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Effectiveness of ketogenic therapy in patients with obesity and diabetes: a narrative review

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Abstract

Over the past few decades, there has been a major increase in type 2 diabetes (T2D) prevalence, a long-term medical condition in which your body doesn't use insulin properly in most regions of the world. After adjusting for the impact of aging populations, diabetes prevalence in adults (85–95% T2D) almost doubled between 1980 and 2020 worldwide. Increases were more pronounced in low- and middle-income countries and in men compared to women. The aim of this study is to evaluate the performance of a very low-calories ketogenic diet (VLCKD) as an effective nutritional approach for both TD2 and obesity. A ketogenic diet (KD) positively affects blood glucose levels, body weight, glycosylated hemoglobin, neurological disorders, and plasma lipid profiles. We combined ClinicalTrials.gov data and data from PubMed from 2020 to 2022. Only published papers that met the requirements of reporting clinical trials investigating an adult sample of T2D obese patients were included. The review shows the beneficial therapeutic value of a VLCKD in the management of T2D and long-term obesity and its capacity to help achieve disease remission. Evidence from the literature underlines the need to redefine guidelines to offer a dietary and low-carb option to combat insulin resistance (IR) and related diseases.

Keywords

Type 2 diabetes, obesity, very low-calories ketogenic diet, HbA1c

Introduction

Lifestyle modification, with a focus on healthy eating, weight control, and regular physical activity, is increasingly considered essential for maintaining good health in adults and children and preventing metabolic diseases When recommending healthy food choices, a ketogenic diet (KD) has been shown to be a

good alternative to a western diet mainly as a therapeutic option in the treatment of obesity, type 2 diabetes (T2D) and other morbid conditions, with good results in terms of weight loss and control of the main metabolic parameters, at least in the short and medium term [1].

Diabetic patients show abnormalities in their lipid profile. In the diabetic patient, there is an increase in the level of both the low-density lipoprotein (LDL) fraction of cholesterol and very LDL (VLDL), with a simultaneous capacity of the high-density lipoprotein (HDL) level. These alterations in the lipid profile contribute to cardiovascular risk [2, 3]. Hyperglycemia and an abnormal lipid profile cause glycation, oxidation, hydroxylation, and methylation, leading to chronic inflammation.

Protein glycation is the primary cause of diabetes complications. Glycated hemoglobin, or HbA1c, is an essential measure of glycemic control, and dietary carbohydrate restriction improves HbA1c significantly [4, 5].

The main requirement for optimal diabetes management remains glycemic control along with moderate weight control. In this context, it has been found that dietary carbohydrate restriction utilizing a KD is very successful in lowering body weight and enhancing T2D. As a result, the goal of this review paper is to learn about the present state of information regarding the advantages and potential hazards of employing low-calories ketogenic diets (LCKDs) in the treatment of T2D [6].

Previous meta-analyses have shown the positive impact of a very LCKD (VLCKD) on weight loss in obese patients [7, 8], as well as in experimental studies [9]. Nevertheless, there is still little evidence of the use of a VLCKD as an important and secure method for the long-term treatment of the disease known as T2D. Some studies have shown that lifestyle changes and a weight reduction program using VLCKDs led to better results than a traditional low-calories diet (LCD) [10]. The first phase of insulin secretion has been shown to recover with the use of a VLCKD, which led to a considerable decrease in the demand for hypoglycemic medications such as insulin [11]. The use of VLCKDs has recently been recognized by the American Diabetes Association (ADA) as a legitimate treatment approach for the care of individuals with T2D and obesity [12].

LCKDs

In the clinical field, the first documented use of a KD to treat specific pathologies dates back to the 1920s, when Wilder et al. [13] used it to control seizures in pediatric patients with forms of epilepsy that were not treatable with the drugs available at that time. Such use returned to the fore in the 1990s and has become increasingly widespread [14].

In the 1960s and 1970s, with the overweight and obesity pandemic, there were numerous studies on the use of LCDs, which could lead to a rapid and significant reduction in body weight without affecting lean mass. Thereafter, different protocols of protein sparing modified fast (PSMF) were proposed. These were diets characterized by a reduced calorie intake with an almost total absence of carbohydrates and a tailored intake of proteins aimed at minimizing the loss of muscle mass [15].

In recent years, there has been a renewed interest in this dietary model, with the proposal of promising protocols regarding its use not only for the treatment of epilepsy and obesity but also for other pathologies, such as certain types of cancer, some neurological diseases—namely Alzheimer's and Parkinson's disease—various forms of headache, diabetes, and metabolic syndrome [16–18].

A KD primarily consists of high-fat, moderate-protein, and very low-carbohydrate content. The dietary macronutrients are provided approximately as follows: 55% to 60% fats, 30% to 35% proteins, and 5% to 10% carbohydrates [19].

Most of the energy used by bodily tissues is produced from carbohydrates. The body enters a catabolic condition and insulin secretion is dramatically lowered when the body is depleted of carbs when carbs are consumed in an amount less than 50 g/day. The body is forced to undergo several metabolic changes when glycogen reserves are depleted. When the availability of carbohydrates in the tissues of the body is low, two metabolic processes come into play: ketogenesis and gluconeogenesis [20, 21].

