The Evaluation of the Therapeutic Potential and Risks of the Ketogenic Diet

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Abstract. As the demand for weight loss increases, the ketogenic diet (KD) has gradually attracted public attention and become one of the most popular dietary choices. This diet is characterized by high fat and low carbohydrates and was originally used to treat epilepsy. In recent years, studies have shown that KD has potential benefits in controlling obesity, improving metabolic syndrome, reducing insulin requirements in patients with type 2 diabetes, and alleviating inflammation. However, the effectiveness, safety, and risks of KD during pregnancy still need to be further verified. This article aims to explore the benefits and risks of KD as a dietary treatment and to clarify the differences between ketogenic diets for epilepsy and obesity. Studies have shown that KD improves multiple health indicators by inducing ketone body production and has therapeutic potential in certain neurodegenerative diseases. However, KD is also accompanied by certain side effects, such as hypoglycemia, digestive problems, and malnutrition, especially in children and elderly patients. Although KD performs well in controlling weight and improving blood sugar levels, its effects on cardiovascular disease, microbiome regulation, and cancer control need to be further studied. This article reveals the potential therapeutic value of KD for multiple diseases through a comprehensive evaluation of existing research results and emphasizes the importance of future research on dietary recommendations to promote health improvement.

Keywords: Ketogenic diet; obesity; metabolic health.

1. Introduction

Given the increasing need of weight loss, the ketogenic diet (KD) has been largely known by the public and become the most popular dietary choice. As of 2022, research data indicated that there were 24.5 million Google searches of the KD [1]. The KD is a dietary approach featuring high fat, low carbohydrate intake and was firstly used as a treatment for epilepsy in the eighteenth century. It was also found to be useful for weight control and contribute to the improvements of other health issues, such as altering the manifestations of metabolic syndrome, lowering or removing the need for insulin in individuals with type 2 diabetes, mitigating inflammation, enhancing epigenetic characteristics, modulating the microbiome, improving lipid levels, supporting cancer therapies, and may also promote longevity and cognitive function [2], but with existing concerns. The efficacy, safety, and treatment scope of the keto diet still requires more validation, and there is a potential danger for women during pregnancy. For instance, several studies indicate that low-fat such as the KD diet has lost its superiority in weight control in the long term compared to low-carbohydrate diet (LCD), though it showed its effectiveness in a shorter period [1]. Over time, there are a number of variations of the KD that not only enhance diet adherence but also offer alternatives to cater individual requirements and preferences [3].

The goal of this paper is to study the benefits and risks attributed to the KD as a dietary treatment and clarify the differences between the keto diet for epilepsy and obesity, based on the comprehensive evaluation and analysis of existing research results and certain secondary data. Firstly, this research will specifically elucidate the content and mechanism of the keto diet. Next, it will discuss the health impact and therapeutic potential of the KD from different dimensions. Finally, there will be a clarification of distinctions between non-pharmacologic treatment and KD.

2. The Characteristics of the KD

The KD is typical of low calories, high fat, mid-level protein, and extremely low-level carbohydrate (usually less than 50 g/d) [4]. This dietary approach is aimed to trigger ketosis by limiting carbohydrate intake. Constantly, the liver enhances its synthesis of ketone bodies—such as acetone, acetoacetate, and beta-hydroxybutyrate—from fatty acids to serve as energy sources [5]. Ketosis is believed to modify metabolic processes in a way that treats epilepsy, controls obesity and may also enhance other health indicators, such as preventing cardiovascular disease and neurological disorders, lowering blood sugar levels, and improving lipid profiles. There are four variations of ketogenic treatments being currently utilized: the classical KD, the medium-chain triglyceride (MCT) diet, and the modified Atkins diet (MAD) and the low glycaemic index (LGI) treatment. The classical KD typically has a fat to carbohydrate and protein ratio that varies from 2:1 to 4:1, primarily using long-chain fatty acids [3]. The MCT KD was created to make the KD more palatable by allowing a greater carbohydrate and medium-chain fatty acid intake while still achieving ketosis. This variation of the KD includes a higher percentage of calories derived from MCTs compared to traditional KDs. The initial MCT diet consisted of 60% of its caloric content from MCTs, while a revised approach was introduced that consists of 30% calories from MCT oil or emulsion and another 30% from long-chain dietary fats [3,5]. The MAD offers food options that are comparable to those in the traditional KD, but it is more flexible in ketogenic ratio, generally maintaining a fat-to-protein and carbohydrate ratio between 1:1 and 1.5:1 [3]. The Low Glycemic Index Treatment features a more liberal approach that includes an LCD [3].

