA, Schuftan C, Suskind RM (1993) Comparison of two hypocaloric diets in obese children. *Am J Dis Child* 147(2):160–166
 180. Berkowitz RI, Wadden TA, Gehrman CA, Bishop-Gilyard CT, Moore RH, Womble LG et al (2011) Meal replacements in the treatment of adolescent obesity: a randomized controlled trial. *Obesity (Silver Spring)* 19(6):1193–1199
 181. Peña L, Peña M, Gonzalez J, Claro A (1979) A comparative study of two diets in the treatment of primary exogenous obesity in children. *Acta Paediatr Acad Sci Hung* 20(1):99–103
 182. Sondike SB, Copperman N, Jacobson MS (2003) Effects of a low-carbohydrate diet on weight loss and cardiovascular risk factor in overweight adolescents. *J Pediatr* 142(3):253–258
 183. Willi SM, Martin K, Datko FM, Brant BP (2004) Treatment of type 2 diabetes in childhood using a very-low-calorie diet. *Diabetes Care* 27(2):348–353
 184. de Lau LM, Bornebroek M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM (2005) Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. *Neurology* 64(12):2040–2045
 185. Cunnane SC, Courchesne-Loyer A, St-Pierre V, Vandenbergh C, Pierotti T, Fortier M et al (2016) Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for

- the risk and treatment of Alzheimer's disease. *Ann N Y Acad Sci* 1367(1):12–20
186. Castellano CA, Nugent S, Paquet N, Tremblay S, Bocti C, Lacombe G et al (2015) Lower brain 18F-fluorodeoxyglucose uptake but normal 11C-acetoacetate metabolism in mild Alzheimer's disease dementia. *J Alzheimers Dis* 43(4):1343–1353
187. Verdile G, Keane KN, Cruzat VF, Medic S, Sabale M, Rowles J et al (2015) Inflammation and oxidative stress: the molecular connectivity between insulin resistance, obesity, and Alzheimer's disease. *Mediators Inflamm* 2015:105828
188. Pinto A, Bonucci A, Maggi E, Corsi M, Businaro R (2018) Antioxidant and anti-inflammatory activity of ketogenic diet: new perspectives for neuroprotection in Alzheimer's disease. *Antioxidants (Basel)* 7(5):63
189. Taylor MK, Sullivan DK, Mahnken JD, Burns JM, Swerdlow RH (2018) Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. *Alzheimers Dement (N Y)* 4:28–36
190. Roberts MN, Wallace MA, Tomilov AA, Zhou Z, Marcotte GR, Tran D et al (2017) A Ketogenic diet extends longevity and healthspan in adult mice. *Cell Metab* 26(3):539–546.e5
191. Newman JC, Covarrubias AJ, Zhao M, Yu X, Gut P, Ng CP et al (2017) Ketogenic diet reduces midlife mortality and improves memory in aging mice. *Cell Metab* 26(3):547–557.e8
192. Astrup A, Hjorth MF (2017) Ageing: improvement in age-related cognitive functions and life expectancy by ketogenic diets. *Nat Rev Endocrinol* 13(12):695–696

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Affiliations

M. Caprio^{1,2} · M. Infante³ · E. Moriconi^{1,4} · A. Armani¹ · A. Fabbri³ · G. Mantovani⁵ · S. Mariani⁴ · C. Lubrano⁴ · E. Poggiogalle⁴ · S. Migliaccio⁶ · L. M. Donini⁴ · S. Basciani⁴ · A. Cignarelli⁷ · E. Conte⁷ · G. Ceccarini⁸ · F. Bogazzi⁹ · L. Cimino¹⁰ · R. A. Condorelli¹⁰ · S. La Vignera¹⁰ · A. E. Calogero¹⁰ · A. Gambineri¹¹ · L. Vignozzi¹² · F. Prodam¹³ · G. Aimaretti¹³ · G. Linsalata¹⁴ · S. Buralli¹⁴ · F. Monzani¹⁴ · A. Aversa¹⁵ · R. Vettor¹⁶ · F. Santini⁸ · P. Vitti⁹ · L. Gnessi⁴ · U. Pagotto¹¹ · F. Giorgino⁷ · A. Colao¹⁷ · A. Lenzi⁴ on behalf of the Cardiovascular Endocrinology Club of the Italian Society of Endocrinology

¹ Laboratory of Cardiovascular Endocrinology, IRCCS San Raffaele Pisana, Via di Val Cannuta 247, 00166 Rome, Italy

² Department of Human Sciences and Promotion of the Quality of Life, San Raffaele Roma Open University, Rome, Italy

³ Unit of Endocrinology and Metabolic Diseases, Department of Systems Medicine, CTO A. Alesini Hospital, ASL Roma 2, University of Rome Tor Vergata, Rome, Italy

⁴ Section of Medical Pathophysiology, Food Science and Endocrinology, Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

⁵ Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Endocrinology and Diabetology Unit, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

⁶ Section of Health Sciences, Department of Movement, Human and Health Sciences, "Foro Italico" University of Rome, Rome, Italy

⁷ Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, Bari, Italy

⁸ Endocrinology Unit, Obesity and Lipodystrophy Center, University Hospital of Pisa, Pisa, Italy

⁹ Endocrinology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

¹⁰ Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

¹¹ Endocrinology Unit and Center for Applied Biomedical Research, Department of Medical and Surgical Sciences, University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy

¹² Andrology, Women's Endocrinology and Gender Incongruence Unit, Department of Biomedical, Experimental and Clinical Sciences, University of Florence, AOU Careggi, Florence, Italy

¹³ Endocrinology, Department of Translational Medicine and Department of Health Sciences, University of Piemonte Orientale, Novara, Italy

¹⁴ Geriatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

¹⁵ Department of Experimental and Clinical Medicine, Magna Graecia University of Catanzaro, Catanzaro, Italy

¹⁶ Department of Medicine, Internal Medicine 3, University Hospital of Padova, Padua, Italy

¹⁷ Section of Endocrinology, Department of Clinical Medicine and Surgery, University "Federico II" of Naples, Naples, Italy