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Nutritional treatment with the ketogenic diet in children with refractory epilepsy: a narrative review

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Abstract

The two mainstays of therapy for refractory epilepsy are medication and surgery. Child behavioral and cognitive aspects of epilepsy can be improved by using a specialized dietary regimen such as the ketogenic diet (KD). The purpose of this review is to expand our understanding of KD as a nutritional therapy for children with refractory epilepsy and to provide insight into the physiological aspects of its efficacy as an alternative to anti-seizure medication. Either directly or indirectly, ketones, glucose restriction, and polyunsaturated fatty acids regulate epileptic seizures. For KD to be effective, all three of these components must be present, even though the exact mechanism is unknown. Increasing gamma-aminobutyric acid, mitochondrial biogenesis, and oxidative phosphorylation levels can also serve as a means of promoting stable synaptic function while also decreasing neural activity and excitability. Most side effects of KD are caused by mild metabolic abnormalities such as acidosis, hyperuricemia, hypercholesterolemia, hypocalcemia, and hypomagnesemia. Since medium-chain triglycerides (MCTs) produce more ketones per calorie than long-chain triglycerides, individuals who consume MCTs can consume more carbohydrates and protein. This review demonstrated that KD therapy led to positive outcomes for patients with refractory epilepsy. Further study is needed to evaluate whether less restrictive and easier-to-follow diets, such as the modified Atkins diet and MCT diets, have a similar effect on seizure treatment as the standard KD.

Keywords

Ketogenic diet, refractory epilepsy, ketone bodies, medium-chain triglycerides, modified Atkins diet

Introduction

About 50 million individuals worldwide suffer from epilepsy, a chronic, noncommunicable brain disorder. Repeated seizures can involve brief episodes of uncontrollable movement involving different parts of the body (partial) or the entire body (generalized). They frequently end with a loss of consciousness as well as control over the gastrointestinal or urinary systems. Any neurological signs or symptoms that may be related to intermittent aberrant brain activity represent one of those seizures.

Epilepsy can result in many kinds of implications, including early mortality, social isolation, financial losses, and disability [1]. Prolonged seizures cause neuronal damage and possibly death [2]. Anti-seizure medication (ASM) can be used to treat up to 70% of patients with epilepsy. In some cases, surgery might be the only option for treatment. When both ASM and surgery are not effective, it is recommended to use dietary therapy as an alternative treatment strategy.

The ketogenic diet (KD) allows the body to use fat for energy instead of carbohydrates by resembling the metabolic changes that occur during fasting. The liver converts long- and medium-chain fatty acids into ketones, which include acetone, acetoacetate, and beta-hydroxybutyrate. They act as a main source of energy and cause ketosis by crossing the blood-brain barrier. This condition causes the body to eliminate glutamate more rapidly, delay vesicle transport, and increase glutamate-to-gamma-aminobutyric acid (GABA) conversion [3].

For refractory epilepsy, pharmacological and surgical treatments continue to be the mainstay of treatments. Considering a specific dietary regimen like KD can improve the behavioral and cognitive aspects of children with epilepsy. In children treated with a KD for epileptic episodes, some studies showed improved mood, less anxiety, enhanced focus and concentration, stronger receptive vocabulary, and an increased rate of information processing [1, 4].

KD is beneficial for patients with refractory epilepsy of all ages without surgery, but each patient's diet must be modified, and adults and teenagers may benefit from less restrictive diets. This review aims to further understand KD as a nutritional treatment for children with refractory epilepsy and provide insight into the physiological factors that contribute to its effectiveness as an alternative to ASM.

Different types of KD

There are five different kinds of KDs [5]:

(1) Classic KD (cKD): The most restricted type of KD, known as cKD, requires that every food item meet predefined calorie requirements and have its ketogenic index tested [6]. In most cases, this ratio is 4:1. Initiation should be carried out under medical supervision post-fasting (12–48 h), with 1 g/kg of protein, 60–75 mL/kg of liquids, and 80–90% of daily energy requirements. Metabolism alterations and gastrointestinal problems, such as symptomatic hypoglycemia, severe acidosis, and dehydration, can be monitored when receiving medical therapy.

(2) KD with medium-chain triglycerides (MCTs): This method is based on a daily estimate of the total amount of energy from carbohydrate, protein, MCT, and long-chain triglyceride (LCT) distribution. When transported into cell mitochondria for oxidation, MCTs are absorbed more easily than LCTs and move directly to the liver through the portal circulation [7]. MCTs cause more ketosis than LCTs, which reduces the need for total fat. This allows for a reduction in the total amount of fat consumed while increasing the intake of proteins and/or carbohydrates [8].

