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REVIEW

Advancing Obesity Management: the Very Low-Energy Ketogenic therapy (VLEKT) as an Evolution of the "Traditional" Ketogenic Diet

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Abstract

Purpose of Review This narrative review comprehensively analyzes VLEKT as an advanced nutritional strategy for obesity management. The focus is on the beneficial effects on key disease organs, such as adipose tissue and liver, as well as the modulation of intestinal permeability and its fundamental role in influencing the gut microbiota and inflammatory pathways.

Recent Findings The impact of VLEKT on obesity-related comorbidities, including metabolic syndrome, cardiovascular disease, endocrine disorders, metabolic dysfunction-associated steatotic liver disease (MASLD), neurological disorders, and kidney alterations, is also investigated. Moreover, to assess its wider application in obesity treatment, the combination of ketogenic regimes with additional strategies such as physical activity, bariatric surgery, and digital health technologies is examined. Despite promising clinical results, adherence to VLEKT and potential nutritional deficiencies require careful follow-up and individualized programming monitored by specialists. Future research should focus on elucidating the molecular mechanisms underlying the effects on physiological systems, and long-term safety. Nevertheless, VLEKT is an innovative approach to obesity treatment, offering a target-oriented and highly effective strategy for people fighting against overweight and its associated medical complications.

Summary Obesity is a multifactorial and chronic disease associated with numerous comorbidities; given its increasing prevalence, effective and personalized intervention strategies are crucial to inhibit the "obesity pandemic" according to a "food re-educational" protocol. Among dietary interventions, the ketogenic diet (KD) has attracted attention for its effectiveness in weight management and metabolic benefits. A variant, the very low-calorie ketogenic diet (VLCKD), more recently defined as very low-energy ketogenic diet (VLEKD), combines the metabolic benefits of ketosis with substantial calorie restriction, improving overall health.

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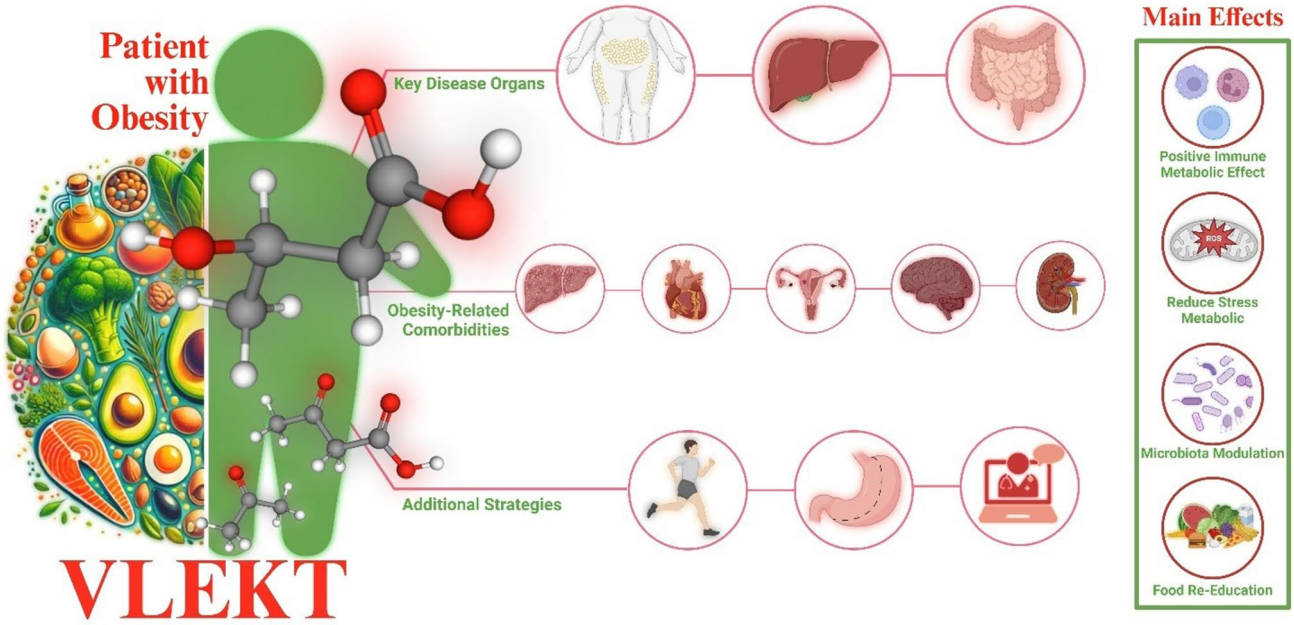
Graphical Abstract



Keywords Ketogenic diet (KD) · Very low calorie ketogenic diet (VLCKD) · Very low-energy ketogenic therapy (VLEKT) · Obesity metabolism · MASLD · Obesity

Introduction

Obesity is a complex and chronic disease characterized by the excessive accumulation of body fat; it is influenced by a multiplicity of genetic, neurological, metabolic, gastrointestinal, and behavioral factors [1]. Additionally, obesity remains one of the most significant risk factors for numerous comorbidity conditions, including cardiovascular disease, type 2 diabetes (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD), musculoskeletal disorders, and various forms of cancer [2].

It is estimated that 2–4% of total healthcare expenditure in Europe is attributable to obesity, and this amount is expected to double by 2050. In 2000, the Organization for Economic Co-operation and Development (OECD) considered Italy a symbol of healthy living with an obesity rate of 8% of the population, compared to 30% in the United States [3]. However, current trends in Italy have aligned it more closely with the European average [4]. Several factors contribute to this shift, but it is likely driven by the increased consumption of high-calorie foods and a progressively more sedentary lifestyle. This can be accurately described as triggering a global "obesity pandemic".

Different intervention strategies for obesity are available, and the initial approach is typically focused on lifestyle modifications and behavioral or psychotherapeutic interventions, which are of paramount importance. When necessary, pharmacological therapies for weight management may complement these measures or, when appropriate, bariatric surgery may be considered. While these latter interventions can produce more immediate results, they necessitate ongoing medical supervision and are associated with potential risks and complications. In any case, a combination of these approaches is always recommended to optimize therapeutic outcomes [5, 6].

Nutritional practices are a critical determinant in the etiology and progression of obesity, as well as a fundamental component in its effective management and intervention approaches. Excessive calorie consumption, often linked to diets high in ultra-processed foods, added sugars, and unhealthy fats, is a major factor driving weight gain [7]. Thus, analyzing and modifying dietary patterns is critical to a well-rounded approach to tackling obesity. Medical nutrition therapy is necessary to manage the condition, employing structured and patient-friendly dietary strategies yielding the most effective health outcomes [8]. In this comprehensive context, we delve into the clinical applications of one of the most intensely debated and widely discussed dietary strategies: the ketogenic diet (KD).

Developed approximately 100 years ago for the treatment of epilepsy, KD saw a significant decline in usage after 1938 with the advent of the first antiepileptic drugs. However, in the 1970s, Dr. Robert Atkins revived interest in this diet,

utilizing it as an effective strategy for weight loss. The KD experienced a resurgence in popularity in the early 2000s in the United States, partly due to its promotion through television programs [9]. Although widely recognized for its significant benefits in promoting weight loss, the diet remains a topic of heated debate among the public and the scientific community. This controversy stems from persistent concerns about its potential side effects, which continue to spark caution and critical analysis. Based on this, the very low-calorie ketogenic diet (VLCKD) has emerged as an evolution of the "traditional" KD, specifically designed to address the issue of obesity. The VLCKD integrates the principles of ketogenic metabolism with significant caloric restriction, thereby optimizing weight loss and enhancing metabolic outcomes [10]. According to the latest definitions, the Italian Society of Nutraceuticals (SINut) and the Italian Association of Dietetics and Clinical Nutrition (ADI), through the "KetoNut" panel of experts, have proposed a new definition for VLCKDs to standardize the nomenclature. The new definition introduces the acronym Very Low-Energy Ketogenic Therapy (VLEKT), which, in the context of patients with obesity, aims to contribute to more homogeneous and interpretable evidence in clinical trials related to KDs [11].