The endogenous synthesis of glucose by the body, mainly in the liver from the amino acids glutamine and alanine, lactic acid, and glycerol is known as gluconeogenesis. Ketogenesis begins producing ketone bodies (KBs) as an alternative energy source when the availability of glucose further decreases and endogenous glucose synthesis is unable to meet the body's needs. The process starts with fatty acid being broken down in the liver to generate acetyl-CoA and ATP [22], and acetyl-CoA is converted to KBs. Following the enzymatic metabolism of thiolase, HMG-CoA synthase, and HMG-CoA lyase, KBs are synthesized in the liver and released into the bloodstream [23]. However, the lack of succinyl CoA:3-oxaloacid CoA transferase (SCOT) in the liver and red blood cells prevents the utilization of KBs as energy sources and prevents the cleavage of KBs before they reach other tissues and organs [23]. Due to low blood glucose feedback during ketogenesis, the stimulus for insulin production is likewise low, which significantly diminishes the stimulus for storing fat and glucose. The increased breakdown of lipids into fatty acids may be influenced by other hormonal changes. Acetoacetate, which is produced during the metabolism of fatty acids, is then changed into acetone and β-hydroxybutyrate. These are the fundamental KBs that develop in the body throughout the course of a KD. Nutritional ketosis is the term given to this metabolic state. The body's metabolism will continue to be in ketosis as long as it is deprived of carbs. Given that KBs are synthesized in small amounts without causing significant changes to blood pH, the nutritional ketosis state is regarded as relatively safe. It varies significantly from ketoacidosis, a disease that can be fatal in which the production of KBs occurs in excessively high concentrations, changing the pH of the blood to an acidotic state.

KBs are small water-soluble molecules that are freed into the circulation and can be used to produce energy in most tissues. Ketones are able to pass the blood brain barrier without difficulty and are essential fuel for the cells of the nervous system when glucose availability is reduced. At the tissue level, the KBs are further converted into acetyl-CoA and utilized as substrates in the Krebs cycle, a fundamental metabolic cycle used by cells to produce energy in the presence of oxygen.

When the availability of carbohydrates is reduced, as occurs during a KD, hepatic glycogen stores are depleted, and the body begins to break down both dietary triacylglycerides and triacylglycerides contained in adipose cells through the process of lipolysis as the final stage, and monoacylglycerol lipase hydrolyzes the final fatty acid to generate glycerol and a net total of three fatty acids. Herein, fatty acids are used for energy production through a process called beta-oxidation that results in a strong accumulation of acetyl-CoA, whereas glycerol can be involved in the gluconeogenesis process by contributing to overall glucose production in the liver.

When acetyl-CoA is present in large quantities it is used for the synthesis of KBs:

(A) Acetoacetic acid is the direct product of the processes that take place in the liver. It can be converted into the other two compounds.

(B) Acetone is produced by the decarboxylation of acetoacetate, and it can be converted to pyruvate, or lactate to produce energy, or it can be excreted through the urine or, being very volatile through the breath. It is responsible for the fruity odor typical of people in ketosis.

(C) β-hydroxybutyric acid, formed by decarboxylation of acetoacetate, is the most abundant of the three [24].

The muscle tissues, kidneys, and heart can all readily use KBs that are produced in the body to provide energy. KBs can also pass the blood-brain barrier, providing the brain with a new source of energy. RBCs lack mitochondria and hepatocytes have very little SCOT which is necessary for ketolysis. This allows KBs to be produced in the hepatocytes and consumed in the mitochondria of extrahepatic tissue.

A variety of factors impact the formation of KBs, including the percentage of body fat, resting basal metabolic rate (BMR), and body mass index (BMI). When compared to glucose, KBs synthesize more adenosine triphosphate (100 g of glucose yields 8.7 g of ATP); 100 g of β-hydroxybutyrate produces 10.5 g of ATP. Ketosis therefore allows the body to draw on the large amount of available energy stored in fats as opposed to the low amount of energy stored in glycogen. The production of KBs, a water-soluble alternative

to glucose obtained from fat and utilized by the brain, allows the body to continue producing fuel in the absence of a food source of energy, even when there is a caloric shortage. Additionally, KBs improve antioxidant capacity and reduce free radical damage [25].

Results

A search of the PubMed database was carried out, spanning literature published from 2020 to 2022. Only published papers that met the requirements of reporting clinical trials investigating an adult sample of T2D patients were included. The keywords of the search were "T2D", "Obesity", "Very low-calories ketogenic diet", and "HbA1c".

The literature search yielded two studies: one randomized clinical trial [20] and one retrospective observational study [21]. The characteristics of the included studies are presented in Table 1.

