Impacts of Ketogenic and Mediterranean Diets on Obesity-Induced Type 2 Diabetes

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Abstract. The prevalence of type 2 diabetes is increasing, and its complications, disability, and premature death affect the quality of life of people. Obesity is associated with metabolic disorders that augment an individual's susceptibility to the development of type 2 diabetes. The implementation of measures to combat obesity can effectively mitigate the incidence of type 2 diabetes in a significant number of patients. Lifestyle interventions and medication are often effective in addressing obesity and type 2 diabetes. There is no consensus on the optimal dietary composition for T2DM, while both the ketogenic diet and the Mediterranean diet have demonstrated significant improvements in T2DM. However, existing studies have solely separately analyzed their effects, leaving uncertainty regarding which diet type offers greater advantages. This paper comprehensively analyzes previous studies on ketogenic diet and Mediterranean diet, and proposes suggestions to increase the exploration of ketone body mechanism, long-term clinical trials of ketogenic diet, measurement of the quantitative change of inflammatory factors under Mediterranean diet, and comparative and synergistic experiments, so as to provide reference for the experimental parameters in future research.

Keywords: Obesity; type 2 diabetes mellitus; ketogenic diet; Mediterranean diet.

1. Introduction

Diabetes especially type 2 diabetes mellitus (T2DM) presents a significant challenge to global healthcare systems. As per the International Diabetes Federation Diabetes Atlas 2023, the current number of adults living with diabetes stands at 537 million. Projections indicate that by 2045, this figure is expected to escalate by an additional 783 million individuals (equivalent to one in every eight people worldwide having diabetes) [1].

Obesity can induce metabolic dysregulation, thereby predisposing individuals to the development of T2DM. The pathogenesis of metabolism related T2DM can be simplified as hyperglycemia resulting from decreased insulin sensitivity due to diminished functional beta cell mass. The development and progression of the condition are significantly influenced by obesity, which enhances genetic/epigenetic susceptibility, induces microenvironmental changes that impair insulin signaling, deteriorates beta-cell function, and disrupts the microbiome-gut-brain axis [2]. Thus, ameliorating obesity can alleviate T2DM in numerous patients. Lifestyle interventions (such as dietary modifications and physical activity) along with medication often serve as effective treatments for both obesity and T2DM.

The ketogenic diet (KD) is designed based on very low carbohydrates. It is characterized by low calories, high fat and moderate protein content. Its carbohydrates do not exceed 50g per day. This dietary pattern has now been introduced as a nutrition-based intervention for epilepsy [3]. Research by Chong Zhou et al. has shown that the ketogenic diet can effectively reduce body weight, with reductions in glycosylated hemoglobin (HbA1c) and triglycerides observed, while increasing high-density lipoprotein (HDL) levels. Furthermore, it improves central obesity which is detrimental to diabetic patients and has a hypoglycemic effect. However, there is no evidence that the KD has any significant effect on insulin levels in people with T2DM, and its exact mechanism of the KD for weight loss remains unclear.

The Mediterranean diet (MD) is characterized by a low intake of red meat and a high intake of fruits, vegetables, legumes, nuts and fish. It also includes moderate amounts of low-fat dairy products

and alcohol [4]. Our current research shows that MD plays an important role in improving human health conditions, including cardiovascular risk factors, neurodegenerative diseases, etc. Previous studies have shown that MD is inversely associated with T2DM prevalence and that adherence to this dietary pattern can also help effectively lower blood glucose levels. However, this dietary pattern currently lacks evidence of molecular mechanisms, and the causal relationship between MD and the reduced incidence of T2DM cannot be accurately established.

This paper aims to compare and analyze the effects of MD and KD on patients with T2DM from various perspectives, in order to identify the respective advantages and limitations of these dietary patterns. Through comprehensive analysis, this study intends to provide valuable insights and recommendations for optimizing the dietary management of T2DM patients in the future.

2. Pathogenesis of T2DMs

Current understanding of the pathogenesis of T2DM suggests that it is a complex and interconnected condition. The main physiological and pathological process of T2DM is persistent hyperglycemia caused by impaired insulin secretion of islet β cells and/or cellular insulin resistance, resulting in inadequate glucose uptake by cells [5]. Consequently, this dysregulation disrupts carbohydrate, lipid, and protein metabolism, ultimately culminating in macrovascular and microvascular complications.

Apart from genetic abnormalities or aging, various factors can influence proper insulin secretion by beta cells. In this context, lipotoxicity, glucotoxicity, oxidative stress caused by reactive oxygen species, activation of inflammatory pathways, as well as reduced insulin receptor function and/or diminished incretin action on beta cells contribute to beta cell stress and subsequent impairment of insulin secretion.