This review critically evaluates ketogenic dietary strategies for obesity management, tracing the evolution from the "traditional" KD to the VLEKT. It examines their effects on key organs, including adipose tissue, the liver, and the gut, as well as their role in modulating gut microbiota and metabolic pathways. Additionally, the review considers obesity-related conditions and complementary interventions such as physical activity and bariatric surgery. Summarizing current evidence, it highlights the potential of VLEKT approaches as sustainable solutions for obesity and its associated health complications.

Metabolic Processes and Macronutrient Distribution in Ketosis Regimens

The KD triggers a major reorganization of energy metabolism, characterized by the transition from glucose to fats and ketone bodies as the main energy substrates. Under normal conditions, energy metabolism primarily relies on glycolysis, converting glucose to pyruvate for the Krebs cycle (TCA cycle) and oxidative phosphorylation to produce energy. A significant reduction in carbohydrates in the diet (generally between 20 and 50 g per day depending on individual metabolism) leads to a decrease in insulin levels and a simultaneous increase in glucagon secretion. This hormonal switch favours the depletion of glycogen in the liver, reducing the availability of glucose and triggering the metabolic adaptation known as ketogenesis. This mitochondrial process mobilizes fatty acids from adipose tissue through lipolysis, releasing free fatty acids and glycerol into the circulation. In the liver, free fatty acids undergo beta-oxidation to produce acetyl-CoA, the key substrate for ketone body synthesis. When oxaloacetate is scarce, acetyl-CoA accumulates and forms acetoacetyl-CoA, which is then turned into acetoacetate via HMG-CoA synthase. Acetoacetate is reduced to beta-hydroxybutyrate (BHB), which enters the bloodstream and is transported to various tissues, including muscles, kidneys, the heart, and the brain. Here, ketone bodies are converted back to acetyl-CoA, which fuels the TCA cycle to generate ATP and meet energy demands (Fig. 1). Hormonally, the reduction of insulin and the increase in glucagon further favor the mobilization of fats and the maintenance of gluconeogenesis to provide minimal glucose amounts needed by tissues such as red blood cells, which cannot utilize ketone bodies [12–14]. However, these adaptations come with notable challenges, including the risk of electrolyte imbalances and shifts in the acid-base balance, which can lead to a mild reduction in blood pH. Since these patients are in "nutritional ketosis" with a preserved pancreatic beta reserve, this doesn't result in the pathological metabolic acidosis observed in diabetic ketoacidosis but rather a compensated, physiological state of mild ketosis-related acid-base adjustment.

While these changes warrant careful monitoring, they are manageable with appropriate interventions, such as adequate hydration and a sufficient intake of essential micronutrients, critical strategies to support the body's adaptation processes and mitigate potential adverse effects. Proactively addressing these needs is key to safeguarding overall health during the adaptation phase [15, 16].

The KD is a powerful low-carbohydrate approach that prioritizes health by actively discouraging the intake of harmful ultra-processed and refined foods, as well as those with a high glycemic index/load or rich in trans fatty acids. Instead, it promotes the strategic use of fats as the primary energy source, driving the body into a state of ketosis. This metabolic shift not only enhances energy production but also plays a significant role in naturally suppressing hunger, making the KD an effective and sustainable dietary intervention [17].

Although all KDs restrict carbohydrates, each intervention differs in terms of daily calorie intake, macro- and micronutrient composition, and specific duration. However, the nomenclature has often been unclear, employing the same abbreviations for different protocols. This has potentially caused errors in the interpretation of available evidence and limited the impact of studies in clinical practice. According to the European Food Safety Authority (EFSA), VLEKTs are defined as ketogenic when they provide an energy intake below 700–800 kcal per day, a protein intake

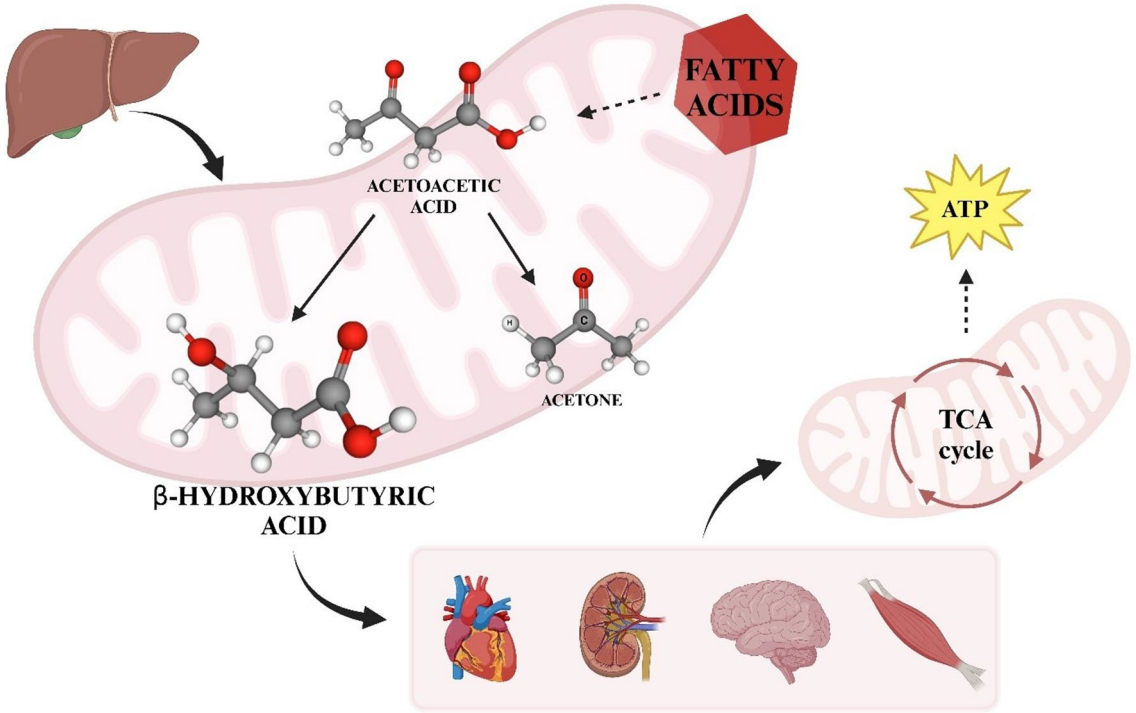


Fig. 1 Metabolism of ketonic bodies. The figure shows the energy flow from fatty acids to ketone bodies and their utilization for energy production. In the liver mitochondria, acetoacetic acid, derived from fatty acids, is converted to β-hydroxybutyric acid (BHB) and acetone. Then, ketone bodies are transported to various organs, such as the heart, kidneys, brain, and muscles. In mitochondria, these molecules are used for ATP production via the TCA cycle

Table 1 Comparison of KD and VLEKT in terms of macronutrient distribution and total caloric intake

	KD	VLEKT
Fats	70–80% of total calories	40–60% of total calories
Proteins	10–20% of total calories	25–35% of total calories
Carbohydrates	5–10% of total calories	5–10% of total calories
Total Calories	Calculated according to total energy expenditure	Severely hypocaloric (700–800 kcal/day)

of 1.2–1.4 g/kg of ideal body weight (approximately 75 g/day), a very limited carbohydrate content (30–50 g/day, 5–10%), and a fixed amount of fats (20 g/day, 15–30%), primarily olive oil. Additionally, they must include sufficient micronutrients to meet the Dietary Reference Intake (DRI) [18, 19]. The composition of a "traditional" KD generally involves a 3–4:1 ratio of fats to carbohydrates and proteins. Instead, the caloric content does not have a fixed limit and is adapted to the patient's energy requirements (Table 1) [20]. In detail, the KeNuT protocol, promoted by the Italian Society of Endocrinology (SIE), is a structured nutritional approach for the management of obesity and its metabolic complications. Based on an initial VLEKT, with less than 30 g of carbohydrates per day, it involves the use of meal replacements followed by a gradual reintroduction of fresh foods up to a low-calorie Mediterranean diet (MD). This model favors a selective weight loss on fat mass, preserving the muscles and improving metabolic parameters [21]. Moreover, in terms of "food re-education", the progressive integration of fresh foods such as meat, fish, eggs and vegetables with a low glycemic index improves adherence to the diet, promotes weight maintenance and supports a more natural and sustainable diet [22].

