

Effect of ketogenic diet in type 2 diabetes mellitus

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ABSTRACT

Diabetes is a prevalent chronic condition globally, where dietary intervention plays a crucial role in its management. The ketogenic diet, high in fat, moderate in protein and low in carbohydrates, was studied to determine its impact on people with type 2 diabetes. Pertinent research was collected and analysed. Ketogenic diet has positive effects on type 2 diabetes, which can decrease blood sugar, lose weight and improve insulin resistance. However, the ketogenic diet also has some negative effects, which can lead to some side effects, such as hypoglycemia, uneven nutrition, and abnormal gastrointestinal function, due to its special dietary structure. Therefore, when adopting ketogenic diet, the quality and quantity of diet need to be strictly controlled. In conclusion, ketogenic diet has a positive impact in patients afflicted by type 2 diabetes, but attention should be paid to the side effects that may be triggered, and monitoring and adjustment should be carried out to ensure the safety and effectiveness of the diet.

KEYWORDS

Type 2 diabetes; Ketogenic diet; Effect; Mechanism; Keto; Very-low-carb diet

1. INTRODUCTION

The Centers for Disease Control and Prevention (CDC) reports that the number of diabetics has almost tripled in the last decade, making it one of the world's largest chronic diseases. An estimated 6.7 million people will die from diabetes this year, according to the International Diabetes Federation's (IDF) Diabetes Atlas for 2021 report. As of 2021, it is predicted that more than 537 million adults (ages 20 to 79 years) globally suffer from diabetes. Type 2 diabetes stands as the most prevalent manifestation of diabetes, making up between 90 and 95 per cent of all diabetes patients [1]. The pathogenesis of T2DM is mainly caused by the deficiency of β -cells in the pancreas, which results in insulin resistance. Thus, T2DM patients have a relative lack of insulin.

Lifestyle interventions, including better diet and moderate exercise, are essential for the care of diabetic patients. Nutrition interventions are also important to assist people affected by type 2 diabetes to better manage disease and to lower the likelihood of complications associated with diabetes. Recently, a variety of nutritional interventions, such as the ketogenic diet (KD), have investigated as therapeutic diets for diabetes [2]. The definition of a KD is that it has a high fat content, a medium protein intake, and extremely low carbohydrate input (generally below 20 to 50 g/day, according to table 1, with energy supplied by ketone bodies [3]. Standard ketogenic diets, typically 70 percent fat, 20 percent protein, and just 10 percent carbohydrates, are the most widely explored and advocated.

Table 1. Suggested definitions of different carbohydrate diets (Adapted from Feinman et al.) [3]

Features	Number of grams per day	Percentage of energy from carbohydrates
Ketogenic diet (diet with a very low carbohydrate content)	<20–50 g	<10
Low carbohydrate	<130 g	<26
Moderate carbohydrate	130–230 g	26–45
High carbohydrate	>230 g	>45

But, despite its promising use, studies of ketogenic diets in individuals suffering from type 2 diabetes are still limited. This review synthesizes and analyzes existing clinical research and data on effects of KD in patients afflicted by type 2 diabetes. This paper will explore the effects and mechanisms of KD on blood glucose control, weight control, insulin sensitivity, and possible side effects.

2. METHODS

This study used literature research method to evaluate the effectiveness of KD on type 2 diabetic patients. By collecting relevant literature and conducting a comprehensive analysis, including literature review, thematic analysis, data extraction, and comprehensive evaluation methods, we aimed to identify the actual benefits and potential risks of KD in type 2 diabetes. To ensure the scientific validity and standardization of the study, we performed a systematic literature search in accordance with PRISMA guidelines in databases such as PubMed, Science Direct and Web of Science. A systematic literature search was conducted according to PRISMA guidelines in databases such as PubMed, Science Direct and Web of Science to ensure scientific validity and standardisation. Through a comparison and synthesis of various studies in the literature, we aim to assess the effectiveness of the KD in managing type 2 diabetes, as well as any potential risks associated with it.