Table 1. Summary of included studies

Study ID	Design/sample	Intervention	Findings	Conclusion
Li et al. [20]	A 12-week randomized clinical trial Sample: 60 overweight or obese patients newly diagnosed with T2D KD: *n* = 30 Control group: *n* = 30	For the KD group: carbohydrate 30–50 g, protein 60 g, fat 130 g, and total calories 1500 ± 50 kcal For the control group: carbohydrate 250–280 g, protein 60 g, fat 20 g, total calories 1500 ± 50 kcal	For the two groups, the BMI, TG, waist, weight, HbA1c, FINS, TC, FBG, HDL, and LDL were reduced following the intervention ($P < 0.05$). Blood glucose, blood lipid, and body mass drop rates in the KD group were substantially greater than in the control group ($P < 0.05$)	In patients with T2D who are obese or overweight, a KD can control not only weight but blood lipids and glucose levels as well
Moriconi et al. [21]	A 12-month retrospective observational study Sample: thirty patients with obesity and T2D, aged between 35 years and 75 years VLCKD: *n* = 15 LCD: *n* = 15	15 Subjects received a VLCKD diet, and 15 received an LCD diet, with the same follow-up and assessments for the duration of the investigation in both groups	Significant weight loss was observed in the VLCKD group at 3 (8.5% from baseline, $P = 0.000$) and 12 months (11.5% from baseline, $P = 0.000$), while there was no significant change in weight in the LCD group ($P = 0.706$ at T1, $P = 0.623$ at T2) In the VLCKD group, there was a significant decrease in HbA1c at both time points, while in the LCD group, minor and statistically insignificant changes were observed	The research confirmed that a VLCKD is an effective and safe tool in the management of T2D and obesity. VLCKDs can result in a decrease, or even suspension, of pharmacological therapy, potentially causing remission of the disease

T2D: type 2 diabetes; TG: triglycerides; FINS: fasting insulin; TC: total cholesterol; FBG: fasting blood glucose; VLCKD: very low carbohydrate ketogenic diet; LCD: low-calories diet; BMI: body mass index; KD: ketogenic diet; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Findings after pooling the reviewed publications [10–13] demonstrated a substantial decrease in BMI, weight, HbA1c percentage, and fasting blood glucose (FBG). The findings of lipid analysis demonstrated a decrease in cholesterol and triglycerides (TG).

In 2022, 60 obese diabetes patients participated in a 12-week randomized clinical study carried out by Li et al. [20]. The participants were randomly divided into two sections, each with 30 cases: the KD section, which received the KD, and the control section, which received the standard diabetic diet. Body weight, blood lipids, blood glucose, uric acid, and insulin levels were measured prior to and following the intervention along with the observation of relevant significant changes over the 12-week duration of each dietary pattern.

Following the intervention ($P < 0.05$), LDL-cholesterol (LDL-C), BMI, weight, waist circumference, fasting insulin (FINS), HbA1c, TG, HDL cholesterol (HDL-C), total cholesterol (TC), and FBG all showed a decrease in the two groups, with a more significant rate of decrease in the KD group than in the control group. Uric acid (serum uric acid), however, revealed an increasing trend in the KD group, whereas it did

not change significantly ($P > 0.05$) in the control group. The long-term willingness to follow the KD was lower than for the routine diabetes diet.

In 2022, Moriconi et al. [21] conducted a 12-month retrospective observational study on 30 obese diabetic patients in the Diabetes Unit of the Division of Endocrinology of Rome. Fifteen patients received a VLCKD, while 15 patients received an LCD, and both groups were subjected to identical evaluations and follow-ups over the duration of the study [21].

After 3 and 12 months, significant weight reduction was seen in the VLCKD group, but in the LCD group, no significant weight change was noted. Anthropometric measurements [waist circumference (WC), hip circumference (HC), and BMI] were considerably lower in the VLCKD group, whereas these parameters remained substantially unaltered in the LCD group. Overall cholesterol declined in the VLCKD group at all follow-ups, whereas the lipid profile in the LCD group remained mostly unaltered. HbA1c was substantially reduced in the VLCKD group at both times, while minor and statistically insignificant effects and changes were reported in the LCD group.

In the VLCKD group, anti-diabetic medications were reduced or completely stopped. Nearly 50% of the participants in the LCD group required more anti-diabetic drugs, indicating a clear link between failing to follow a food plan and needing more pharmacological therapy.

A review of meta-analyses and clinical trials by Dyńka et al. [26] paid particular attention to the effect of a KD on the prophylaxis and treatment of diabetes mellitus and showed a beneficial effect of the ketogenic nutritional model on HbA1c, glucose, insulin, and other metabolic values in diabetic patients. The impact of the KD on the pharmacotherapy of T1D and T2D was shown and contrasted with the standard recommended nutritional management plan for this disease [26].

Impact of a KD on the pharmacotherapy of T1D and T2D

It was demonstrated in several scientific studies that: a KD can decrease insulin requirements in patients with T1D using insulin pumps [27]; patients using treatment with sodium-glucose cotransporter 2 inhibitors should discontinue them before starting a KD because of the increased risk of developing diabetic ketoacidosis [28]; those receiving treatment with glucagon-like 1 peptide receptor agonists in the course of a KD should be closely supervised, and their administration may have to be discontinued because of an increased risk of hypoglycemic episodes and diabetic ketoacidosis [29]. In the case of metformin, no evidence of generic contraindications has been shown [30]. In the ketogenic nutritional model, it is, therefore, possible to suspend or reduce pharmacotherapy and the possibility of disease remission has also been suggested, therefore a KD in patients with T2D appears to be a promising strategy that can be used to improve blood glucose control. Continuous status follow-up of these patients' health remains important.