VLEKT Benefits and Considerations for Obesity Management

Findings from the literature indicate that even short-term KD interventions, such as a program lasting only four weeks, serve as a rapid and effective method for promoting weight loss and reducing abdominal adiposity. This approach leads to significant improvements in parameters including body weight, body mass index (BMI), waist and hip circumference, and body fat percentage, while maintaining cardiorespiratory fitness levels [23, 24]. The enhanced weight loss is closely tied to a greater appetite reduction compared to the MD alone. Notably, post-diet BHB levels were associated with decreased hunger [25]. Even after

adjusting for factors like age, gender, baseline BMI, and diet type, BHB levels remained a key predictor of weight and fat mass loss [26–28]. For longer periods of up to 12 weeks, however, the risk of nutritional deficiencies may become more significant, mainly due to the restrictive nature of the diet itself. A reduced intake of foods rich in calcium, such as milk products and legumes, combined with a high fat intake, could lead to a further decline in serum calcium levels, increasing the risk of bone problems [29]. Therefore, to maintain a nutritional balance and prevent potential adverse effects, it is essential to adopt strategies that include more detailed dietary planning, as is the case with VLEKT, with possible targeted supplementation of essential minerals and vitamins. Although no adverse effects on hematological parameters have been observed, KD in subjects with obesity may lead to increased adiposity and a deterioration of liver parameters [30]. Consequently, careful monitoring of KD therapy must be scheduled. Additionally, in normal-weight adults, KD appears to have an unfavorable effect on total cholesterol and low-density lipoprotein (LDL) cholesterol. Indeed, although the increase in high-density lipoprotein (HDL) cholesterol may partially balance the negative changes in lipid profiles, in normal-weight individuals the risk of hypercholesterolemia should be considered [31]. Anyway, the effect of VLKET on dyslipidaemia and lipid metabolism yield contradictory results in the literature [32]. Among the potential effects, it is notable that nutritional ketosis may exert specific influences on the menstrual cycle, including changes in frequency and intensity, or the restoration of menstruation in women with obesity and prolonged amenorrhea [33]. Weight reduction in women with polycystic ovary syndrome has been demonstrated to enhance metabolic abnormalities and body composition and VLEKT could be considered a potential short-term therapeutic approach [34].

VLEKT is similarly effective to KD in reducing the BMI, total body fat, and cardiovascular risk, as well as improving the quality of life in patients with obesity [35–37]. Moreover, recent studies suggest that VLEKT may have therapeutic potential in the management of disordered eating behaviors such as binge eating and food addiction, by reversing these symptoms inducing remission [38]. Indeed, VLEKT can integrate obesity treatment with stress management, exerting a short-term positive effect on the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, which leads to a significant reduction in salivary cortisol levels [39]. It also seems that ketosis induced by a VLEKT regimen produces an epigenetic profile more like that of individuals with a normal body mass [40]. The rapid changes in body weight induced by VLEKT also allow an early reduction of the inflammatory condition, supporting its use as a first-line dietary intervention to fight inflammation associated with obesity [41]. In this context, ω-3 supplementation becomes crucial for patients with obesity, as it promotes the reduction of fat mass and visceral fat, while preserving free fat mass, further enhancing the overall benefits of the VLEKT approach [42]. Meanwhile, supplementation of medium-chain triglycerides (MCT) at a dosage of 20 g/day increases the benefits related to weight loss, BMI reduction, and waist circumference, and the effect is amplified when MCTs are introduced before the ketogenic phase [43]. In contrast, in obesity sufferers, vitamin D levels return to normal, then increase only after the indicated diet regime is suspended, supporting the hypothesis that the vitamin is stored in adipose tissue and subsequently released during weight loss [44].

The restrictive nature of a VLEKT necessitates careful nutritional planning and ongoing monitoring, particularly in long-term applications, to minimize potential adverse effects. Consequently, it is essential to rigorously examine how these alterations impact various organs and systems, thereby ensuring that the VLEKT may evolve into a progressively safer and more optimized strategy for addressing obesity.

The Impact of VLEKT on Adipose Tissue in Obesity

Adipose tissue is a vital organ of the body, as it not only mediates fat as the primary site for energy storage but also plays a crucial role in metabolic regulation and hormonal secretion, making it a pivotal point in explaining the physiological and pathological mechanisms underlying obesity [45, 46]. Adipose tissue dysfunction has been identified as a key contributor to the development of metabolic diseases, connecting chronic inflammation, insulin resistance, and ectopic lipid accumulation with the progression of obesity-related complications [47, 48]. The effects of low-carbohydrate diets, including the KD and VLEKT, vary significantly by gender, particularly in adipose tissue responses. Men tend to experience greater reductions in body weight and subcutaneous fat compared to women, despite both genders showing lower insulin levels and increased ghrelin and fibroblast growth factor-21 (FGF-21), key hormones regulating appetite, metabolism, and energy expenditure. Notably, only males with obesity exhibit elevated tumor necrosis factor-alpha (TNF-α) levels, although without behavioral changes [49]. Additionally, phase angle values, an indicator of body mass quality, again improve more in men than in women. These results suggest that physiological sex differences should be taken into account when designing nutritional interventions [50]. Clinically, the KD has proven effective in managing lipedema, reducing abnormal fat accumulation,

and alleviating pain [51]. In fact, despite lipedema being by definition resistant to diet and physical activity, the latter plays a key role in its management, bringing benefits to mitochondrial function, lymphatic drainage, and the reduction of inflammation [52]. While it has recently been suggested that the VLEKT may be an effective therapeutic approach, proving superior to other diets such as the MD or intermittent fasting, especially in cases of lipedema associated with obesity [53].

Experimental studies in male Wistar rats highlight its protective role in adipose metabolism, preserving insulin sensitivity, enhancing lipolysis, boosting thermogenesis in brown adipose tissue, and modulating the renin-angiotensin system. While the KD helps counteract metabolic dysfunction from obesogenic diets, it does not entirely prevent increased adiposity, underscoring the diet's limitations [54, 55]. One study indicated that SIRT1, a stress-responsive cellular regulator, may enhance KD's effectiveness in managing metabolic disorders. In a study on male C57BL/6J mice, KD elevated serum BHB levels and SIRT1 expression in white adipose tissue [56].