3. MECHANISM OF KETONE FORMATION

Acetoacetate (AcAc), beta-hydroxybutyrate (BHB) and acetone are the main ketone bodies that are used as energy substrates. Acetone is predominantly generated by the natural decarboxylation of AcAc, excreted through the lungs and kidneys as a volatile substrate, or further metabolized to pyruvate, lactate, and acetate. Fatty acids are the primary substrates for ketone synthesis. They are released by adipose tissue through adipokine signaling in response to high concentrations of glucagon and epinephrine and low levels of insulin. These fatty acids are then subjected to beta-oxidation to generate acetyl-CoA. Normally, acetyl-CoA is oxidised in the citric acid cycle (TCA/ Krebs cycle) and energy is released via the electron transport chain in the mitochondria. Nevertheless, during prolonged fasting, glucose deprivation, or strenuous exercise, when the production of acetyl-CoA exceeds the TCA cycle capacity, ketone body biosynthesis is initiated. This often occurs due to a decrease in TCA cycle activity caused by a shortage of intermediates. Acetoacetyl-CoA is formed when two acetyl-CoA molecules are individually converted by acetoacetyl-CoA and β -hydroxy- β -methylglutaryl-CoA (HMG-CoA). This is facilitated by the ketogenic enzyme sulfatase. HMG-CoA synthetase converts acetoacetyl-CoA into HMG-CoA, which is then split by HMG-CoA lyase to regenerate acetyl-CoA and produce one molecule of AcAc. BHB-dehydrogenase further reduces AcAc to BHB [4] below. Ketogenesis is regulated by insulin and glucagon, with insulin inhibiting and glucagon stimulating the process. Figure 1 illustrates the mechanism of ketone body production.

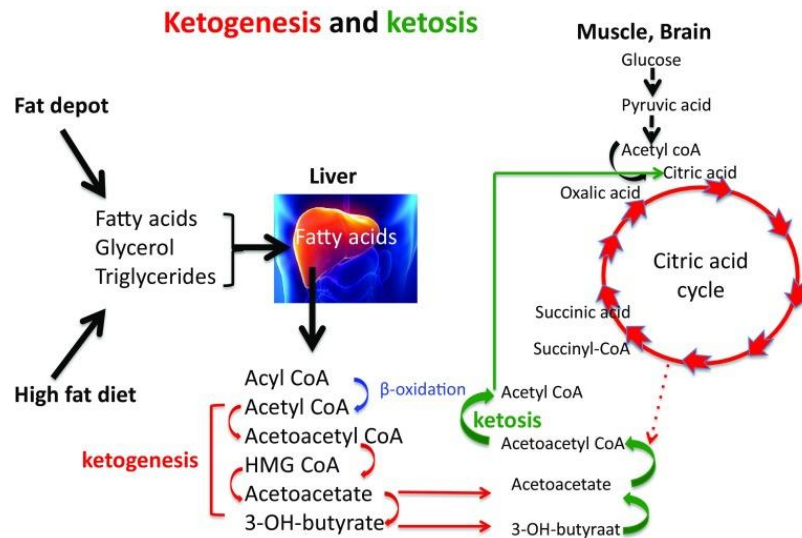


Figure 1. The whole process of ketogenesis in liver [4].

4. HOW KD HELPS CONTROL BLOOD GLUCOSE

4.1. KD's benefits for controlling blood glucose levels

Glycaemic control is a key goal of treatment for patients afflicted by type 2 diabetes, but some indications suggest that a KD might help these patients control blood glucose. For example, a randomized crossover intervention trial compared the effects of a KD and a Mediterranean diet on glycated hemoglobin (HbA1c) levels in patients afflicted by type 2 diabetes. This study involved 40 patients with pre-diabetes or type 2 diabetes who were assigned to follow a well-designed KD and a Mediterranean+ diet for 12 weeks each. The KD group experienced a decline in HbA1c measurements and significantly lower mean blood glucose levels. This study suggests that a KD may be able to improve glycaemic regulation in individuals diagnosed with type 2 diabetes [5].

Another study involving 25 participants randomized them into an intervention group (very low carbohydrate KD and lifestyle recommendations) and a comparison group. After a 32-week online intervention, the intervention group participants exhibited a larger decline in HbA1c levels than the comparison group. Over half of the intervention group participants achieved HbA1c levels below 6.5%, while none of the control group participants achieved this target. The study suggests that the KD leads to a significant improvement in glycated hemoglobin levels [6].

Lifestyle therapy, including dietary interventions, is the first-choice treatment for improving glycemic levels in patients afflicted by type 2 diabetes. The prevailing dietary policy emphasise a 'healthy diet' that is low in saturated fat and sugar. The focus is on low glycaemic indices foods. Nevertheless, the KD may be more effective in lowering blood glucose levels, according to studies comparing the KD with a healthy diet. To assess the potential safety and benefits of the KD as a management strategy for type 2 diabetes, further clinical trials are needed. In addition, it is important to consider individual differences and adherence to ensure the applicability and effectiveness of the KD in clinical practice [7].

