Research Progress of Dietary Intervention Effect of Ketogenic Diet on Type II Diabetes Patients

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Abstract. Control of carbohydrate intake is an important auxiliary means for Diabetes mellitus type 2(T2DM) management, and ketogenic diet (KD) as a new dietary pattern has attracted much attention in recent years. This article analyzes and systematically reviews the effects of KD on biochemical indicators and complications of type 2 diabetes (T2DM). Studies have shown that KD can effectively reduce blood sugar and lipid levels in the short term, and help to reduce weight, while also showing a certain improvement in cardiovascular disease and diabetic neuropathy and other complications. However, this dietary pattern may cause adverse reactions such as constipation and hypoglycemia during implementation, and there is currently a lack of long-term large-scale clinical study data to support its safety. Overall, KD shows promising application in the management of T2DM, but further optimization of dietary protocols and more in-depth clinical studies are needed to evaluate its long-term effects and potential risks.

Keywords: ketogenic diet; Diabetes mellitus type 2; dietary intervention.

1. Introduction

Diabetes is a chronic metabolic disease, and according to the data of the World Health Organization in November 2024, about 830 million people in the world have diabetes, and more than 95% of people with diabetes have type 2 diabetes (T2DM). The pathologic cause of T2DM is insulin resistance, or insufficient insulin secretion, which leads to elevated blood sugar levels that, over time, can cause serious damage to the heart, blood vessels, eyes, kidneys and nerves.

Balancing the ratio of carbohydrate and fat intake has been shown to be a key mechanism for maintaining blood glucose homeostasis in integrated T2DM control systems. Although the sugar-restricted dietary model recommended by the current clinical nutrition guidelines has shown certain effects in short-term blood glucose control, the limitations of metabolic regulation and the lack of compliance have become increasingly prominent. Therefore, a ketogenic diet (KD) has been proposed. The principle of KD is to reduce carbohydrate and replace it with fat, and induce a ketosis state. A number of experiments have shown that KD can directly or indirectly control a number of factors affecting T2DM. However, this dietary pattern has not been widely promoted, and the vast majority of people with diabetes know nothing about it. The main reasons for this are the current lack of support for a large number of clinical trials supporting the long-term efficacy, safety and health benefits of KDs, as well as the lack of individualized precision treatment for patients at different stages of the disease. In addition, because the KD requires strict metrics and is very specific to macronutrients, rapidly reducing carbohydrate intake in a short period of time can cause side effects such as headache, dehydration, constipation, back pain, insomnia, low-grade acidosis, and kidney stones (rare, but possible).

The objective of this study was to demonstrate the clinical effects of low KD on diabetic patients from the aspects of blood glucose control, weight and fat metabolism, insulin demand change, cardiovascular and metabolic risk, neuroprotection and cognitive function. At the same time, the current difficulties in the implementation of KD were analyzed, and new clinical strategies were proposed, such as setting the best treatment window period for KD in different populations, exploring more individualized and precise diet programs, and conducting multidisciplinary collaborative management, such as drug adjustment and nutritional support, to alleviate the side effects of diet structure adjustment, providing new ideas for future research directions.

2. Definition and Physiological Basis of KD

2.1. Definition of KD

Low Carb High Fat Diet (LCHF) refers to reducing the carbohydrate content of the diet and increasing the intake of high-quality fat as the main energy source. Taking the typical 2,000-calorie Western diet as an example, carbohydrate intake is reduced from 275 grams per day to 100 grams per day (and below). KD is a kind of LCHF. In the 1920s, in order to imitate the metabolism of fasting, modern doctors introduced it as a treatment for epilepsy [1], and later it was more applied in other medical aspects, such as weight loss, T2DM, cardiovascular disease (CVD), etc [2]. Because the purpose of this diet is to induce a state of ketosis, it is very specific for all macronutrients, planning a daily diet in a 4:1 ratio (for every 5 grams of food consumed, 4 grams of fat and 1 gram of protein and carbohydrates) [3].

2.2. Metabolic Mechanism of KD in Adjuvant Treatment of T2DM

The principle of the KD is that when glucose reserves become insufficient, the central nervous system (CNS) cannot use fatty acids as a source of nutrients. Therefore, after 3-4 days of carbohydrate restriction, CNS is forced to find alternative energy sources. This alternative energy source is ketones [4]. Because ketone bodies are produced through lipolysis, the body is in a state of ketosis when it consumes large amounts of fat in place of carbohydrates. In people with T2DM, extreme carbohydrate restriction reduces the absorption of simple sugars in the gut, resulting in lower blood sugar levels and reduced blood sugar fluctuations [5].

3. Direct and Indirect Effects of KD on T2DM

People with T2DM are more likely to develop CVD, diabetic neuropathy, and many other complications, which are the leading causes of diabetes-related death. Many experiments have shown that KD can not only reduce blood glucose fluctuation directly by lowering blood glucose level, but also indirectly or directly affect the progression of diabetes by regulating blood lipids, insulin sensitivity, reducing weight, reducing cardiovascular metabolic risk, promoting neuroprotection and cognitive function.