The VLEKT demonstrates the therapeutic potential of dietary strategies, particularly in the reduction of protumoral markers such as survivin. Particularly overexpressed in the visceral adipose tissue (VAT) of individuals with obesity, survivin levels decrease significantly with weight loss obtained through VLEKT, as reflected by reduced levels in peripheral blood leucocytes. This reduction is closely associated with improvements in inflammation and metabolic profiles, underlining the effectiveness of VLEKT in addressing obesity-related conditions [57]. Instead, the adipose tissue-resident γδ T cells, pivotal in immune-metabolic regulation, are positively influenced by the KD, which reduces inflammation in adipose tissue. But despite the initial benefits, prolonged ad libitum KD feeding in mice has revealed drawbacks, such as obesity, impaired metabolic health, and a substantial depletion of γδ T cells, reversing the initial benefits. These findings indicate the need for balanced dietary approaches and caution against prolonged KD [58]. In short, the VLEKT has shown pronounced short-term benefits, particularly in reducing VAT, associated inflammation, and oxidative stress production. This diet has been particularly effective in improving adiposity and preventing obesity-related diseases [59]. For example, advanced imaging techniques like magnetic resonance imaging confirm the VLEKT's superiority over standard low-calorie diets in reducing VAT, offering a valuable tool for monitoring adipose tissue changes during weight-loss interventions [60]. Finally, the role of adiponectin, an adipose-derived protein with anti-inflammatory properties, has been emphasized as a critical marker of metabolic and inflammatory health. The short-term effectiveness of VLEKT in enhancing adiponectin levels further supports their use in addressing obesity and related metabolic dysfunctions [61].

Current studies confirm that VLEKT offers rapid and significant short-term benefits, making it a highly effective approach for targeted interventions in obesity management. This efficacy results from its direct impact on adipose tissue, which acts as the mainstay of the ketosis process by supplying fatty acids for energy production. In contrast, while offering some benefits, "traditional" KD does not completely prevent the increase in adiposity in obesity and may present problems with prolonged use. It is therefore concluded that VLEKT is the preferred option for achieving short-term impact results by directly addressing the metabolic role of adipose tissue in ketosis.

The Impact of VLEKT on Liver Function in Obesity

The liver is the main site producing ketone bodies, and KDs significantly increase its metabolic workload, leading to alterations in biochemical and molecular processes (Fig. 2). By stimulating the oxidation of fats and reducing insulin levels, these diets can have a positive impact on liver function, which can be beneficial in dealing with various metabolic disorders [62]. In addition to serving as an energy source, BHB plays a critical role in epigenomic modulation and gene expression, particularly in the upregulation of the enzymes HMGCS2 and FGF21 [63].

The KD provides a compelling metabolic and therapeutic strategy, particularly in addressing hepatic steatosis and liver disease. Its benefits may be largely driven by the activation of the hepatic FGF21-KLB pathway, which plays a critical role in suppressing lipogenesis [64]. Moreover, KD has been shown to improve insulin resistance, reduce oxidative stress, and enhance the liver's antioxidant capacity. Additionally, by positively modulating energy metabolism, KD contributes to improved aerobic endurance. However, these advantages come with significant risks. KD can result in severe nutritional deficiencies, increase the risk of hyperammonaemia, and potentially cause long-term liver damage. The high lipid intake associated with KD poses a metabolic challenge which may counteract some of its benefits. Given these potential dangers, careful consideration and medical supervision are essential before adopting KD as a long-term dietary approach [19, 65–67]. From a molecular perspective, a key factor in promoting weight loss during the KD is Growth Differentiation Factor 15 (GDF15), a cytokine that is crucial for regulating appetite and energy metabolism. In mice lacking GDF15 or its receptor GFRAL, the beneficial effects of the KD are abolished, underscoring the central

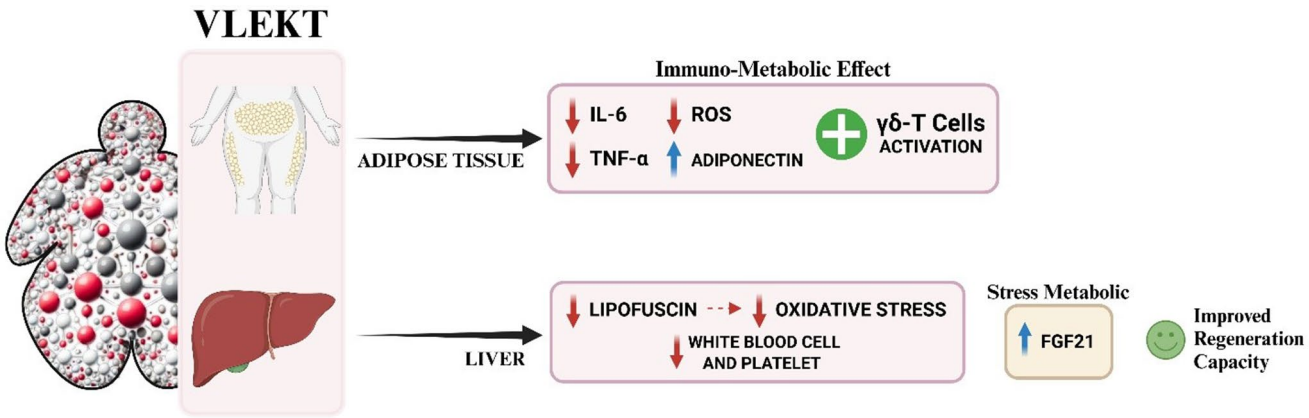


Fig. 2 Effects of VLEKT in modulating adipose tissue and the liver in patients with obesity. The figure shows the therapeutic effects of VLEKT in modulating adipose tissue and the liver in subjects with obesity. VLEKT has an immune-metabolic effect on various markers in the adipose tissue and the liver. In particular, in the liver, it improved the tissue regeneration capacity and increased an important metabolic marker of stress

role of GDF15-GFRAL signaling. The KD activates hepatic PPARγ, which drives the transcription of GDF15. The absence of hepatic PPARγ leads to reduced GDF15 levels and a diminished efficacy of the KD; however, these effects can be rescued by recombinant GDF15 administration or overexpression [68]. Another study observed the down-regulation of Liver-Expressed Antimicrobial Peptide-2 (LEAP2), an endogenous antagonist of the ghrelin receptor, due to BHB. This effect was demonstrated both in vivo and in vitro, highlighting the crucial role of BHB in modulating hunger signalling during periods of energy deprivation [69].

Low-carbohydrate diets, especially those rich in unsaturated fatty acids like ω-3 and ω-9, have shown significant therapeutic benefits, particularly for weight loss and liver health recovery in obesity. Santamarina et al. highlighted their antioxidant and epigenetic effects in treating hepatic complications [70]. The KD also demonstrates efficacy in women with obesity and with liver dysfunction and conditions like polycystic ovary syndrome or breast cancer, improving liver function, elasticity, and BMI more effectively than conventional treatments.

Considering the effects of VLEKT on the liver, it is essential to recognize its crucial role in maintaining a redox balance, regulating lipid and glucose metabolism. Evidence from VLEKT regimens shows that a variation in lipofuscin levels, a marker of oxidative damage, is a significant predictor of changes in metabolism and body composition [71]. In pathological liver conditions such as MASLD, the VLEKT has demonstrated a significant impact, including rapid mobilization and reduction of liver fat content compared to standard low-calorie diets [72, 73]. Indeed, recent studies demonstrate the benefits of VLEKT, as well as of MD and intermittent fasting. In addition, supplementation with vitamin E, ω-3, and silymarin is recommended, as these can help improve liver health [74]. Moreover, decreases in white blood cell and platelet counts suggest a reduction in liver-associated low-grade inflammation, along with improvements in liver biomarkers such as γGT levels [75]. More pathological aspects influenced by KD and VLEKT will be addressed in subsequent sections. In any case, the VLEKT contributes not only to reducing hepatic inflammation and fibrosis but also to regulating cellular communication via extracellular vesicles (EVs). Notably, changes in small EVs observed pre- and post-dietary intervention appear to influence hepatic metabolism through both transcriptomic and lipidomic pathways [76, 77].

