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Application of ketogenic diet in the treatment of diseases

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Abstract. The ketogenic diet (KD) has gained recognition for its unique dietary composition that focuses on high fat, low carbohydrate, and moderate protein intake. Originally developed as a treatment for refractory epilepsy, the KD has expanded its applications to address a variety of health conditions, including obesity, diabetes, cancer, and even novel coronavirus pneumonia (COVID-19). This review delves deeply into existing literature to uncover the historical origins of KD, shed light on the complexities of ketogenic metabolism, and summarize the therapeutic benefits of KD in various diseases along with its mechanisms. In addition to exploring the positive aspects of KD, this study meticulously scrutinizes the potential short- and long-term adverse reactions and contraindications associated with the diet. Furthermore, strategic recommendations are proposed to optimize the outcomes of KD therapy. By offering a comprehensive analysis, this review endeavors to furnish valuable theoretical foundations that can elevate the clinical implementation of the KD in medical practice.

Keywords: Ketogenic diet, Epilepsy, Obesity, T2D, COVID-19

1. Introduction

The ketogenic diet (KD) is a specialized dietary approach characterized by high fat, low carbohydrate (typically less than 50g per day), moderate protein, and specific nutrient ratios [1]. More recently, a very low-calorie ketogenic diet (VLCKD) has emerged with even stricter guidelines, including carbohydrate intake below 50g/day, protein intake of 1-1.5g/kg, fat intake between 15-30g/day, and a total daily calorie intake ranging from 500-800 calories [2]. Initially utilized to manage refractory epilepsy through a starvation-mimicking mechanism [3], KD has since expanded its applications to various conditions like obesity [4], diabetes [5], cancer [6]. Emerging research indicates the effectiveness of KD in treating novel coronavirus pneumonia (COVID-19) as well [7]. This review comprehensively examines the advancements in KD research, along with the short- and long-term adverse effects and contraindications associated with its use in treating these conditions. The aim is to enhance the public's understanding of dietary interventions for diseases and offer theoretical support for optimizing KD strategies in clinical settings.

2. Origin and ketogenic process of KD

KD is a specialized eating plan characterized by low carbohydrate, high fat, and moderate protein intake, where the majority of energy comes from fats (around 70%) and proteins (approximately 20%), while carbohydrates contribute fewer calories (about 10%) [1]. By reducing carb intake and increasing fat consumption, KD alters the body's primary energy source, shifting it from glucose to fat utilization for

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energy [1]. The use of starvation as a treatment for epilepsy was first documented by G. Guelpa and A. Marie in 1911, with this approach becoming more established in the early 1920s [8]. In 1921, Woodyatt et al. were the first to highlight that a high-fat diet alone could generate ketone bodies, without the need for hunger stimulation [9]. The term "KD" was coined by Wilder and Winter, who emphasized that the ratio of "ketogenic" molecules to glucose molecules should be at least 2:1 to induce ketosis [9]. Since 1921, KD has been employed in managing refractory epilepsy, although the introduction of phenytoin in the 1940s marked a shift towards drug-based epilepsy treatments, leading to a decline in ketogenic therapy usage [10]. It wasn't until the 1990s that KD was rediscovered as more effective than antiepileptic drugs for treating refractory epilepsy, reigniting interest in this dietary approach [10].

Glucose serves as the primary energy source for the human brain [11]. Following several days of fasting or a significantly reduced carbohydrate diet (below 20 g/day), the body's inadequate glucose reserves result in insufficient oxaloacetic acid production, leading to an excess of acetyl-CoA and the production of ketones (acetoacetic acid, beta-hydroxybutyric acid, and acetone) to replace glucose as the central nervous system's energy source [11]. This ketosis process primarily occurs within the liver's mitochondrial matrix [11].

3. Application of KD

Over the past decades, numerous animal experiments and clinical studies have further confirmed the effectiveness of the KD in managing refractory epilepsy. Moreover, KD has shown promising advancements in addressing metabolic diseases like obesity, type 2 diabetes (T2D), COVID-19, and tumors. This review will provide a detailed description of the role and mechanisms of KD in these diseases.