Impact of a KD on the course of T1D

There exists a major gap in the research literature on the impact of a KD on diabetes; studies on the topic are scarce often because of concerns regarding ketoacidosis in diabetic patients. Frequently, the physiological condition of nutritional ketosis is regarded as a risk factor for ketoacidosis, which can develop as the result of T1D complications. These two notions should be clearly distinguished. Ketoacidosis is the simultaneous occurrence of very high serum concentrations of KBs (15–25 mmol/L) and glucose (250 mg/dL and higher), which leads to a dangerous decrease in blood pH value to a level below 7.3. The physiological condition of nutritional ketosis is characterized by a low value within the normal range (70–99 mg/dL) of glucose concentration and a slight concentration (compared with ketoacidosis) of KBs (usually within the range of 0.5–3 mmol/L) and causes no reduction in blood pH value. In the case of either healthy patients or those with T2D, concerns about developing ketoacidosis following the adoption of a KD are without scientific basis.

In T1D, the autoimmune process combined with the breakdown of pancreatic beta cells can be related to disorders of intestinal homeostasis that may result from a decrease in the number of lactate- and butyrate-producing intestinal bacteria [31]. A KD results in an increase in β-hydroxybutyrate, which has a

defensive role in the autoimmunization process of pancreatic cells and inhibits inflammatory states by decreasing the number of proinflammatory intestinal Th17 cells [32]. The efficacy of a KD was also shown in an almost four-year-old child with myoclonic-astatic epilepsy and T1D, and no major episodes of hypoglycemia or ketoacidosis were noted [33]. Other cases of children with T1D on a KD reported improvements in the glucose profile. Potential risks indicated by the application of this nutritional scheme in children with T1D are increased TC levels, which, however, based on present knowledge, are of negligible significance inside this range, and recurrent episodes of hypoglycemia, which may be a real problem. Some authors report unmet requirements for calcium, magnesium, and phosphorus in children, which, however, are not attributable to the KD per se, but to an inadequate KD [34]. The outcomes of studies on the treatment of T1D with a KD in adults are promising, and among the shown benefits we find a significant decrease in hypoglycemic episodes, HbA1c levels, and postprandial insulin requirements [35]. Total and HDL-C concentration levels did not change significantly, while TG concentration decreased [36]. These results were derived by following an LCD without knowing whether this amount was sufficient to induce ketosis since the level of KBs was not monitored. As a result of the studies conducted, the authors concluded that a properly conducted KD influences blood glucose control in T1D, with a low rate of adverse events in both adults and children.

Impact of a KD on the prevention and treatment of T2D

Based on the studies provided, the most important aspect is the significant effect of a KD on glycemic values in diabetic subjects. The meta-analyses and systematic reviews considered report the effectiveness of a KD in improving glycemic parameters, body mass, and lipid profiles, a reduction in waist circumference, glucose concentration, HbA1c and TC, LDL fraction, and TG levels, and an improvement in HDL-C levels. Better glycemic control and the positive effect of a KD on insulin sensitivity in T2D, as well as a decrease in the intake of antidiabetic drugs, have also been previously reported. The authors suggested that the diet can be recommended for T2D [37, 38].

Insulin resistance (IR) has a major role in the pathogenesis of many diseases, such as T2D, cardiovascular disease, nonalcoholic fatty liver disease, obesity, and neurodegenerative diseases [39]. The mechanism of IR is not only associated with an alteration of the insulin signaling pathway, but also involves disruption of multiple metabolic pathways involving carbohydrates, amino acids, lipids, KBs, and even bile acids. Metabolites of these metabolic pathways can affect insulin sensitivity directly and indirectly.

Several factors associated with lifestyle and diet contribute to IR and a specific condition in which exposure to a given amount of insulin, which is structurally and functionally normal, induces an abnormal biological response that is lower than expected. It is closely related to visceral obesity, in which there is an increased portal flux of free fatty acids that interfere with the hepatic degradation of insulin, inducing a condition of hyperinsulinemia that, in turn, contributes to the central localization of adipose tissue. Moreover, hyperinsulinemia leads to a reduction in the surface density of insulin receptors as well as a decrease in their binding affinity for insulin, with the development of a condition known as IR. It is also noteworthy that insulin receptors are decreased in muscle cells, but are increased in fat cells.

This explains the cause of hyperglycemia and lipid synthesis: glucose finds it difficult to enter muscle cells because the density of insulin receptors and the number of glucose transporter-4 (Glut-4) are reduced, while the opposite occurs in the adipose tissue since the insulin receptors maintain their functionality: the number of Glut-4 is increased and, entering the adipose cell, they activate lipid synthesis. All this occurs in the visceral insulin-dependent adipose tissue, with a consequent increase of fat mass in the abdominal area.