The Impact of VLEKT on Intestinal Permeability and Gut Microbiota in Obesity

The human intestinal barrier demonstrates a remarkable adaptability to short-term extreme variations in macronutrient intake without showing significant alterations in permeability, inflammation, and tight junction protein expression [78]. Gut permeability plays a key role in metabolic health by mediating interactions with the microbiota and microbial metabolites. Emerging evidence suggests that VLEKT can modulate gut microbiota and metabolite production [79,80], particularly in individuals with an impaired gut barrier function, underscoring the need to monitor key gut metabolites to optimize therapeutic outcomes, such as short-chain fatty acids and endotoxins.

Gut microbiota composition varies widely among individuals due to a complex interplay of dietary practices, cultural background, genetics, pathological conditions, and antibiotic usage [81]. This inter-individual variability, driven by metabolic, digestive, and immune factors rooted in host genetics, explains why identical diets can affect microbial composition differently among individuals. Research using

diabetic NOD/ShiLtJ mice has confirmed this intricate relationship between the diet and microbiome, highlighting genetics as a significant mediator [82, 83].

In individuals with obesity, KD can significantly impact the gut microbiota. A dietary intervention combining two-week KD, a two-week carbohydrate transition, and a balanced low-energy diet, revealed notable changes in microbial species abundance and interactions, as analyzed through 16 S rRNA sequencing. The KD was well-tolerated, addressing adherence challenges while supporting effective weight loss [84]. Microbial species like *B. obeum* and *R. torques*, positively correlated with the BMI, play notable roles in these pathways [85].

While specific microbiome metabolites linked to weight loss remain under investigation, mice studies reveal a reduced abundance of L. murinus ASF361, an enzyme-producing bacterium, during KD, leading to elevated bile acid levels and associated metabolic changes [86]. Other research, comparing KD with a balanced diet (BD) in obesity mouse models, suggests that BD restores microbiota composition closer to that in non-obese controls, whereas KD shifts microbial populations, with a reduction of *Bacteroidetes* and an increase in *Actinobacteria* [87]. In humans, the effects of low-carbohydrate diets on gut microbiota appear to be less pronounced, especially when combined with exercise. Exercise independently enhances beneficial species like *Blautia* and reduces *Alistipes*, a genus linked to T2DM. Studies further reveal distinct microbial profiles associated with T2DM, certain taxa being positively or negatively correlated with the disease, such as *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, *Akkermansia*, and *Roseburia*, that are negatively associated with the disease, while *Ruminococcus*, *Fusobacterium*, and *Blautia* are positively associated [88].

VLEKT interventions in individuals with obesity demonstrate significant weight loss but raise concerns about gut barrier function, and some studies reported increased dysbiosis markers and altered permeability. However, the VLEKT has shown positive effects on gut microbiota in T2DM patients, enhancing intestinal homeostasis markers and reducing obesity-associated taxa, showing a favorable change [89]. Notably, the administration of probiotics during VLEKT appears to amplify weight loss and improve the inflammatory environment, although the gut microbiota changes induced by VLEKT alone were more pronounced than those achieved through probiotics, emphasizing the need for careful consideration when combining these approaches [90].

Comparative studies of low-calorie and phased ketogenic diets reveal favorable microbiota shifts, including reductions in dysbiosis-associated *Proteobacteria* and increases in beneficial *Verrucomicrobiaceae* and *Bacteroidetes*. These findings highlight the potential of tailored dietary strategies, possibly supplemented with probiotics, to beneficially modulate gut microbiota and support obesity management (Fig. 3) [91].

In conclusion, VLEKTs offer significant metabolic benefits, particularly through gut microbiota modulation [92]. However, long-term impacts on gut health warrant further study.

The Impact of VLEKT on Obesity-Related Comorbidities

Ketogenic dietary regimens have gained renewed attention as a nutritional strategy for managing obesity associated disorders, which are frequently linked to chronic low-grade

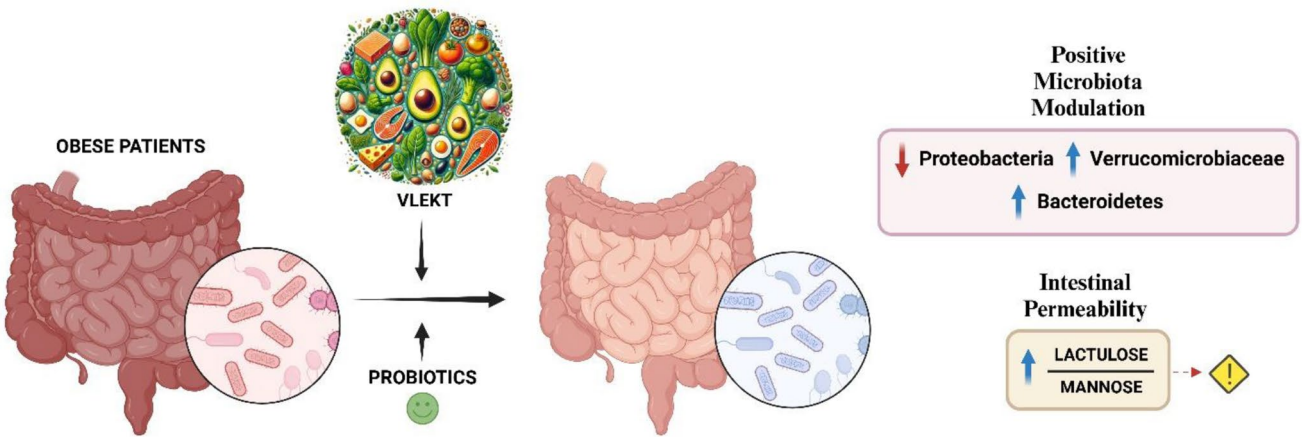


Fig. 3 Effects of VLEKT on the gut and microbiota of patients with obesity. The figure shows the effects of VLEKT on gut permeability and the microbiota in subjects with obesity. VLEKT, preferably in combination with probiotics, shows positive modulations of the gut microbiota, evidenced in the indicated bacterial species. In addition, there is a decrease in the lactulose/mannose ratio, which modulates intestinal permeability and must be monitored

Table 2 Effects of nutritional ketogenesis in modulating principal obesity comorbidities

Disease	Effect of Nutritional Ketogenesis	Reference
MASLD	↓ ALT, AST, γGT, FIB-4 SCORE and Insulin resistance ↑ FGF21 ↓ Lipid oxidation ↑ De novo lipogenesis	[99, 100, 102, 103]
Hypertension	↓ hsCRP, TNF-alpha, IL-6 and C-reactive protein ↓ Systolic blood pressure	[108, 109, 144]
T2DM	↓ glycemia, HbA1c, insulin, C-peptide and HOMA-IR ↑ Secretory function of pancreatic β-cells ↓ Administration of drugs	[115, 116, 122]
Polycystic Ovary Syndrome	↓ Insulin resistance ↑ Fertility ↑ Metabolic and ovulatory dysfunction ↓ Testosterone and Estradiol	[124, 125, 127]
Chronic Kidney Disease	↑ Glomerular filtration	[134]
Cognitive Disease	↑ Neurogenesis and cognition Modulation of Alzheimer's risk Modulation of autonomic nervous system	[138–141]

inflammation and dysfunction of visceral adipose tissue [93, 94]. Below and in Table 2, is a comprehensive analysis of the primary comorbidities associated with obesity and the nutritional effectiveness of ketosis, paying special attention to the VLEKT and its role in ameliorating these conditions as reported.