3.1. KD and epilepsy

The treatment of epilepsy through dietary control is a key feature of KD. A study involving 55 adult patients with refractory epilepsy revealed that following a 3-month KD intervention, 60% of patients experienced effective seizure control, 76% showed improvements in the severity of epilepsy, and 87% reported an enhanced quality of life [3]. In a separate randomized clinical trial involving 778 participants (712 children and adolescents, and 66 adults), the seizure control rate ranged from 0% to 55% after a 3-month KD intervention, with an impressive seizure reduction rate of up to 85% [12]. A meta-analysis focusing on classical KD in children and adolescents with refractory epilepsy demonstrated that at 1, 3, 6, 12, and 24 months on the diet, 62%, 60%, 52%, 42%, and 46% of patients, respectively, experienced a reduction in seizures by ≥50% [13].

Despite the recognized efficacy of KD, its precise mechanism of action remains incompletely understood. Current potential mechanisms include the regulation of neurotransmitters, inhibition of apoptosis factor expression, reduction of inflammation, promotion of energy metabolism gene expression, and modulation of intestinal flora [14,15]. In conclusion, while KD has shown significant advancements in treating refractory epilepsy, further research into its mechanisms is imperative to optimize and advance KD therapy in the future.

3.2. KD and obesity

Obesity is a chronic, relapsing and progressive disease and a global public health challenge. Recent clinical investigations have unveiled the substantial impact of KD on weight management in obese individuals. A retrospective analysis involving 70 severely obese patients revealed notable reductions in body mass index (BMI), fat mass, and gamma-glutamyltranspeptidase levels after implementing a VLCKD intervention [4]. Upon further subgroup analysis, it was found that obese men exhibited greater weight loss and enhanced liver function compared to women [4]. Another retrospective study focusing on 40 overweight or obese male patients highlighted that VLCKD not only led to reductions in body weight, blood sugar, and triglyceride levels, but also enhanced the function of the hypothalamic-pituitary-testicular axis while reducing the risk of lower urinary tract symptoms [16]. In a controlled study involving 20 participants undergoing VLCKD for 8 weeks, reductions were noted in BMI, low-

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density lipoprotein cholesterol (LDL-C), triglycerides, insulinemia, and liver transaminase levels [17]. The mechanisms behind KD-induced weight loss may involve appetite suppression, inhibition of fat synthesis, increased lipolysis, and enhanced gluconeogenic metabolic consumption [18]. Consequently, KD presents promising prospects for application in the obese population, particularly among obese males. However, given the lengthy KD treatment duration and various influencing factors, considerations should be given to the patients' health status, lifestyle, and long-term adherence when devising diet plans. It is crucial to propose personalized KD interventions to optimize outcomes.

3.3. KD and diabetes

Past research has indicated that elevated blood ketone levels in type 1 diabetes (T1D) patients may heighten the risk of microvascular, brain, liver, and kidney diseases. Consequently, the use of KD is typically geared towards managing blood sugar in T2D patients [5]. In a recent study comparing the effects of VLCKD on health outcomes in patients with T2D, it was found that after 24 weeks of VLCKD, patients' blood sugar levels returned to normal, the average dosage of insulin and sulfonylureas was halved, and some were even able to discontinue sulfonylureas. Additionally, the level of glycosylated hemoglobin (HbA1c) in this group decreased to 6.2%, meeting the target levels set by the American Diabetes Association and the American Endocrine Society [19]. Importantly, patients with VLCKD did not experience adverse reactions such as insulin resistance and chronic dehydration [19].

In a study by Dashti et al., the therapeutic effect of KD on diabetic obese patients and non-diabetic obese patients was compared over 56 weeks. It was observed that various indicators, including body weight, BMI, blood sugar, total cholesterol, LDL-C, triglycerides, and urea, significantly decreased in both groups, with a more pronounced decrease in diabetic obese patients [20]. Additionally, kidney function remained normal in both groups [20]. Therefore, the study suggests that long-term use of KD is safe for obese individuals with diabetes.

The mechanism by which KD lowers blood sugar involves improving the body's oxidation state, thereby reducing HBA1c levels, and the ketone bodies produced by KD directly reduce blood sugar levels by curbing liver glucose release [21].