In addition, insulin, by inhibiting lipase activity, decreases the breakdown of fat, leading to difficulty in losing weight if we do not use dietary therapies that drastically reduce insulin levels. Cells need glucose in order to function; in the presence of IR, the body tries to re-balance the system by producing greater amounts of insulin to compensate for the decreased glucose entry into cells. To make things worse, IR is also responsible for a further increase in insulin secretion, with progressive exhaustion of pancreatic secretion and consequent progression to overt diabetes.

A KD is a low-carbohydrate/high-fat and moderately protein diet. When the carbohydrate diet is limited, insulin secretion is reduced significantly, the gluconeogenesis pathway is activated to provide glucose needed for energy from non-carbohydrate sources, mainly lactic acid and glycerol, but glucose derived from gluconeogenesis is not enough to meet the body's demand, and the major source of energy is switched to fat intake through hepatic catabolism of fatty acids and KD produced by the liver, which can cross the blood-brain barrier to contribute energy to the central nervous system [40].

By decreasing the glycemic response created by carbohydrates and improving IR, a KD can improve both insulin-dependent diabetes mellitus (IDDM)/T1D and T2D. At the moment, the literature has little available evidence of the effects of KDs on T1D, however, some trials have shown that patients with T1D could also benefit from a KD [26]; they reported better glucose control with a near-normal HbA1C level (5.3–5.7%), a lower rate of major adverse effects, but many patients also reported frequent episodes of hypoglycemia, suggesting that attentive blood glucose monitoring in these patients is essential.

Discussion

Benefits of a KD in T2D patients

These investigations have demonstrated the advantages of a KD for T2D patients, including weight reduction, a reduction in HbA1C, and an improvement in the blood lipid profile.

Weight loss

Being overweight is a clinical condition characterized by chronic low-grade inflammation, which in turn is considered the main factor responsible for weight excess-related complications, such as metabolic syndrome, diabetes, dyslipidemia, psoriasis, and cardiovascular disease [41, 42]. Li et al. [20] conducted a comparison of the effectiveness of a KD and that of the classic Mediterranean diet and demonstrated that a KD is more efficient in weight reduction than a low-fat diet. With the drastic reduction in carbohydrate intake, the body depletes its glucose reserves and starts burning fat for energy, producing KBs. Excessive lipolytic metabolism is one of the causes of this weight reduction. This process can become significant as early as 2–4 days after starting the diet. A further possible cause of weight reduction in a KD could be hypothalamus-induced hunger reduction, although the primary process remains unclear, as KBs act in both orexigenic and anorexigenic ways. Thus, more research must be carried out to identify the effect of KBs on appetite and satiety.

Leonetti et al. [43] conducted an observational investigation that demonstrated that a VLCKD was safe and effective in patients with morbid obesity, with or without T2D, who were scheduled for laparoscopic bariatric surgery. The introduction of a VLCKD directly prior to bariatric surgery led to a temporary but substantial pre-operative weight reduction, which reduced the peri-operative risks and challenges of both surgery and anesthesia, without the potential drawbacks of carbohydrate removal in the immediate proximity of the surgery [43]. Casanueva et al. [44] also reported that a KD was an excellent approach, to be considered as a part of a multi-component strategy and under strict medical supervision, whereas Castaldo et al. [9] reported that a specific very low carbohydrate diet protocol named Oloproteic Diet, is a key intervention to induce weight loss before bariatric surgery showing beneficial effects on the reduction in liver volume, the metabolic profile, and intra- and post-operative complications. The authors demonstrated that caloric deprivation, with an almost complete absence of carbohydrates, could neutralize the anabolic effect of insulin on fat metabolism.

Reduction of HbA1c levels

One of the primary guidelines-based objectives in the control of T2D is the decrease of HbA1c levels. Consistently low HbA1c readings would reduce the likelihood of developing diabetes complications. Restricting carbs has well-documented and immediate advantages for people with diabetes, but there are issues surrounding its long-term effectiveness and safety. These advantages can be attained even if weight reduction is absent [32].

Histological findings reported by Al-Khalifa et al. [33] in an experimental investigation performed on rats supported the belief that a VLCKD has a very positive impact on the improvement of the diabetic state through stabilization of hyperglycemia, which may lead to enhanced B cell activity.

Hussain et al. [34] observed that a KD was more efficient than a low-calorie diet in decreasing HbA1c. This effect is likely because of the KBs' ability to lower the metabolism of glucose. Nevertheless, the process of glucose metabolism reduction by KBs still needs to be clarified.

Choi et al. [45] in their meta-analysis explore the effectiveness of a ketogenic protocol in metabolic control in patients with excess weight or obesity and with or without T2D. They analyse 14 randomised controlled trials reported in Embase, PubMed, and the Cochrane Library conducted on patients with excess weight or obesity on a KD for metabolic control. The effects of KDs on glycaemic control were greater for diabetic patients than low-fat diets, indicated by a reduction in glycated hemoglobin and the homeostatic model assessment index, while comparable effects were observed for non-diabetic patients. Other authors confirmed that KDs proved to be more effective than low-fat diets in improving metabolic parameters associated with glycaemic, weight, and lipid control in patients with excess weight or obesity, especially those with pre-existing diabetes [45].