Metabolic Disorders

Metabolic disorders are conditions characterized by alterations in metabolism, the complex set of chemical processes that the organism utilizes to convert food into energy. These disorders are often linked to obesity, as excess body fat contributes to metabolic imbalances, such as insulin resistance, hypertension, and dyslipidemia [95, 96]. These factors collectively contribute to obesity-related complications, underscoring the need for effective management strategies such as the KD and VLEKT. Indeed, as expressed in the previous paragraphs, at the molecular level, VLEKT influences gene expression in the liver, suggesting a potential role in metabolic modulation [97].

MASLD is a primary metabolic disorder characterized by hepatic fat accumulation, independently of significant alcohol consumption. It encompasses a spectrum of liver abnormalities, ranging from simple steatosis to steatohepatitis, and is frequently associated with obesity, T2DM, hypertension, and other metabolic disorders. MASLD is increasingly recognized as a significant public health concern [98].

A pilot study on patients with MASLD has already shown that a hypocaloric KD led to improvements in metabolic markers and liver tests, including ALT, AST, and FIB-4 scores. The diet was found to be well-tolerated and free from negative safety signals, suggesting its potential in the dietary management of MASLD [99]. During VLEKT regimens, a significant positive change in the hepatic steatosis index is observed, and serum FGF21 may play a role in the MASLD improvement induced by nutritional intervention [100]. This improvement also appears to be due to the remodeling of hepatic mitochondrial fluxes. It has been demonstrated that KD rapidly reduces intrahepatic triglycerides and hepatic insulin resistance despite the increase in non-esterified fatty acids [101]. The improvement in MASLD resulting from VLEKT also shows significant gender-related differences. Men showed a more pronounced reduction in γ-glutamyl transferase (γGT), an important marker of liver function, than women. This effect was particularly evident when comparing men with pre-menopausal women, where the difference in the reduction of γGT was statistically significant. This is likely due to hormonal changes, as such gender-related variations diminish post-menopause [102]. Furthermore, it must be stressed that prolonged KD in mice with obesity and MASLD increases lipid oxidation and alters metabolic fluxes within the TCA cycle, reducing *de novo* lipogenesis. Consequently, prolonged exposure to a ketogenic environment could exacerbate hepatic mitochondrial dysfunction and promote oxidative stress and inflammation [103, 104].

In the light of this evidence, the VLEKT regimen shows promise in improving MASLD, independently of all cofactors associated with MASLD, such as T2DM, hypertension, high pressure, and obesity [105], but again it is shown that prolonged use may raise the risk of hepatic mitochondrial dysfunction and oxidative stress, evidencing the need for customized approaches in such metabolically sensitive patients.

Cardiovascular Disorders

Obesity-related hormonal, inflammatory, and endothelial alterations trigger mechanisms that exacerbate hypertension and cardiovascular diseases [94]. Due to the anti-inflammatory properties, KD demonstrates potential in preventing and managing these disorders. Anti-inflammatory effects stem from eliminating simple sugars, restricting carbohydrates, and including ω-3 fatty acids, promoting ketosis [94]. It is not known to what extent organs rebalance lipid oxidation during the KD and whether this may have beneficial effects beyond weight loss. In any case, ketone bodies provide "rescue fuel" for the diseased heart, affecting its metabolism [94]. In one study, KD significantly reduced

myocardial free fatty acids uptake and oxidation increasing ketone body oxidation. However, the beneficial effects of the KD are probably not caused by changes in myocardial substrate use but rather by weight loss and yet unknown metabolic adaptations in other organs and tissues [106]. Moreover, prolonged KD use may cause hypercholesterolemia and increase atherosclerotic risks [107]. Importantly, the VLEKT demonstrated its safety and efficacy over a 24-week program subdivided into multiple phases, involving 33 overweight or with obesity women. The intervention also proved effective in improving cardiometabolic parameters. Systolic blood pressure decreased by 3.5 mmHg after phase 1 and remained stable throughout the program, providing additional benefits such as improved insulin sensitivity and lipid profiles [108]. Furthermore, in a population of women with obesity, all newly diagnosed and hypertensive treatment naïve, a prospective study highlighted that reduced inflammation induced by VLEKT (reduction of high sensitivity C-reactive protein and increasing phase angle) could also benefit blood pressure levels [109]. In summary, ketogenic regimes and in particular the VLEKT show promise in improving cardiometabolic health and managing hypertension.

Endocrine Disorders

Several endocrine disorders are associated with obesity, including T2DM, insulinoma, Cushing's syndrome, hypothyroidism, polycystic ovarian syndrome, and growth hormone deficiency [110].

T2DM is a metabolic syndrome defined by chronic hyperglycaemia resulting from insulin resistance and impaired insulin secretion, closely linked to obesity because excess adiposity contributes to increased insulin resistance and chronic low-grade inflammation, that are key factors in the disease [111].

It is now known that a ketogenic meal induces a minimal insulin secretory response compared to a Mediterranean meal, with significant reductions in glucose levels and insulin secretion rate [112]. Consequently, the KD is suggested to be particularly beneficial for patients with insulin resistance or T2DM. Medical nutrition therapy, such as the VLEKT, has proven particularly effective in improving glycemia, HbA1c, insulin, and C-peptide levels in patients with obesity and an impaired glucose metabolism, as compared to the MD [113, 114].

The VLEKT significantly improves the secretory function of pancreatic β-cells and enhances insulin sensitivity in overweight or male patients with obesity and metabolic hypogonadism [115]. Similarly, in adult women with obesity and hyperglycemia, a 12-week VLEKT has been shown to significantly improve glycemic control by reducing glucose levels, HbA1c, and HOMA-IR [116]. Rafiullah et al. demonstrate in a meta-analysis that the VLEKT is more effective than recommended diets for T2DM in improving glycemic control. However, the benefits were not sustained beyond 12 months, and the available evidence is insufficient to recommend the widespread adoption of this dietary approach [117]. Conversely, additional studies have confirmed that the KD may help reduce the morbidity and mortality associated with metabolic dysfunction in these patient populations [118]. In particular, a two-meals-a-day KD was associated with more significant improvements compared to a conventional diabetic diet, although a slight increase in uric acid levels was also observed in the KD group [119, 120]. Nutritional approaches, such as a high-protein KD and intermittent nutrition, have been shown to improve glycemic regulation, potentially aiding in T2DM prevention [121]. The VLEKT may also reduce reliance on antidiabetic medications. A study by Moriconi et al. reported decreased HbA1c levels, improved eating behaviours, and an enhanced quality of life, with 26.6% of patients discontinuing all antidiabetic drugs and 73.3% continuing only metformin. In contrast, 46.6% of those on a standard low-calorie diet required increased medication [122].

In addition to T2DM, nutritional ketosis is used to treat polycystic ovary syndrome. This endocrine disorder is characterized by hormonal imbalances, menstrual irregularities, and the presence of ovarian cysts, often associated with metabolic symptoms [123]. The first line of treatment for polycystic ovarian syndrome is lifestyle changes, including diet control, exercise, and weight control. According to different studies, dietary interventions have been shown to eliminate clinical symptoms of the disease. These improvements are attributed to the macronutrient distribution, especially carbohydrates in the diet of women with polycystic ovarian syndrome, due to their effect on insulin secretion from the pancreas [124].