Cellular insulin resistance is an active area of research. It involves intrinsic pathways such as mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress, as well as extrinsic mechanisms related to alterations in adipocytes' functionality such as modulation of fatty acid levels and inflammation.

T2DM treatment necessitates not only glycemic control, but also effective management of body weight and regulation of lipid levels in order to mitigate the risk of cardiovascular and coronary heart diseases, encompassing myocardial infarction, atherosclerosis, and stroke [6]. In patients with T2DM, atypical lipid profiles are characterized by elevated levels of triglycerides and LDL cholesterol, reduced levels of HDL cholesterol, as well as the presence of small, dense LDL particles. This specific lipid pattern is strongly correlated with an augmented cardiovascular risk factor, thereby establishing it as one of the primary causes of mortality among people with T2DM.

3. Ketogenic Diet

According to the most precise and comprehensive definition, KD induces an augmented production of ketone bodies (such as beta-hydroxybutyrate, acetoacetate, and acetone) within an organism [7]. A typical KD in includes eggs, meat and fish (especially oily fish), vegetable oils, offal, non-starchy vegetables (broccoli, spinach, kale), avocados, olives, and nuts. The diet pattern with a low carbohydrate content, high fat content, and moderate protein content. While glucose serves as the primary energy source in other diets, a ketogenic diet induces a metabolic shift where ketones are prioritized as the predominant fuel for the body, thereby altering its preference for energy sources.

Based on meta-analyses, systematic reviews, randomized controlled trials (RCTs), additional studies, and comprehensive analysis of existing literature, the utilization of a KD in the management of T2DM is scientifically justified [3,5,8]. The KD has demonstrated favorable effects in T2DM by effectively reducing and stabilizing serum glucose and insulin levels, lowering HbA1c concentrations, mitigating markers of insulin resistance such as HOMA-IR, and promoting weight loss. Furthermore, the KD exhibits anti-inflammatory properties and induces beneficial alterations in lipid parameters.

When discussing the KD, ketosis inevitably becomes a focal point. Here is a concise introduction to ketone bodies and ketosis. The liver's mitochondria synthesize ketone bodies, which are four-carbon molecules, through a process called "ketogenesis." It is believed that ketone bodies serve as more efficient substrates compared to glucose. This heightened efficiency can be understood in terms of ATP production, with each glucose molecule producing approximately 5.2 ATPs, while each ketone body yields around 5.4 ATPs. In their basal state, serum concentrations of ketone bodies typically remain low, ranging from 0.1 to 0.4 mM in humans and rodents alike. However, when there is a lack of carbohydrates due to fasting/dieting, exercise or diabetes-related diseases, ketone bodies are produced by excessive fat breakdown [9]. In this case, the concentration of ketones in the blood increases accordingly, and some ketones can be excreted through the urine, forming ketonuria. At this time, it is called ketosis. When the amount of ketone bodies produced in the liver exceeds the capacity of extrahepatic tissues to use them, the blood ketone body concentration will be too high, forming hyperketonemia. Acetoacetate and beta-hydroxybutyric acid in ketones are acidic substances. When they accumulate in the blood in excessive amounts, the blood becomes acidic and acidosis is caused, called ketoacidosis. This is the most serious condition and may lead to coma or circulatory failure.

Physiological ketosis, resulting from fasting, prolonged exercise, or a KD, represents the most common cause with mild to moderate increases in circulating ketone body levels [10]. In addition, diabetic patients cannot use glucose effectively as an energy source due to insufficient insulin secretion or insulin resistance, so they need to rely on fat for energy. Therefore, the pathological processes caused by T2DM may also lead to ketosis. Taking the above into account, although a ketogenic diet can help control blood sugar levels in some cases, excessive dependence on fat for energy will increase the risk of ketosis and complications. Therefore, when following a ketogenic diet, it is necessary to strictly control the fat intake and maintain a moderate carbohydrate intake to avoid ketosis.

Ketones are recognized for their ability to elicit various physiological responses, encompassing antioxidant, anti-inflammatory, and cardioprotective functions [11]. Elevated ketone levels induce oxidative stress in the mitochondria, subsequently triggering an adaptive (stimulatory) response characterized by the activation of Nrf2, sirtuins 1 and 3 (key regulators of cellular defense mechanisms), and AMPK.

The existing literature lacks clarity regarding the specific effects of ketone bodies on T2DM. Future studies should focus on elucidating the underlying mechanisms of ketone bodies and consider supplementing serum ketone body concentrations when observing physical and chemical indicators. It can be concluded that the KD safely induces ketosis in vivo while improving T2DM outcomes. This promising avenue warrants further exploration for graduate students interested in investigating the therapeutic potential of the KD.