A systematic review identified randomised controlled trials lasting at least 6 months. One group of authors compared the efficacy and safety of a KD characterised by ≤ 50 g carbohydrate or ≤ 10% total energy from carbohydrates per day versus a control diet [carbohydrates above the VLC/KD threshold] in adults with pre-diabetes or T2D. The authors showed reductions in HbA1c and TG in subjects with pre-diabetes or T2D [46]. Westman et al. [47] also concluded, in a randomised study with patients with obesity and T2D (n = 49), that an LCD led to greater improvements in glycemic control. The intervention led to improvements in HbA1c, fasting glucose, FINS, and weight loss.

Lipid profile

Cardiovascular disease is a major consequence of T2D. Dyslipidemia is regarded as a cardiovascular disease risk factor. Numerous investigations, however, have shown that a KD improves lipid profiles. In reality, research conducted by Li et al. [20] found that a KD reduced LDL and TG levels while increasing HDL levels. Insulin activates key enzymes in biochemical pathways that store energy derived from carbohydrates, and in the absence or scarcity of carbohydrates the reduced levels of insulin lead to a reduction in lipogenesis and in fat accumulation [9].

Conclusions

For people with obesity-related T2D, clinical studies have shown that carbohydrate restriction and weight loss can improve hyperglycemia, obesity, and T2D. Reducing carbohydrate intake, generally below 50g/day, leads to increased ketogenesis to provide fuel to the body. Recent clinical research has reinvigorated the use of a KD for people with obesity and diabetes. The underlying causes of T2D are hyperinsulinemia and IR leading to a chronic hyperglycemia state in the patient. This is a typical result of increased energy intake leading to obesity. A KD reduces the glycemic response that comes from dietary carbohydrates and improves IR. While current treatment of T2D emphasizes drug therapy and a higher carbohydrate diet, a KD appears to be an effective drug-reducing alternative and may even be a preferred option when drugs are not available [35].

The KD has recently received much attention for its promise to treat obesity and T2D. Its suitability will also have to go through an assessment of the risks, benefits, and applicability of the diet to avoid unnecessary harm and costs to patients [38]. Several dietary patterns have received expert support over the past half-century, but there are limits to the evidence that precludes any single pattern from being considered superior to the others. Considering the growing prevalence of obesity, it is critical to objectively support all approaches that show evidence of net benefit [36].

To conclude, a KD presents numerous advantages in managing T2D. These advantages include weight reduction, improved lipid profile, and reduced HbA1c levels. Research shows the beneficial therapeutic value of a VLCKD in the management of T2D and long-term obesity and its capacity to help achieve disease remission.

The globalized world suffers varying degrees of IR, as evidenced by the high prevalence of obesity, metabolic syndrome, prediabetes, and T2D. Numerous studies in the scientific literature demonstrate the efficacy of low-carbohydrate dietary patterns in the management of IR. Given the abundant and robust evidence on the efficacy of specific interventions on IR patients and their increasing proportion, there is a need to redefine guidelines to offer a low-carbohydrate dietary option to combat IR and related pathologies [47–49]. Further and larger randomized clinical trials are needed to confirm these data.

Abbreviations

BMI: body mass index

HDL-C: high-density lipoprotein cholesterol

IR: insulin resistance

KBs: ketone bodies

KD: ketogenic diet

LCD: low-calories diet

LCKDs: low-calories ketogenic diets

LDL: low-density lipoprotein

LDL-C: low-density lipoprotein cholesterol

T2D: type 2 diabetes

TC: total cholesterol

TG: triglyceride

VLCKD: very low-calories ketogenic diet

Declarations

Author contributions

PP: Conceptualization, Data curation, Writing—original draft. PL: Conceptualization, Data curation, Writing—original draft. LR: Conceptualization, Writing—review & editing, Validation, Funding. MDE: Conceptualization, Validation, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

The datasets for this study can be found in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8811985/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7996853/.

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References

1. Sukkar SG, Muscaritoli M. A clinical perspective of low carbohydrate ketogenic diets: a narrative review. Front Nutr. 2021;8:642628. [PubMed] [PMC]
2. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al.; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 2008;359:229–41. Erratum in: N Engl J Med. 2009;361:2681. [DOI] [PubMed]
3. Volek JS, Phinney SD, Forsythe CE, Quann EE, Wood RJ, Puglisi MJ, et al. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Lipids. 2009;44:297–309. [DOI] [PubMed]
4. Sarmah S, Roy AS. A review on prevention of glycation of proteins: potential therapeutic substances to mitigate the severity of diabetes complications. Int J Biol Macromol. 2022;195:565–88. [DOI] [PubMed]
5. Jayedi A, Zeraattalab-Motlagh S, Jabbarzadeh B, Hosseini Y, Jibril AT, Shahinfar H, et al. Dose-dependent effect of carbohydrate restriction for type 2 diabetes management: a systematic review and dose-response meta-analysis of randomized controlled trials. Am J Clin Nutr. 2022;116:40–56. [DOI] [PubMed]
6. Dashti HM, Mathew TC, Al-Zaid NS. Efficacy of low-carbohydrate ketogenic diet in the treatment of type 2 diabetes. Med Princ Pract. 2021;30:223–35. [DOI] [PubMed] [PMC]
7. Castellana M, Conte E, Cignarelli A, Perrini S, Giustina A, Giovanella L, et al. Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: a systematic review and meta-analysis. Rev Endocr Metab Disord. 2020;21:5–16. [DOI] [PubMed]
8. Cunha GM, Guzman G, Correa De Mello LL, Trein B, Spina L, Bussade I, et al. Efficacy of a 2-month very low-calorie ketogenic diet (VLCKD) compared to a standard low-calorie diet in reducing visceral and liver fat accumulation in patients with obesity. Front Endocrinol (Lausanne). 2020;11:607. [PubMed] [PMC]
9. Castaldo G, Schiavo L, Pagano I, Molettieri P, Conte A, Sarno G, et al. Clinical impact of enteral protein nutritional therapy on patients with obesity scheduled for bariatric surgery: a focus on safety, efficacy, and pathophysiological changes. Nutrients. 2023;15:1492. [DOI] [PubMed] [PMC]
10. Goday A, Bellido D, Sajoux I, Crujeiras AB, Burguera B, García-Luna PP, et al. Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. Nutr Diabetes. 2016;6:e230. [DOI] [PubMed] [PMC]