3.1. Direct Effects of KD on Blood Sugar (Glycated Hemoglobin), Body Weight and Other Aspects of T2DM Patients

The direct factors closely related to diabetes include obesity, hyperglycemia, dyslipidemia and decreased insulin sensitivity. These factors work together to significantly affect the occurrence and development of T2DM.

Blood sugar level is the most direct physiological indicator of diabetes. Diabetes is essentially a disease of abnormal blood glucose metabolism, which is caused by elevated blood glucose due to insulin resistance or secretion defects in T2DM. Therefore, controlling blood sugar is a core goal of diabetes management. Glycated hemoglobin (HbA1c) in diabetics is hemoglobin with sugar groups that can be used to estimate a person's blood sugar levels over the past three months. Therefore, it is often used as a relevant indicator to evaluate blood sugar in diabetic patients. According to the 2007 American Diabetes Association (ADA) guidelines, HbA1c values should be kept below 7% for all people with diabetes [6].

There is a close relationship between blood glucose and obesity, especially in the occurrence and development of T2DM, and obesity is an important risk factor. Severe obesity in children and adolescents increases the risk of T2DM in young adults and young adults. Public health publications note that obese individuals are at increased risk for T2DM (T2DM), heart disease, and high blood pressure [7]. As early as 1950, experiments showed that 10% weight loss could eliminate 10% of clinical diabetes patients [8]. This is because the basic mechanism of obesity is excess glucose and insulin. When the available glucose (energy) in the body exceeds the glucose (energy) needed for

physiological, heart, and skeletal muscle function, it is stored in fat cells in the form of triglycerides, or "fat" [9].

Moreover, obesity (especially abdominal obesity) can lead to insulin resistance, which is one of the core pathological mechanisms of T2DM. Insulin resistance means that the body's sensitivity to insulin decreases, and blood sugar cannot enter the cells effectively for use, resulting in a rise in blood sugar. Obesity is also associated with elevated blood lipids. Therefore, we can comprehensively evaluate the direct effect of KD on T2DM by monitoring blood glucose, body weight, blood lipids, insulin sensitivity and other indicators.

Wellington Hospital in New Zealand recruited 14 overweight T2DM patients aged 30 to 65 years with a body mass index (BMI) between 30 and 50 kg/m2 for a 6-month trial, all on a low-carbohydrate, high-fat/protein diet. Body weight, insulin sensitivity, HbA1c, lipids, and blood pressure were measured at 0, 12, and 24 weeks [10]. The diabetic patients in the study were well tolerated on the low-carbohydrate diet and achieved weight loss (mean weight loss 9.7 ± 1.8 kg), improved blood glucose control (HbA1c-1.1 ± 0.25%), reduced demand for hypoglycemic drugs, and no significant change in insulin sensitivity within 24 weeks. Weight loss is achieved by reducing total energy intake and associated improvements in glucose metabolism without significant adverse effects. However, this study does not dispel concerns about the long-term effects of a low-carbohydrate diet. For example, the durability of weight loss and health benefits through low carbohydrate intake needs further verification. Secondly, no short-term positive response has been shown, and long-term observation is needed to observe its possible long-term effects. Therefore, the results of this small study support the need for large-scale randomized trials in the diabetic population for at least 2 years.

In contrast to the absence of a concurrent control group in the previous trial, a 32-week balanced randomization approved by the UCSF Institutional Review Board (1: 1) Trial recruited 25 patients 18 years of age and older with T2DM with a body mass index ≥25 and elevated HbA1c levels (6.5-9%) and assigned them to a control group (n=12) (American Diabetes Association's "Create Your Plate" diet: Low-fat diet, 1/2 non-starchy vegetables, 1/4 lean protein, 1/4 starch and sweets) and experimental group (n=13) (KD: reduce carbohydrate intake to 20-50 grams per day). A urine acetoacetic acid test kit (Keto’s tix, Abbott) was used to detect whether there were ketone bodies in the urine to ensure that the subjects were in ketosis [11]. All measures were assessed before randomization and at 16 and 32 weeks after the intervention began. Results: Compared with the control group, the KD group had a decrease in blood sugar (HbA1c) (1.0%), body weight (8%), and triglyceride levels. However, due to the limitations of experiment size, target population and follow-up time. The experiment publisher screened a large number of participants to find eligible participants. A larger trial with longer follow-up is needed to better understand the persistence of the effects on blood sugar control and weight in the wider population.