4.2. The mechanism of KD on blood glucose level control

There are several mechanisms by which the KD may help to control blood glucose levels in patients afflicted by type 2 diabetes. Reducing insulin secretion by limiting carbohydrate intake is an important mechanism. In individuals with type 2 diabetes, insulin resistance can lead to the production of too much insulin, resulting in elevated blood glucose levels. The KD effectively lowers insulin levels and helps to better manage blood glucose levels by limiting carbohydrate intake [8]. In

addition, the high-fat foods in the KD stimulate fat metabolism, resulting in the production of ketones in the body. Under normal conditions, the body mainly relies on glucose as a source of energy. However, on a KD, by restricting carbohydrate intake, the body begins to use fat to produce alternative energy sources such as ketones. These ketones can be used by certain tissues and organs. This reduces their dependence on glucose and helps to stabilise blood glucose levels [4]. Additionally, ketogenic diets have been demonstrated to enhance insulin sensitivity and facilitate weight loss, both of which contribute to improved glycemic control. By inhibiting hepatic glycogenolysis and suppressing key enzymes involved in glucose synthesis, the KD reduces hepatic glucose output. This will result in a decrease in blood glucose concentration, allowing to better control their blood glucose levels. Ketone bodies increase the body's blood glucose concentration by acting directly on the glucose output of liver cells.

5. WEIGHT IMPACT OF KETOGENIC DIET

5.1. Losing Weight Using the Ketogenic Diet

Table 2 presents studies conducted by other researchers on the role of KD in diabetes. Based on the findings from the 10 clinical trials included, we were able to conduct a comprehensive analysis of the effects of the KD on weight in subjects suffering from type 2 diabetes. The diverse characteristics and methodologies employed in these trials offer a comprehensive perspective for evaluating the impact of the KD.

Overall, the effect of a KD on body weight has been significant. Clinical trials have consistently shown that most interventions involving a KD lead to significant weight loss in patients afflicted by type 2 diabetes. Specifically, results from nine trials demonstrated noteworthy weight reduction following the implementation of a KD, ranging from 2.2 kg to 24.5 kg, with an average weight loss of approximately 9.7 kg [2, 8, 9-16].

Table 2. Summary of selected studies showing beneficial effects of LKD in type 2 diabetes

Reference	Design and Methods	Results
Goday et al. [9]	The safety, tolerability, and effectiveness of a VLCKD were assessed and compared with a LCD in individuals with type 2 diabetes over a four-month period	The VLCKD diet group exhibited significantly superior weight loss and waist circumference reduction in comparison to the control group.
Cunha et al. [10]	Reducing visceral and hepatic fat deposition in obese individuals through a 2-month VLCKD intervention compared to LCD	Compared with LCD, the VLCKD group was more effective in terms of average weight reduction, VAT, and reduced liver fat content
Li et al. [11]	The impact of a regular dietary regimen on recently diagnosed, overweight, or obese individuals with type 2 diabetes	The weight, BMI, HbA1c and other indexes of KD group decreased significantly relative to the comparison group.
Saslow et al. [12]	The objective is to explore the impact of MCCRd and LCKD on individuals affected by both obesity and type 2 diabetes	In contrast to the MCCRd group, individuals in the LCKD group experienced more significant decreases in both HbA1c levels and body weight.
Hall et al. [13]	After isocaloric ketogenic diets, overweight men experienced changes in energy expenditure and body composition.	Subjects lost a total of 300 kcal/day of negative energy balance, losing weight and body fat.
Lichtash et al. [14]	A 14-month exploration of IF and KD as alternative therapies for type 2 diabetes in normal-weight females	This situation exemplifies the efficacy and enduring impact of IF and KD in individuals with normal weight who have type 2 diabetes.
Ivan et al. [15]	Effects of the Italian Ketogenic Mediterranean Diet on Overweight and Obese Individuals with Prediabetes or Type 2 Diabetes	The extremely low-calorie ketogenic Mediterranean diet demonstrates a substantial impact on reducing body weight, BMI, fasting glucose levels, HbA1c, insulin, C-peptide, as well as total cholesterol, LDL, and triglycerides.
Di Rosa et al. [16]	Compare the time it takes for MD versus VLCKD to achieve an initial weight loss of 5% in overweight and obese subjects, and how is body composition affected	Both dietary regimens are efficacious in the improvement of anthropometric measures and body composition, but their time requirements to achieve their goals are different.
Yancy et al. [8]	Effect of the LCKD on the overweight and obese patients diagnosed to have type 2 diabetes for 16 weeks.	Participants' Hemoglobin A1C decreased by 16 percent, average body weight decreased by 6.6 percent
Dashti et al. [2]	Investigating the beneficial effects of the ketogenic diet in obese diabetics	There was a significant decrease in body weight, body mass index, blood sugar, total cholesterol, LDL cholesterol, triglyceride, and urea levels observed between week 1 and week 56.