11. Caprio M, Infante M, Moriconi E, Armani A, Fabbri A, Mantovani G, et al.; Cardiovascular endocrinology Club of the Italian Society of Endocrinology. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE). J Endocrinol Invest. 2019;42:1365–86. [DOI] [PubMed]
12. Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care. 2019;42:731–54. [DOI] [PubMed] [PMC]
13. Wilder RM, Winter MD. The threshold of ketogenesis. J Biol Chem. 1922;52:393–401. [DOI]
14. Gasch, AT. Use of the traditional ketogenic diet for treatment of intractable epilepsy. J Am Diet Assoc. 1990;90:1433–35. [PubMed]
15. Bistrian DR, Winterer J, Blackburn GL, Young V, Sherman M. Effect of a protein-sparing diet and brief fast on nitrogen metabolism in mildly obese subjects. J Lab Clin Med. 1977;89:1030–5. [PubMed]
16. Cicero AF, Benelli M, Brancaleoni M, Dainelli G, Merlini D, Negri R. 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. 2015;22:389–94. [DOI] [PubMed] [PMC]
17. Nebeling LC, Miraldi F, Shurin SB, Lerner E. Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. J Am Coll Nutr. 1995;14:202–8. [DOI] [PubMed]
18. Danan A, Westman EC, Saslow LR, Ede G. The ketogenic diet for refractory mental illness: a retrospective analysis of 31 inpatients. Front Psychiatry. 2022;13:951376. [DOI] [PubMed] [PMC]
19. Rafiullah M, Musambil M, David SK. Effect of a very low-carbohydrate ketogenic diet vs recommended diets in patients with type 2 diabetes: a meta-analysis. Nutr Rev. 2022;80:488–502. [DOI] [PubMed]
20. Li S, Lin G, Chen J, Chen Z, Xu F, Zhu F, et al. The effect of periodic ketogenic diet on newly diagnosed overweight or obese patients with type 2 diabetes. BMC Endocr Disord. 2022;22:34. [DOI] [PubMed] [PMC]
21. Moriconi E, Camajani E, Fabbri A, Lenzi A, Caprio M. Very-low-calorie ketogenic diet as a safe and valuable tool for long-term glycemic management in patients with obesity and type 2 diabetes. Nutrients. 2021;13:758. [DOI] [PubMed] [PMC]
22. Lieberman M, Marks AD. Marks' basic medical biochemistry: a clinical approach. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009.
23. Fukao T, Mitchell G, Sass JO, Hori T, Orii K, Aoyama Y. Ketone body metabolism and its defects. J Inherit Metab Dis. 2014;37:541–51. [DOI] [PubMed]
24. Puchalska P, Crawford PA. Metabolic and signaling roles of ketone bodies in health and disease. Annu Rev Nutr. 2021;41:49–77. [DOI] [PubMed] [PMC]
25. Masood W, Annamaraju P, Khan Suheb MZ, Uppaluri KR. Ketogenic diet. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
26. Dyńka D, Kowalcze K, Ambrozkiewicz F, Paziewska A. Effect of the ketogenic diet on the prophylaxis and treatment of diabetes mellitus: a review of the meta-analyses and clinical trials. Nutrients. 2023; 15:500. [DOI] [PubMed] [PMC]
27. Bolla AM, Caretto A, Laurenzi A, Scavini M, Piemonti L. Low-carb and ketogenic diets in type 1 and type 2 diabetes. Nutrients. 2019;11:962. [DOI] [PubMed] [PMC]
28. White-Cotsmire AJ, Healy AM. Ketogenic diet as a trigger for diabetic ketoacidosis in a misdiagnosis of diabetes: a case report. Clin Diabetes. 2020;38:318–21. [DOI] [PubMed] [PMC]
29. Garay PS, Zuniga G, Lichtenberg R. A case of euglycemic diabetic ketoacidosis triggered by a ketogenic diet in a patient with type 2 diabetes using a sodium-glucose cotransporter 2 inhibitor. Clin Diabetes. 2020;38:204–7. [DOI] [PubMed] [PMC]
30. Oleksyszyn J. The complete control of glucose level utilizing the composition of ketogenic diet with the gluconeogenesis inhibitor, the anti-diabetic drug metformin, as a potential anti-cancer therapy. Med Hypotheses. 2011;77:171–3. [DOI] [PubMed]