3.2. Indirect Effects of KD on Complications in T2DM Patients

3.2.1 CVDs

According to the World Health Organization (WHO, 2023), CVD remains the leading cause of death worldwide, as well as one of the fatal complications of diabetes. The KD has potential benefits for CVD in several ways: the state of ketosis has anti-inflammatory properties and helps protect the heart by reducing intake of simple sugars, limiting carbohydrates and increasing intake of omega-3 fatty acids; At the same time, ketone bodies can serve as an alternative energy source for the heart, especially to provide support during cardiometabolic abnormalities. In addition, the KD helps to improve vascular endothelial function, delay its aging, and effectively reduce a variety of CVD risk factors through weight loss, lowering blood pressure and other ways [12]. These mechanisms suggest that the KD has potential advantages in the prevention and treatment of CVD.

3.2.2 Diabetic Neuropathy

Diabetic peripheral neuropathy (DPN) is a complication of T2DM that causes sensory changes, including slow nerve conduction, neurodegeneration, sensory loss, pain, and portal disorders.

Although strict glycemic control can prevent neuropathy from progressing, it remains largely untreatable [13].

Although there is no clinical experiment yet, a mouse experiment conducted by the University of Kansas divided 7-week-old male mice into control feeding, high-fat feeding and ketogenic feeding, and performed sensory behavior tests every two weeks [14]. After 4 weeks, lumbar DRGs 4-6 neuron single-cell suspension was harvested, and intradermal nerve fiber (IENF) density was measured. Results: The mice fed the KD never developed mechanical abnormal pain, and the neurites in sensory neurons grew and the density of epidermal axons increased. The KD can relieve the associated neuralgia and promote neuronal activity and axon regeneration. This mouse study provides a scientific basis for the discovery of the potential of KD in the treatment of DPN and related neuralgia.

Through these experiments, it can be found that although there is still insufficient research data on the long-term impact of KD on diabetes, the existing experimental results all show that KD can effectively reduce the blood sugar level of patients in the short term, help weight loss, improve lipid metabolism and other indicators, and also has a certain ability to alleviate diabetes-related complications. Therefore, if more long-term clinical trials can be further carried out in the future to accumulate more comprehensive experimental data, and at the same time optimize and adjust the possible shortcomings of the KD, it may be expected to develop a more scientific, effective and sustainable diet program to provide a new breakthrough in the prevention and treatment of diabetes.

4. The Risks of The KD

Although the KD shows potential as an emerging diabetes treatment model, its long-term efficacy, safety, and health benefits have not been validated in many clinical trials. In addition, the individualized precision treatment plan for patients with different stages of disease has not yet been perfected, resulting in greater controversy over its safety. At the same time, the potential risk of complications also discouraged many patients.

Diabetic ketoacidosis, for example, usually occurs in people with type 1 diabetes, who are thought to be immune to the disease because they produce their own insulin. However, two T2DM patients in Sweden were hospitalized for ketoacidosis, and their common feature was a KD [15]

In addition, because the gastrointestinal tract is not adapted to high fat, increased fat can lead to diarrhea. In addition to digestive symptoms, it can also cause side effects such as headaches and dehydration. [16]

5. Reduce the Harm of KD by Adjusting Diet and Targeting People

In view of the existing side effects. In the follow-up management of T2DM, medical workers should reduce the potential side effects of KD through medication adjustment and nutritional support, such as reducing the dose of sulfonylureas and insulin to avoid hypoglycemia. sodium-dependent glucose transporters 2 (SGLT2) inhibitors were used with caution to reduce the risk of diabetic ketoacidosis. Related studies [17] also listed drug excipients (dextrin, fructose, glucose, lactose, lactose maltitol, maltodextrin, mannitol, sucrose sorbitol, starch xylitol) that are not recommended to be used in conjunction with the KD.

At the same time, create a personalized diet that increases non-starchy vegetables and good fats (avocados, olives, low-carb nuts, etc.), and supplements electrolytes and dietary fiber.

Health care workers should identify the appropriate population (such as obese T2DM and insulin resistance), and strictly exclude contraindications (such as pregnancy, pancreatic failure and fat metabolism disorders). In addition, the application of the KD needs to be personalized according to the patient's disease stage (early, middle, and late) to ensure its safety and effectiveness.

6. Conclusion

In recent years, KD as a potential new diet to alleviate T2DM has received widespread attention. Multiple studies have shown that KD has a positive effect on the management of T2DM by directly reducing blood glucose levels by restricting carbohydrate intake while improving lipid metabolism by weight loss. In addition, its potential to improve T2DM-related complications, such as CVD and psychiatric disorders, is also of concern. However, most of the existing clinical studies are limited to short-term interventions with small sample sizes, resulting in a low level of evidence on the effectiveness and safety of KD, which needs to be further verified by large-scale and long-term studies. At the same time, possible side effects of the KD still need to be addressed in future studies.

In the future, medical workers need to further explore the mechanism of action of keto diet and develop personalized diet plans for T2DM patients with different conditions, including precise nutritional ratio and intervention duration. In addition, exploring new management strategies and monitoring patients' metabolic markers and health status in real-time will help optimize the use of KDs in T2DM treatment and provide a more reliable basis for its safety and efficacy.

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