Furthermore, although dietary therapy has demonstrated short-term benefits in terms of weight loss and blood sugar reduction, prolonged exposure may give rise to potential adverse effects [8]. For instance, KD has been associated with dyslipidemia, hepatic lipid accumulation, liver lipidosis, fibrosis, and inflammation. Moreover, dietary shifts are frequently accompanied by a range of symptoms, including somnolence, fatigue, impaired cognitive function, nausea, dyspnea, abdominal discomfort, insomnia, dyspepsia, depression and other manifestations. Collectively referred to as keto flu in the literature, these effects typically persist for up to one week before the body initiates fat loss. Furthermore, nutritional deficiencies can contribute to dehydration and even hepatic encephalopathy. Existing animal studies have predominantly focused on the immediate impact of KD on blood glucose fluctuations and clinical amelioration; therefore, further investigation is warranted to explore the long-term effects of KD on T2DM.

4. Mediterranean diet

The Mediterranean diet consists of ingredients such as extra virgin olive oil, a variety of vegetables and fruits, legumes, nuts, red wine, and whole grain cereals. It is characterized by a low saturated fat content and a high proportion of monounsaturated and polyunsaturated fats [12]. Furthermore, it involves a substantial intake of bioactive compounds such as polyphenols and omega-3 fatty acids that possess anti-inflammatory and antioxidant effects. These properties, combined with specific intrinsic characteristics like a high carbohydrate-to-fat ratio, an optimal balance between monounsaturated fat to saturated fat, and adequate fiber consumption render the Mediterranean Diet a suitable dietary approach for weight loss. The MD typically ameliorates T2DM symptoms by reducing HbA1c and reducing central obesity, stabilizing blood glucose and insulin levels; however, evidence regarding its effect on fasting blood glucose homeostasis, insulin level, and insulin resistance index remains inconclusive. Unlike KD, the long-term effects of the MD have demonstrated a positive impact on T2DM.

The precise mechanism underlying the therapeutic benefits of MD in T2DM remains incompletely elucidated. Potential mechanisms encompass lipid-lowering effects, mitigation of inflammation and oxidative stress, modulation of nutrient sensing pathways through selective amino acid restriction, as well as generation of gut microbiota-derived metabolites that impact metabolic health [4]. Further quantitative evaluation of inflammatory markers (examples include hsCRP (high-sensitivity C-reactive protein), IL-6 (interleukin), MHR (monocyte to high-density lipoprotein cholesterol ratio), MLR (monocyte-to-lymphocyte ratio), TNF-α (tumour necrosis factor alpha) and WBC (white blood cell) [13,14]) and oxidative stress can be conducted to verify the mechanism of MD's effect on T2DM.

In the selection of experimental measurement indicators, the Dietary Inflammation Index (DII) can be added. DII is establishing a connection between diet and inflammation, which is a crucial factor in the development of prediabetes and the progression of insulin resistance. However, it should be noted that the underlying biological mechanism linking DII to prediabetes and insulin resistance remains unclear.

Previous studies have demonstrated the superiority of the Mediterranean diet compared to control groups, yet its clear advantage over DASH (Dietary Approaches to Stop Hypertension), vegetarian diets, and low-fat diets remains inconclusive [6]. Therefore, larger-scale and longer-term clinical trials are warranted to validate the applicability and flexibility of the Mediterranean diet regimen. Additionally, comparative experiments controlling for variables should be conducted on both the Mediterranean diet and ketogenic diet to visually assess their respective effects. Also, try to combine the two diets and test their effectiveness, as scientific research has shown that MD and KD show synergistic effects [14]. Combined dietary schemes may potentially address the limitations of each diet by adjusting the proportion of energy sources in the diet, thereby optimizing glycemic regulation while minimizing adverse effects.

5. Conclusion

Both KD and MD exhibit ameliorative effects on obesity induced T2DM by mitigating obesity, inflammatory response, and oxidative stress. Although the precise physiological mechanism remains incompletely elucidated, clinical data supports this notion. Considering KD's mode of action and its long-term impact, further investigation is warranted, particularly regarding the mechanisms underlying the effect of a ketogenic regimen on T2DM. In-depth exploration of inflammatory markers can facilitate a comprehensive understanding of the MD's mechanism of action. However, further experiments and data are needed to investigate the specific effects of the two on the same individuals or groups. So, follow-up studies can compare these two diets within the same experiment to assess potential synergistic effects when used in combination.

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