31. Nuwaylati D, Eldakhakhny B, Bima A, Sakr H, Elsamanoudy A. Low-carbohydrate high-fat diet: a SWOC analysis. Metabolites. 2022;12:1126. [DOI] [PubMed] [PMC]
32. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition. 2015;31:1–13. [DOI] [PubMed]
33. Al-Khalifa A, Mathew TC, Al-Zaid NS, Mathew E, Dashti HM. Therapeutic role of low-carbohydrate ketogenic diet in diabetes. Nutrition. 2009;25:1177–85. [DOI] [PubMed]
34. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Nutrition. 2012;28:1016–21. [DOI] [PubMed]
35. Westman EC, Tondt J, Maguire E, Yancy WS Jr. Implementing a low-carbohydrate, ketogenic diet to manage type 2 diabetes mellitus. Expert Rev Endocrinol Metab. 2018;13:263–72. [DOI] [PubMed]
36. Zhou J, Lu Y, Jia Y, Lu J, Jiang Z, Chen K. Ketogenic diet ameliorates lipid dysregulation in type 2 diabetic mice by downregulating hepatic pescadillo 1. Mol Med. 2022;28:1. [DOI] [PubMed] [PMC]
37. Zhou C, Wang M, Liang J, He G, Chen N. Ketogenic diet benefits to weight loss, glycemic control, and lipid profiles in overweight patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trails. Int J Environ Res Public Health. 2022;19:10429. [DOI] [PubMed] [PMC]
38. Joshi S, Ostfeld RJ, McMacken M. The ketogenic diet for obesity and diabetes—enthusiasm outpaces evidence. JAMA Intern Med. 2019;179:1163–4. Erratum in: JAMA Intern Med. 2019;179:1303. [DOI] [PubMed]
39. Ramasubbu K, Devi Rajeswari V. Impairment of insulin signaling pathway PI3K/Akt/mTOR and insulin resistance induced AGEs on diabetes mellitus and neurodegenerative diseases: a perspective review. Mol Cell Biochem. 2023;478:1307–24. [DOI] [PubMed]
40. de la Monte SM, Longato L, Tong M, Wands JR. Insulin resistance and neurodegeneration: roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis. Curr Opin Investig Drugs. 2009;10:1049–60. [PubMed] [PMC]
41. Castaldo G, Rastrelli L, Galdo G, Molettieri P, Rotondi Aufiero F, Cereda E. Aggressive weight-loss program with a ketogenic induction phase for the treatment of chronic plaque psoriasis: a proof-of-concept, single-arm, open-label clinical trial. Nutrition. 2020;74:110757. [DOI] [PubMed]
42. Castaldo G, Pagano I, Grimaldi M, Marino C, Molettieri P, Santoro A, et al. Effect of very-low-calorie ketogenic diet on psoriasis patients: a nuclear magnetic resonance-based metabolomic study. J Proteome Res. 2021;20:1509–21. [PubMed] [PMC]
43. Leonetti F, Campanile FC, Coccia F, Capoccia D, Alessandroni L, Puzziello A, et al. Very low-carbohydrate ketogenic diet before bariatric surgery: prospective evaluation of a sequential diet. Obes Surg. 2015;25:64–71. [DOI] [PubMed]
44. Casanueva FF, Castellana M, Bellido D, Trimboli P, Castro AI, Sajoux I, et al. Ketogenic diets as treatment of obesity and type 2 diabetes mellitus. Rev Endocr Metab Disord. 2020;21:381–97. [DOI] [PubMed]
45. Choi YJ, Jeon SM, Shin S. Impact of a ketogenic diet on metabolic parameters in patients with obesity or overweight and with or without type 2 diabetes: a meta-analysis of randomized controlled trials. Nutrients. 2020;12:2005. [DOI] [PubMed] [PMC]
46. Parry-Strong A, Wright-McNaughton M, Weatherall M, Hall RM, Coppell KJ, Barthow C, et al. Very low carbohydrate (ketogenic) diets in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2022;24:2431–42. [DOI] [PubMed] [PMC]
47. Westman EC, Yancy WS Jr, Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. Nutr Metab (Lond). 2008;5:36. [DOI] [PubMed] [PMC]

48. Volek JS, Phinney SD, Krauss RM, Johnson RJ, Saslow LR, Gower B, et al. Alternative dietary patterns for Americans: low-carbohydrate diets. Nutrients. 2021;13:3299. [DOI] [PubMed] [PMC]
49. Hallberg SJ, Gershuni VM, Hazbun TL, Athinarayanan SJ. Reversing type 2 diabetes: a narrative review of the evidence. Nutrients. 2019;11:766. [DOI] [PubMed] [PMC]