2.1. Positive Effect

Initially, the KD was utilized as a therapeutic approach for children with epilepsy and for those patients who failed to respond to anticonvulsant drugs [1,6]. The popularity of the KD has surged due to its advantages in treating neurodegenerative disorders, metabolic conditions, and obesity. Recent studies have indicated that this diet is an effective method for modulating both central and peripheral inflammatory responses in various neurodegenerative diseases, including autism spectrum disorder (ASD), Alzheimer’s disease, glucose transporter 1 deficiency syndrome, and autoimmune multiple sclerosis [3,6]; throughout activating PPARs, βHB, and other components generated in the state of ketosis, KD might alleviate inflammatory responses that are influenced by autophagy in neurodegenerative disorders, given that PPARs are helpful to adjust lipid and glucose metabolism in the brain in the state of ketosis [3]. Additionally, the KD may help mitigate cognitive decline associated with weight gain and positively influence mood among individuals who are overweight [6].

2.2. Negative Effect

Side effects are accompanied by the benefits of the KD. Most of them are generally manageable. Common adverse reactions can include low blood sugar, lipid abnormalities, gastrointestinal issues, a deficiency in carnitine, bone conditions like osteopenia and osteoporosis, kidney stones, and potentially growth retardation [5]. The KD may present certain challenges in pediatric patients as well, such as limited food options and difficulties in maintaining adherence to the diet for an extended period. Short-term consequences of this dietary approach might encompass feelings of nausea, constipation, fatigue, dehydration, and imbalances in electrolyte levels [7]. There is evidence that women who limited their carbohydrate consumption, characterized by intake less than the fifth percentile compared to the control group were 30% more susceptible to have infants with neural tube defects, experiencing reduced folic acid levels [1]. Another nutritional concern that should be addressed is the higher loss of fat-free mass observed with KD, putting elderly or chronic disease patients at risk of malnutrition, orthostatic hypotonia and initial dehydration [8]. Therefore, close monitoring and more long-term studies are required to address these safety concerns.

3. The KD for Controls of Epilepsy and Obesity

3.1. The KD Therapy for Epilepsy Control

3.1.1 Epilepsy

Epilepsy is a long-term neurological condition marked by recurrent seizures, which are involuntary movements that can involve either part or the entirety of the body. These episodes may sometimes lead to loss of consciousness and affect bladder or bowel control. It is estimated that globally, between 50 and 70 million individuals suffer from epilepsy, with around 2.4 to 4.6 million new diagnoses occurring annually. Various factors can trigger epilepsy, including brain tumors, strokes, infections in the brain, severe head trauma, congenital brain defects, damage from prenatal or perinatal injuries, and specific genetic disorders [9]. Common treatments for epilepsy encompass both medical interventions and surgical options as well as vagus nerve stimulation. However, about 30% of those affected do not achieve sufficient seizure management through these methods and develop resistance to medications [9,10]. For patients who experience drug-resistant epilepsy, adopting a KD may be an option worth exploring.

3.1.2 Mechanisms

The exact mechanisms by which the KD enhances seizure control remain unclear, and several theories have been put forward. Some researchers propose that the KD may influence neurotransmitter levels related to the initiation of seizures. Others suggest that it might provide neuroprotective benefits by increasing calbindin levels, inhibiting apoptotic factors like caspase 3, and raising kynurenic acid concentrations. In fact, studies indicate that the KD can lower oxygen free radicals through an increase in polyunsaturated fatty acids and neuronal uncoupling proteins [11]. These mechanisms imply that the KD could potentially improve clinical outcomes for individuals with epilepsy by targeting various biochemical pathways.

3.1.3 Effectiveness

Studies from multiple centers showed that approximately two-thirds of children who responded to KDT maintained this response at latest follow-up, of which one third of children achieved this without further anti-seizure treatments being added. In one study, for instance, 30 of 40 (75 %) children maintained ⩾50 % seizure reduction post KDT; in a survey of children previously on KDT, 79 % had >50 % seizure reduction compared to pre-diet, whereas 52 % had >50 % seizure reduction at the point of diet discontinuation [12]. Individuals who achieved seizure freedom on diet were more likely to maintain response compared to those who had a reduction in seizures but were not seizure-free on diet.