Elevated blood glucose is primarily driven by gluconeogenesis, a process that can be inhibited by the activation of adenylate-activated protein kinase (AMPK). Animal experiments have shown that while KD can lower blood sugar levels, it can also inhibit the phosphorylation of AMPK and upregulate the expression of gluconeogenesis-related genes [22]. Therefore, the specific molecular mechanism behind KD's blood sugar regulation requires further fundamental research. It's worth noting that KD can induce or exacerbate sodium-glucose cotransporter 2 (SGLT-2) inhibitor-associated ketoacidosis [23]. While KD effectively reduces the blood sugar levels of diabetic patients, the precise molecular mechanisms governing its blood sugar regulation remain to be elucidated, and how to manage patients throughout the process to minimize negative reactions related to KD is a pertinent issue deserving attention in the future.

3.4. KD and tumor

In healthy cells, ketone bodies synthesized by KD promote fatty acid oxidation, converting into acetyl-CoA that enters the tricarboxylic acid cycle to generate adenosine triphosphate (ATP) for maintaining cellular functions [6]. Unlike normal cells, tumor cells primarily rely on ATP from aerobic glycolysis for growth and are unable to effectively utilize ATP from ketone bodies [6]. This has led some researchers to speculate that KD may hinder cancer cell proliferation by restricting their energy supply [6]. Currently, KD is being utilized as a supplementary therapy for various cancers such as breast cancer, gastrointestinal tumors, and glioma. Research by Khodabakhshi et al. demonstrated that KD could notably reduce BMI, body weight, and fat mass in breast cancer patients without causing severe adverse reactions [24]. In a clinical study involving 41 non-metastatic rectal cancer patients, those who underwent KD intervention exhibited a higher complete response rate compared to the control group (50% versus 14%), suggesting that KD might enhance the sensitivity of rectal cancer patients to radiotherapy [25]. In the case of glioma, KD hampers glucose uptake and glycolysis in tumor stem cells,

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leading to reduced ATP levels and suppression of stem cell marker expression, thereby hindering tumor stem cell proliferation and self-renewal [26]. The anti-tumor mechanism of KD potentially involves reducing glucose levels [27], modulating the mTOR signaling pathway [28], suppressing inflammation [28], enhancing oxidative stress [29], impeding tumor angiogenesis and invasion [30], regulating fatty acid metabolism, and altering gut flora [31]. Overall, KD shows promise in inhibiting tumor growth and enhancing patients' quality of life, but it also complements the effectiveness of other anti-cancer treatments while reducing their toxic side effects. Going forward, bigger, multicenter clinical trials are needed to find out how well KD can treat different types of cancer and if it can help keep people at high risk from getting cancer.

3.5. KD and COVID-19

Recently, Soliman et al. proposed a novel approach to potentially prevent or assist in treating 2019 novel coronavirus (SARS-CoV-2) infection by combining intermittent fasting with medium-chain triglyceride supplementation. The core principle of this strategy is to disrupt viral replication by shifting the host's metabolic state from relying on carbohydrates through glycolysis to a ketogenic state fueled by fats [32]. This metabolic shift aims to bolster the body's resilience to mitochondrial stress, fortify antioxidant defenses, boost autophagy and DNA repair capabilities, and decrease insulin production, thereby enhancing the immune response of at-risk individuals to SARS-CoV-2 infection [33]. In a retrospective analysis involving 102 COVID-19 patients, those who underwent KD intervention exhibited lower mortality rates (8.8% vs. 27.9%), reduced ICU admissions (2.9% vs. 19.1%), and encountered no associated adverse effects compared to patients on a standard diet, and there were no related adverse effects [7]. Advanced age represents a significant risk factor influencing the progression and prognosis of COVID-19. Following the implementation of KD in elderly mice infected with SARS-CoV-2, researchers observed significant alleviation of clinical symptoms in the intervention group when contrasted with the control group. This positive outcome can be attributed to the elevated levels of ketone bodies in the system, which elevate the γδT lymphocyte ratio, suppress NLRP3 inflammasome activation, and diminish the presence of pathogenic monocytes in lung tissue [34]. As a result, KD has the potential to improve the clinical symptoms and prognosis of elderly COVID-19 patients.

While existing studies suggest the potential of KD as an adjunctive therapy for COVID-19, comprehensive large-scale, multicenter clinical trials are necessary to ascertain its specific efficacy and potential adverse effects. Another thing is that because viral strains are always changing, more basic research is needed to find out how the KD stops different variant strains from spreading disease and making it worse.

3.6. KD and other diseases

KD has promising potential for treating a variety of diseases.