VLCKD, very low-calorie-ketogenic diet; LCD, low-calorie diet; VAT, visceral adipose tissue; HbA1c, glycated hemoglobin; KD, ketogenic diet; BMI, body mass index; MCCRd, moderate-carbohydrate calorie-restricted diet; LCKD, low-carbohydrate, ketogenic diet; LDL, low density lipoprotein; MD, Mediterranean Diet; HDL, high density lipoprotein.

The impact of the KD on drop in weight in patients afflicted by type 2 diabetes is influenced by diet type and intervention duration. Very low-calorie ketogenic diets (<800 calories per day) tend to yield greater weight loss compared to moderate or high-calorie counterparts, underscoring the importance of controlling caloric intake [9, 10]. Regarding intervention duration, outcomes indicate that interventions lasting beyond 12 weeks result in more substantial weight loss effects. This suggests that prolonged adherence to the KD is necessary for sustained weight management in patients afflicted by type 2 diabetes [2, 8, 9, 11, 12]. Despite heterogeneity in study design, sample size and specific ketogenic protocols, a combined analysis demonstrates the overall efficacy of the KD for drop in weight in subjects suffering from type 2 diabetes. The results highlight the importance of KD for weight maintenance in type 2 diabetes, contributing to improved insulin sensitivity and glycaemic

control while reducing complications [2, 11, 15, 16]. Adverse events associated with KD, such as constipation, fatigue and dizziness, should be monitored and managed in clinical practice to ensure safety and tolerability.

Furthermore, assessing the adaptability and sustainability of ketogenic diets in real-life scenarios for subjects suffering from type 2 diabetes is crucial. Although clinical trials support the efficacy of ketogenic diets for weight loss, ongoing research is needed to determine their practical implementation and maintenance. Considering lifestyle and individual differences will aid in developing more sustainable ketogenic diets [10, 15, 16]. Overall, this analysis confirms that KD is effective for decrease in weight among patients afflicted by type 2 diabetes. Nevertheless, additional studies are needed to address methodological differences and establish optimal strategies for ketogenic diet-based weight control in type 2 diabetes. These insights can offer comprehensive guidance for clinical practice, advancing the understanding and application of ketogenic diets in type 2 diabetes management.

5.2. How the Ketogenic Diet Works to Lose Weight

Subjects suffering from type 2 diabetes, the ketogenic diet (KD) has been shown to have a beneficial effect on weight management. Studies suggest that the diet achieves this by reducing energy intake and appetite, increasing energy expenditure, and promoting fat metabolism. It is important to note that the exact mechanism behind this effect is not fully understood. Consuming a high amount of fat on a KD enhances the body's ability to use fat for energy, leading to a decrease in fat reserves and ultimately facilitating weight loss.

The depletion of glycogen stores initiates specific energy-producing processes such as gluconeogenesis and ketogenesis. Gluconeogenesis requires an estimated 400-600 kcal/day, resulting in a metabolic advantage of burning an additional 200-300 calories compared to a diet rich in carbohydrates [4]. In contrast, non-ketogenic diets do not immediately increase fat oxidation, as most fatty acids are quickly stored as triglycerides by adipocytes. This limits the availability of fatty acids for utilization by adipose tissue and does not compensate for the decrease in fatty acids and carbohydrates consumed due to insulin secretion. On the other hand, the KD reduces insulin concentrations, promoting lipolysis, fat oxidation, and increased energy expenditure. The decrease in resting respiratory quotient (RQ) and the subsequent increase in the utilization of fat as a proportion of total energy expenditure could potentially explain the efficacy of ketogenic diets for loss of body mass.

The KD has the potential to reduce appetite and increase satiety, which may influence body weight. The mechanism behind appetite reduction during very low carbohydrate ketogenic diets (VLCKD) may involve effects on satiety proteins or the modulation of hunger-regulating hormones that promote lipolysis and inhibit adipogenesis. Ketone bodies, particularly beta-hydroxybutyrate (BHB), may also contribute to appetite suppression. One study evaluated the effects of different beverages on appetite in overweight and obese subjects. The group consuming the ketogenic beverage showed a decrease in appetite, while the group consuming a balanced nutritional drink did not. This may be due to the suppressive effect of ketosis on regulatory hormones such as gastric hunger hormone and leptin.