Similarly, studies have documented the effects of VLEKT on ovarian reserve and luteal function, improving metabolic and ovulatory dysfunction, in a relatively short time and resulting an optimal choice for women with polycystic ovarian syndrome and hence their entry into in vitro fertilization practices [125, 126]. VLEKT can be considered a safe dietary approach and can be deemed an adjuvant to pharmacological therapy for the metabolic and ovulatory improvement of women with polycystic ovarian syndrome [127]. A crosstalk between alterations in the BHB and the hypothalamic-pituitary-gonadal axis is observed during the KD, with an increase in the sex hormone-binding globulin as well as lowering free testosterone and estradiol, in men and women with obesity [128].

VLKET is involved also in obesity-related thyroid dysfunction. Carbohydrate and fat intake, along with weight

loss, influence thyroid hormone levels. High-fat diets are negatively correlated with free triiodothyronine and thyroxine levels, while weight loss and changes in BMI are positively associated with triiodothyronine levels. Moreover, changes in obesity, such as leptin secretion from adipose tissue, may influence thyrotropin-releasing hormone (TRH) release. Additional investigation is required to understand the effects of how VLEKT affects thyroid function, but it seems that long-term use of VLKET may be related to the development of hypothyroidism [129].

VLEKT also has beneficial effects for patients with Cushing's disease, which is caused by excessive production of cortisol or adrenocorticotropic hormone. Currently, there are no clinical studies on the use of a VLKET in patients with hypercortisolism for the treatment of its comorbidities [130]. However, based on the above-mentioned metabolic favourable effects of a VLKET, it can be hypothesized that it may be successfully employed for the treatment of Cushing's syndrome comorbidities such as T2DM, obesity, arterial hypertension, insulin resistance, and dyslipidemia, conditions [131].

In conclusion, although VLEKT shows significant potential in improving glycaemic control, insulin sensitivity, and reducing antidiabetic drug dependency in patients with T2DM, its long-term sustainability and wide applicability require further investigation.

Kidney Disorders

The impact of the KD and VLEKT on kidney function remains controversial due to limited and inconsistent research. A high protein content in KD is often considered potentially harmful to kidney function and is generally not recommended for individuals with impaired renal filtration [132]. Ketone bodies, acidic compounds excreted by the kidneys, may reduce alkaline reserves or bicarbonate ions. As renal dysfunction progresses, the kidneys' ability to compensate for acidosis diminishes, increasing the risk of metabolic acidosis in chronic kidney disease patients [133]. A prospective observational study was conducted with 92 patients on a VLEKT for about 3 months: no clinically significant changes in kidney function were observed; notably, 27.7% of patients with mild renal failure experienced normalization of glomerular filtration following the dietary intervention [134]. This study underscored that VLEKT is a safe and effective dietary intervention in patients with obesity affected by mild chronic kidney disease when conducted under medical supervision, although caution should be taken in screening for micronutrient lack, as well as in accurately monitoring protein consumption [134]. A recent observational cross-sectional study assessed the efficacy and safety of phase 1 of VLEKT in 73 individuals with overweight or obesity and mild renal impairment. The findings suggested again that VLEKT is a safe option for managing obesity-related complications, even in individuals with early-stage kidney disease. However, due to the observational nature of this study, future randomized controlled trials must assess the effects of each phase of VLEKT on renal function to gain a more comprehensive understanding of its long-term safety and efficacy [135].

Further research is needed to determine the long-term effects of VLEKTs and explain outcome variability across patient populations. The consensus statement from Italian medical societies aims to guide healthcare professionals in managing obesity in non-dialysis chronic kidney disease patients by providing practical dietary recommendations to prevent chronic kidney disease progression [136].

Neurological Disorders

The association between obesity and reduced brain function appears increasingly evident, despite difficulties and limitations in analysis techniques [137]. Obesity and its comorbidities are associated with an impaired cognitive performance, accelerated cognitive decline, and neurodegenerative changes in later life, highlighting the profound negative impact that this condition can have on brain health. These side effects related to obesity may persist even after weight normalization, probably because, among the organs of the human body, the brain has a relatively low regenerative capacity [138].

One study investigated the impact of obesity and subsequent weight loss on the brain, focusing on the hippocampus in rats with obesity after KD, analyzing the hippocampal proteome, cognitive functions, and neuronal maturation of the animals. The results showed a decline in neurogenesis and cognitive abilities due to obesity, but weight loss led to improvements in these areas, despite some persistent protein alterations. Among the various nutritional approaches evaluated, KD had the most significant influence on brain function [138]. Additionally, the VLEKT demonstrated entirely beneficial effects in enhancing brain health in older adults at risk of Alzheimer's disease, showing a correlation between cerebrospinal fluid biomarkers and weight loss and body fat distribution in response to the dietary intervention; in particular, a modest fat loss was associated with increased levels of cerebrospinal fluid amyloid biomarkers, generally associated with a more favorable profile; greater fat loss was associated with a worsened cerebrospinal fluid profile with decreased Aβ levels. Thus, the diet resulted a promising therapeutic intervention to improve brain health via changes in central and peripheral metabolism [139]. Moreover, VLEKT induced functional modulations of the autonomic nervous system through salivary amylase production

and could be correlated with an increased heart rate variability [140, 141]. Ketosis regimes show promise in addressing obesity-related neurological and behavioral disorders. KD supplementation with exogenous ketones has been linked to mitigating mood declines often seen in early dieting [142]. Additionally, Černelič-Bizjak et al. studied the effects of KD on stress-induced emotional and external eating by monitoring BHB levels in individuals with obesity. The findings suggest KD positively impacts psychological and metabolic mechanisms underlying these behaviors, highlighting its potential for weight loss and as an intervention for neurological and behavioral issues [143].

Other Disorders

VLEKT is proving to be a valuable therapeutic support for several inflammatory diseases, not always closely related to obesity.

Often underappreciated, sleep disorders are common and with various manifestations, including insomnia, sleep-related breathing disorders, and parasomnias [145]. VLKET can improve sleep quality in individuals with obesity by reducing fat mass and improving various anthropometric and metabolic parameters. An enhanced overall sleep quality, a reduction in difficulties falling asleep and nighttime awakenings, a decrease in daytime sleepiness, and an increase in REM sleep were generally observed [146]. Particularly, ketone bodies' production in VLKET offers a valid adjuvant treatment proposal also for obstructive sleep apnoea syndrome [145]. Moreover, a study conducted on 324 women with overweight and obesity showed an improvement of sleep quality that was mostly mediated by the reduction of fat mass related to this nutritional protocol [147].

Studies have shown that ketone bodies produced during ketosis improve symptoms in diseases such as juvenile idiopathic arthritis, lipedema, and fibromyalgia [148–150]. In addition, KD has benefited patients with obesity hypoventilation syndrome and knee osteoarthritis, relieving pain [133, 151].

Other benefits also emerged in comorbidities such as stress urinary incontinence in women with obesity and patients with inflammation of the male accessory glands [152, 153]. Additionally, ketosis nutritional regimens have been proposed as adjuvant therapy for cancer due to carbohydrate restriction, that could slow tumor growth, with positive results in patients with rectal and breast cancer [154, 155]. Despite the promising results, further clinical trials are needed to confirm the efficacy of the diet as a cancer treatment.

Complementary Approaches To VLEKT: Exercise, Bariatric Surgery, and Digital Technology

Physical activity is a cornerstone of a healthy lifestyle, preventing chronic diseases, enhancing mental well-being, and improving overall quality of life [156]. In particular, combining KD with exercise interventions has shown promising results in addressing obesity and related metabolic issues [8]. Although KD effectively reduces body weight and fat mass, it can also lead to adverse effects such as dyslipidemia and muscle mass loss [157, 158]. Combining exercise with a KD can mitigate these side effects. Indeed, the benefits of exercise are widely recognized in improving cardiovascular health, maintaining lean muscle mass, and regulating metabolic markers [8].