3.2. The Control of KDT on Obesity

3.2.1 Obesity

Obesity is a globally prevalent issue during the past few decades, and billions of people suffer from the side effects of overweight and obesity. In fact, 65% of the world's population live in countries where the mortality of overweight and obesity is higher than it of underweight. Obesity is considered as

one of the main risks for cardiovascular disease and along with dyslipidaemia, hypertension and diabetes contributes to the metabolic syndrome [13]. A number of strategies have been proposed to reduce energy intake and increase physical activities. Diet is the most controversial topic about weight control, with different diets suggested to achieve this goal but little scientific evidence that one diet is superior to another. The most commonly accepted dietary strategy is based on relatively high levels of carbohydrates and low fat content, but different studies have shown the priority in terms of weight loss of a LCD compared to a low-fat one given that these low fat diets contribute only modest weight losses and suffer from low long-term adherence issues [11,13]. The KDs are recommended to be more adopted as an effective treatment of obesity-related problems.

3.2.2 Mechanisms

It is undeniable that adopting KD in weight control therapy is efficient, but the underlying mechanisms of KD effects on weight loss remain a debated topic. Several hypotheses have been put forward: Some researchers hypothesized that the outcomes of KD in obese patients could also be linked to its efficacy in fat metabolism, since it promotes a higher consumption of fats and an increased lipolysis while reducing lipogenesis [11]. Conversely, some researchers claim that the results obtained with KDs could be attributed to a reduction in appetite due to higher satiety effect of proteins or to some effects on appetite control hormones. Others suggest a possible direct appetite suppressant action of the ketone bodies [13].

3.2.3 Effectiveness

Given that KD contributes to significant reductions in waist circumference, some studies suggest that KD is a superior intervention to other diets on weight loss. Extreme restriction of daily dietary intake of carbohydrates causes a decline in the absorption of monosaccharides, reduces blood glucose levels, and limits blood glucose fluctuations, indicative of positive regulation of glucose metabolism [14]. Thus, KD is found to be conducive to blood-sugar and blood-fat controls given that the increasing fat consumption from KD may improve lipid profiles. Compared with subjects receiving other types of diets, overweight subjects consuming the KD have a greater extent in lowering HbA1c and raising HDL levels. Furthermore, accumulating evidence has demonstrated a strong relationship between insulin resistance and KD. A mild increase in ketosis in peripheral blood, induced by a KD, might improve peripheral insulin sensitivity, relieve hyperinsulinemia-related stress, reduce external insulin requirements, and inhibit its secretion, thereby improving glycemic profiles and mitigating insulin resistance [14].

4. The Difference between KDT for Epilepsy and for Obesity

The epileptic KD is used in the non-pharmacological treatment of children with intractable epilepsy, and it includes a high fat, LCD, based on a ratio (g fat/g protein + CHO), with sufficient calories to ensure adequate growth. In the updated recommendations, the term KD has been replaced by KD t to emphasize the existence of different standardized regimens, with different ratios, for the treatment of epilepsy and other neurological disorders. It requires strict monitoring of ketone levels. By contrast, KDs for obesity and endocrine-metabolic diseases aims to achieve weight loss and induce ketosis, primarily through calorie restriction. Low-CHO diets can be of medium or high fat content or of medium or high protein content and do not necessarily lead to ketosis.

5. Conclusion

This paper highlights the potential of KDT for treatment of epilepsy, obesity, and previously mentioned diseases and underlying risks existed among pregnant women, children, and the elderly. Additionally, it has provided specific explanation of KD variations and a clarification about the confusion of KDT for epilepsy and obesity. While the paper helps elaborate on the mechanisms and safety, effectiveness of KD on improvements of several health issues, including epilepsy, blood sugar, blood fat, and HDL level, etc., there is lack of explanation of KD effects on cardiovascular disease, regulating microbiome, and cancer control, etc. The mechanisms of ketosis therapy in animals are still unclear, and existed hypotheses require more researches to verify. In conclusion, the findings of this paper suggest that interactions between KD and various diseases provide crucial insights for new therapeutic methods. In the future, developing the therapeutic potential to provide individuals dietary suggestion for health improvements is critical.

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