6. THE RELATIONSHIP BETWEEN KETOGENIC DIET AND INSULIN

6.1. The Impact Of A Ketogenic Diet On Insulin Improvement

Several studies have demonstrated that KD has significant effects on insulin levels in subjects suffering from type 2 diabetes, resulting in improved insulin sensitivity and reduced insulin resistance (IR). For instance, Zhang et al performed a study utilizing a mouse model to compare the impact of a 6-week ketogenic diet (KD) combined with exercise in treating type 2 diabetes [17]. The research

findings indicate that the KD group demonstrated markedly reduced insulin resistance compared to the comparison group. Li et al and Mohorko et al investigated the efficacy of KD in type 2 diabetes and found that it significantly reduced glycaemia and insulin levels [18, 19]. In contrast, Hall et al. reported that the KD demonstrated greater superiority in enhancing blood sugar and insulin levels by comparing a vegetable-based, reduced-fat diet with an animal-derived KD [20]. However, it should be noted that this study did not incorporate participants diagnosed with type 2 diabetes. Goday et al observed marked declines in fasting plasma glucose levels, HbA1c and IR in a study comparing KD with a low-calorie diet [9]. In a wider study, Hussain et al. compared the low-calorie diet (LCD) and the low carb water ketogenic diet (LCKD) and found that both diets improved blood glucose levels, with LCKD showing more significant changes [21]. A commonly used method to assess IR is the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Additionally, the proinsulin-to-insulin ratio and HbA1c serve as indicators of insulin sensitivity. These studies support the notion that the KD can improve insulin sensitivity and reduce IR in patients afflicted by type 2 diabetes. However, additional research is warranted to explore the long-term impact and feasibility of this intervention.

6.2. Mechanism Of Ketogenic Diet To Improve Insulin

Insulin resistance (IR) is a condition where the body becomes less responsive to insulin. This is often caused by modern lifestyles. Modern lifestyles are characterised by excessive consumption of carbohydrates and vegetable oils and limited physical activity. The body tries to regulate blood sugar levels by producing more insulin when insulin sensitivity is impaired. However, IR reduces the effectiveness of insulin in controlling the production and release of glucose, leading to increased blood glucose levels and worsened IR. Triglycerides may accumulate in the liver or circulate as low-density lipoprotein (LDL) cholesterol. IR also increases the likelihood of diabetes and heart problems by reducing the ability of muscle cells to absorb glucose. Conversely, elevated insulin levels correlate with improved insulin sensitivity.

As well as providing essential nutrients, KD helps to maintain a negative energy balance by reducing fat synthesis and lipolysis. This is achieved by reducing carbohydrate intake. The result is lower and more variable insulin secretion and, ultimately, an improvement in insulin sensitivity. Using systems biology approaches and mouse models, researchers have investigated the molecular mechanisms underlying the improved prognosis of type 2 diabetes induced by KD. Significant correlations have been found between ketosis and the major pathways involved in IR. Direct links have been found between the glucose transporter protein type 4, which is involved in IR, and proteins stimulated by KD, in particular acyl-coenzyme A oxidase 1 and hydroxyacyl-CoA dehydrogenase 1.

In trials with ob/ob mice, it was observed that KD had an ameliorating effect on the levels of hyperglycaemia and hyperinsulinaemia. Specifically, when KD ameliorated hyperglycaemia, the levels of specific O-GlcNAc-modified proteins changed. In addition, key enzymes associated with hepatic lipogenesis, acetyl-coA carboxylase 1 and fatty acid synthase, were found to be present in mice fed a normal diet but not in those on KD, indicating that the KD reduced diabetes in the liver of mouse. Moreover, KD led to a decrease in glucose transporter protein type 2 mRNA and fibroblast growth factor 21 expression. Glucose transporter protein type 2 is essential for insulin secretion related to glucose, so reducing its expression implies lower insulin levels and improved insulin resistance (IR) in patients with type 2 diabetes. Fibroblast growth factor 21 is regulated by peroxisome proliferator-activated receptor-alpha, promoting lipolytic metabolism and enhancing IR.