Aerobic exercise in KD-fed mice with obesity reduced triglyceride levels, improved hepatic steatosis, and enhanced lipolysis-related gene expression [157]. Exercise regulates appetite hormones like ghrelin and leptin, supporting diet adherence and lipid metabolism, and improves lean mass through increased irisin levels [159, 160]. However, a short-term low-carb diet with exercise improved cardiometabolic health but led to greater muscle mass loss compared to standard diet interventions [158].

Meanwhile, in the context of VLEKT, a pilot study determined the effectiveness of this regimen combined with interval training, on weight loss, body composition, and physical performance in participants with sarcopenic obesity. A significant improvement in muscle strength and physical performance is observed, with preserved fat-free mass and reduced fat mass, alongside a high-density lipoprotein cholesterol plasma increase [161].

As mentioned above, in severe cases, diet al.one is not enough to treat obesity, so other surgical options are used. Bariatric surgery is currently the most effective treatment for achieving sustained weight loss and for reducing the burden of comorbidities and mortality in individuals with severe obesity. Several bariatric surgery procedures are available, categorized according to their action mechanisms in promoting weight loss, i.e., nutrient malabsorption, gastric restriction, hormonal manipulation, or the combination of these mechanisms [162].

Preoperative weight loss plays a crucial role in facilitating surgery and reducing complications. Recent studies indicate that even modest preoperative weight loss can improve surgical outcomes and reduce complications, and VLEKT is among the several nutrition strategies explored [163, 164]. Furthermore, VLEKT improved metabolic parameters in patients with obesity and obstructive sleep apnea syndrome, scheduled for bariatric surgery, and undergoing preoperative continuous positive airway pressure [165]. Despite these

benefits, adherence to such diets remains a challenge, and enteral nutrition strategies are being proposed as a potential solution for patients with poor adherence [166].

Following bariatric surgery, some patients experience inadequate weight loss or regain lost weight, with limited treatment options. Revisional procedures pose higher risks, while weight loss medications, endorsed by the European Association for the Study of Obesity, remain underutilized despite their safer profile. Nutritional strategies such as VLEKT may complement pharmacotherapy, cognitive behavioral therapy, and, if needed, revisional surgery in a structured treatment approach [167, 168]. In a prospective study on 22 patients with obesity, VLEKT post-bariatric surgery led to significant fat mass reduction while preserving muscle strength [167]. Similarly, in patients with the intragastric balloon and gastric bypass, those on a VLEKT showed a preserved fat-free mass, reduced abdominal circumference, and glycated hemoglobin without major adverse events [169]. Despite these benefits, complications and poor responses remain challenges, limiting surgical interventions to severe cases [168]. Nutritional ketosis has gained attention for its metabolic benefits, including reductions in pro-inflammatory cytokines and lipid peroxides, which may enhance immunity and lower infection and carcinogenesis risks compared to low-calorie diets or bariatric surgery [170]. Additionally, a study by Fernandez-Pombo A. et al. showed that VLEKT normalized elevated erythropoietin levels in 72 patients with obesity, a change not seen in other groups, suggesting that erythropoietin may serve as a marker of metabolic status in obesity therapies [171].

In recent years, the development of digital technologies, in particular smartphone apps, has opened new perspectives. Due to their accessibility, personalization, and interactivity, health apps are emerging as innovative tools to promote sustainable behavioral changes and support weight management. With features like behavior monitoring, goal setting, and motivational support, apps enhance evidence-based interventions. However, their true effectiveness and the need for more personalized and inclusive designs remain areas of concern [172, 173]. A pilot study on an ultra-low carbohydrate diet showed promising results, with 50% satisfaction and significant weight loss in participants. Apps like KetoCycle, Keyto, and Weight Watchers integrate digital tools such as Bluetooth scales and ketosis monitors, boosting user engagement and achieving weight loss exceeding 5% in many cases [174–178]. While mobile technologies facilitate real-time tracking and personalized interventions [179], the involvement of healthcare professionals remains crucial for optimizing weight loss.

Conclusions

The VLEKT is not just a diet, it is a medical therapy that has proven effective in managing obesity and related health conditions, improving metabolism and body composition. However, it is essential to understand that this approach must be strictly managed by a qualified nutritionist or healthcare professional. Due to its extreme rigidity, attempting to follow it without expert supervision can lead to serious nutritional deficiencies and health risks. That's why, medical supervision is not only recommended but essential, especially for long-term use.

The studies reported in this review show that VLEKT offers significant short-term benefits, including VAT reduction, systemic inflammation modulation, liver function improvement, and hormonal regulation These beneficial effects significantly enhance various pathophysiological conditions. However, despite their importance, the majority of the reviewed studies were predominantly focused on routine anthropometric and biochemical parameters, failing to thoroughly explore the crucial biochemical and molecular mechanisms driving these processes. Therefore, it would be particularly interesting to explore these aspects in more detail to understand more clearly the impact of VLEKT at the cellular and metabolic levels. Despite the advantageous evidence, the lack of studies on crucial aspects such as intestinal permeability, and cardiovascular and renal health limits a comprehensive view of the effects. Furthermore, an equally critical limitation is the scarcity of well-structured clinical trials conducted across diverse clinical settings, which is essential to determine the safety, efficacy, and applicability of VLCKD in different patient populations. Addressing these gaps through rigorous, high-quality research is imperative to fully elucidate its role in human health.

The VLEKT stands as a groundbreaking and highly advanced strategy in the fight against the global "obesity pandemic". With its remarkable metabolic advantages, this approach has the power to revolutionize obesity management by addressing its complexities at the core. By maximizing effectiveness while prioritizing safety and personalization, VLEKT may pave the way to a healthier future, setting new standards in obesity treatment and redefining the possibilities of long-term weight control.

Key Reference

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This study introduces a new nomenclature for the **Very Low-Calorie Ketogenic Diet (VLCKD)**, redefining it as **Very Low-Energy Ketogenic Therapy (VLEKT)** to underscore its therapeutic approach beyond mere caloric restriction. Supported by leading experts in nutraceuticals and dietetics, this proposal aims to standardize scientific terminology and enhance the understanding of ketogenic diets' role in managing metabolic and clinical conditions, thereby fostering a more precise and evidence-based application in medical and nutritional practice.

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This study highlights **chronotype** as a significant predictor of weight loss success and body composition improvements in women with overweight or obesity undergoing a **VLEKT**. By demonstrating the influence of circadian rhythms on dietary outcomes, this research offers **valuable insights for the personalization of nutritional strategies**, suggesting that aligning dietary interventions with an individual's biological clock could **enhance the effectiveness of metabolic and weight management therapies**.

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The study by **Calabrese et al.** provides a **comprehensive metabolomic profiling** of patients with obesity and altered intestinal permeability undergoing a **VLEKT**, offering **critical insights into the gut-metabolism interplay** and its role in metabolic health. Meanwhile, the research by **Bellanti et al.** demonstrates that a **multiphase VLKET significantly improves serum redox balance** by reducing oxidative stress, highlighting the **potential of ketogenic interventions in mitigating obesity-related oxidative damage** and enhancing overall metabolic resilience.

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This study by **Li et al.** explores the impact of a **periodic ketogenic diet** on newly diagnosed overweight or with obesity patients with **type 2 diabetes**, demonstrating its effectiveness in **glycemic control**, **weight reduction**, **and metabolic improvement**. These findings provide **compelling evidence for the potential integration of intermittent ketogenic strategies** into diabetes management, offering a promising dietary approach to enhance metabolic health and insulin sensitivity.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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