For instance, KD has been found to have a therapeutic impact on polycystic ovary syndrome (PCOS) by enhancing the expression levels of luteinizing hormone, follicle-stimulating hormone, and sex hormone-binding globulin while reducing androgen secretion [35]. In the case of traumatic brain injury, KD has shown to enhance cognitive function in mice by mitigating astrocyte response and neuronal degeneration [36]. Furthermore, sustained utilization of KD can boost cognitive abilities in patients, leading to improvements in brain metabolic markers and offering potential treatment avenues for Alzheimer's disease [37] and Parkinson's disease [38]. Introducing KD intervention has also been linked to an increase in histone acetylation levels in neurons within the prefrontal cortex, thereby ameliorating social deficit symptoms in autistic mice [39]. Moreover, KD has demonstrated significant improvements in symptoms among children with autism [40], although further clinical investigations are warranted to validate these findings.

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4. KD adverse reactions and contraindications

4.1. Adverse reactions to KD

While the KD holds promise for clinical applications, it is crucial to address the potential side effects associated with this therapy. These adverse reactions primarily manifest in several key areas.

(1) Gastrointestinal issues: this can include symptoms like food aversion, nausea, and constipation [41]. KD has the potential to impact the diversity of intestinal flora and reduce the levels of beneficial bacteria such as Lactobacillus, thereby affecting intestinal health and the host's overall well-being [42]. Moreover, the high fat content in KD could elevate the risk of colorectal cancer with prolonged usage [43].
(2) Metabolic challenges: changes in dietary composition may lead to adverse effects like hypoglycemia, fatigue, hyperlipidemia, and acidosis [40,44]. Continued adherence to KD might accelerate atherosclerosis progression, heightening the susceptibility to cardiovascular and cerebrovascular diseases, particularly in middle-aged and elderly individuals [45].
(3) Urinary system issues: long-term administration of KD could potentially contribute to the development of kidney stones [46].
(4) Additional side effects: these may encompass growth irregularities, disruptions in bone metabolism, decreased bone density, fractures [47], and optic neuropathy [48].

As a result, for healthy individuals, the risks associated with long-term KD use may outweigh the benefits. For patients, healthcare professionals should conduct a thorough evaluation of the feasibility and risks of KD based on individual circumstances, develop personalized treatment plans, and implement careful monitoring to address any potential side effects effectively.

4.2. Contraindications of KD

Prior to commencing KD therapy, it is essential to conduct a thorough evaluation of the patient's fat metabolism function, as well as assess liver and kidney function to identify any contraindications. These contraindications encompass severe cardiopulmonary dysfunction (e.g., arrhythmia, stroke, myocardial infarction, heart failure, respiratory failure), malignancies, conditions impacting fat metabolism (e.g., primary carnitine deficiency), concurrent illnesses (e.g., pancreatitis, active gallbladder disease, severe liver and kidney disorders, T1D). Furthermore, individuals taking SGLT-2 inhibitors concurrently, those unable to tolerate ketoacidosis medications (such as zonisamide) or significant transfusions of blood products containing citrate, and individuals with heightened nutritional requirements due to specific circumstances (such as children in growth phases, pregnant and breastfeeding women, postoperative patients, elderly or frail individuals) should also be excluded from consideration [50-51].

5. Conclusion

In conclusion, the KD demonstrates a certain level of efficacy in addressing epilepsy, obesity, T2D, COVID-19, and various tumor diseases. It has the potential to notably ameliorate clinical symptoms in patients and is considered safer than drug treatments, with fewer toxic side effects, presenting expansive developmental prospects. However, the current research still struggles to explain the exact mechanism of KD, necessitating further long-term clinical trials and studies to assess its safety and long-term efficacy in various diseases.

Adjustments to the implementation process and cycle, along with the provision of relevant symptomatic treatment, can mitigate short-term and long-term adverse reactions that KD, as an unconventional dietary approach, may elicit.

Given that KD alters the traditional dietary structure and relies on ketone bodies as the primary energy source, thorough evaluation of the patient's fat metabolism function, liver and kidney function, among other factors, is imperative to exclude contraindications before initiating KD. In addition, when KD is used in the clinic, it is important to keep a close eye on metabolic markers like blood glucose and blood ketones and do a lot of follow-up to make sure that no bad reactions happen.

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