Furthermore, β -HB inhibits the NF- κ B signalling pathway, which is an important inflammatory pathway implicated in the onset of type 2 diabetes. Some tests have suggested that a reduction in body weight or a reduction in inflammation may have a beneficial effect on IR. It is also thought that IR may be caused by mitochondrial dysfunction and elevated levels of reactive oxygen species. The potential of KD to improve insulin sensitivity and alleviate IR is becoming increasingly clear.

However, to gain a complete understanding of its mechanistic basis and to improve its application in clinical practice, further research is needed [22].

7. SIDE EFFECTS OF KETOGENIC DIET

The KD has demonstrated efficacy in increasing insulin sensitivity, regulating blood sugar levels and helping with weight management. However, it is not without its side effects. Frequently reported side effects include dehydration, increased thirst, headache, dizziness, postural hypotension, and electrolyte imbalances, including lightheadedness and blurred vision. The excessive production and subsequent renal elimination of ketones during the active phase of the diet is responsible for these side effects. For individuals with pre-existing metabolic irregularities due to type 1 diabetes, the complications may be exacerbated by the increased state of hyperketonemia and ketosis associated with the KD. Particularly when dietary intake of these micronutrients is inadequate, electrolyte imbalances such as metabolic acidosis, hyponatremia and hypomagnesemia are common [23].

While the KD may decrease hepatic IR by limiting carbohydrate intake and lowering hepatic triglyceride levels, the increased ketone bodies may have the unintended effect of stimulating insulin secretion, potentially leading to hypoglycaemia. Gastrointestinal disturbances like nausea, vomiting, diarrhea, and constipation are also commonly reported. Diarrhea is often a result of impaired fat absorption and intolerance, while constipation is linked to inadequate fiber intake and reduced thirst due to the suppressive effects of ketones. Furthermore, the increase in ketone levels can cause halitosis, mainly due to acetone. A chronic complication is kidney stone formation, partly due to heightened uric acid concentration—hyperuricemia—resulting from limited fluid intake and ketone-induced thirst suppression.

A study emphasize the potential exacerbation of hyperlipidemia with KD, particularly in those with underlying dyslipidemia discernible only on a high-fat regimen. KD cautions against use in patients with established dyslipidaemia because of the heightened likelihood of developing gallstones, mainly affecting low-density lipoprotein (LDL) and total cholesterol levels. Rare side effects include hypoproteinemia from carbohydrate restriction, glycogen depletion, and hair loss, linked to the body prioritizing protein for essential functions over hair growth when sources are insufficient [24].

KD is implicated in impairing bone density, potentially leading to hypocalcemia and harmful bone conditions. While research on KD's impact on calcium metabolism is limited, maintaining adequate calcium intake and addressing vitamin D deficiencies are prudent, particularly for those with osteopenia or osteoporosis at an increased risk of fractures.

8. DISCUSSION

Consistent with previous research, our study found positive results of KD on glycaemic control. However, potential adverse effects associated with the KD were also identified. To conclude, the KD offers a novel therapeutic strategy to enhance the metabolic condition of individuals diagnosed with type 2 diabetes through dietary composition modifications by modifying their dietary composition. The analysis suggests that dietary modification holds potential for managing individuals diagnosed with type 2 diabetes mellitus, concerning both clinical decision support and enhanced patient results. However, there are still limitations, including a lack of research investigating the specific mechanisms underlying weight, blood glucose and insulin - these areas need to be investigated to assess long-term adherence to the KD. Furthermore, the KD has an impact on lipid levels and gut microbiology in individuals suffering from type 2 diabetes, highlighting the need for further exploration in these domains. It is important that healthcare providers and patients remain vigilant about these potential risks when using KDs for treatment and adopt appropriate prevention and management strategies.

9. CONCLUSIONS

The analysis indicates that the KD effectively manages glycemic regulation, facilitates body mass loss, and enhances insulin resistance and sensitivity in subjects suffering from type 2 diabetes. These effects are due to three main mechanisms: ketone body production, ketone body utilisation and energy metabolism. The ketogenic diet reduces insulin resistance, resulting in reduced insulin secretion and glucose dependence, by restricting carbohydrate intake. The KD has been shown to decrease hepatic glycogen output, which assisting in the adjustment of blood glucose levels. Additionally, it promotes weight loss by reducing energy intake and appetite, while increasing energy expenditure and fat metabolic rate. Individuals diagnosed with type 2 diabetes who follow KD, these mechanisms work together to produce positive results. However, it is important to note that KD can cause adverse effects. These include dehydration, thirst, headache and dizziness.

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