(3) Modified Atkins diet (MAD): MAD is a less restrictive alternative to the standard KD [9, 10]. This diet is initiated on an outpatient basis without a fast, allows for an unlimited amount of protein and fat, and does not restrict calories or fluids [9–11]. The advantages of this diet include a non-fasting beginning. It does not require lengthy calculations; therefore, it may also be used in settings with limited dietician support and minimal resources [12].

(4) Low-glycemic index (GI) diet: This diet aims to maintain stable blood sugar levels in order to reduce postprandial insulin fluctuations [13]. This diet requires fat and protein to be consumed with carbohydrates, allowing the total daily carbohydrate intake to be permitted to be about 40–60 g/day, but it controls the kind of carbohydrates, preferring those with glycemic indices below 50 [14].

(5) Modified KD (MKD): In contrast to other KDs, the MKD is the least restrictive and produces ketosis by promoting a high fat and low carbohydrate consumption without the necessity to limit protein, fluid, or caloric intake. To begin the diet, there is no requirement for a hospital stay or to start fasting [15], which makes it easier to follow and less expensive. The macronutrient adjustments in this diet change the ketogenic index from 3:1 to 1:1.

Mechanism of action

Polyunsaturated fatty acids, glucose restriction, and ketones control epileptic seizures either directly or indirectly. Although the exact mechanism is unknown, all three of these components are essential for KD to be efficacious. In addition to reducing neuronal activity and excitability and maintaining stable synaptic function, it can further function through raising levels of GABA, mitochondrial biogenesis, and oxidative phosphorylation [16].

Thus, fatty components and their effects on cell activity may have therapeutic effects. These alterations impair the ability of neurons to transmit impulses. The production of adenosine triphosphate from ketone bodies does not use glucose as the primary source of energy, which is causing these effects [17].

During ketosis, the body produces fewer reactive oxygen species. Oxidative stress improves the redox state, promotes mitochondrial biogenesis, and increases the expression of certain proteins involved in energy metabolism. By directly affecting transcription factors, ketone bodies increase the amount of glutathione made in the mitochondria and decrease the amount of reactive oxygen species [3].

In cKD (4:1), fat accounts for 90% of energy consumed (mostly LCTs), protein accounts for 8%, and carbohydrates account for 2%. Due to their capacity to passively cross the cell membrane, MCTs are absorbed and digested more quickly than LCTs. These fats also have the ability to increase ketone body synthesis in the liver. Therefore, higher adherence to dietary treatment is made possible when more carbohydrates are added to KD when MCTs are included [18].

Essential fatty acids are the most important nutrients in the diet, but their consumption may be limited due to gastrointestinal adverse effects such as diarrhea and a feeling of satiety. It is recommended that this type of diet be combined with cKD to attain greater acceptability and efficacy with fewer restrictions than previously mentioned diets [19].

Switching from cKD to MAD increases the ketogenic ratio and ketosis. The MAD restricts fat intake to a ratio of 1:1, which means 65% of calories are obtained from fat sources. Carbohydrates are limited to 10–20 g/day for adults and 15–20 g/day for children. Out of 450 children, adolescents, and adults studied with this type of diet, 45% of patients had a 50–90% seizure reduction, and 25% of patients had a 90% reduction [20].

A low-GI diet is part of the KD for refractory epilepsy to maintain blood glucose levels. This diet provides for a larger proportion of carbohydrates than cKD, KD with MCTs, and MAD. The consumption of carbohydrates must be strictly limited, and meals with GIs under 50 should be chosen, with a preference for high-fiber foods [21].

During the selection of the kind of diet, physicians should consider the child's age, the kind and severity of their epilepsy, the need for immediate intervention, family characteristics, the child's eating habits, and the accessibility of trained professionals for diet preparation [18].

It is advised that patients with myoclonic seizures initiate therapy with cKD since patients treated with MAD and later switched to cKD have shown a very significant improvement in their condition [22]. The outcomes are as expected when the cKD is compared to the MAD. In the first month of diet therapy, both adults and adolescents can benefit from MAD comparable to cKD [21].

Efficacy of the KD

Twelve patients, ranging in age from 4–17 years, participated in a prospective study that examined the nutritional effects of a KD-controlled diet for at least 6 months and up to 12 months [4]. Patients received vitamin and mineral supplements, were monitored as outpatients, and were admitted to the hospital to undergo fasting processes aimed at inducing ketosis. Based on the data, there were no hematologic changes, with the exception of one patient who had hyperchloremia and no clinical consequences. Seizures often decreased by 56% after six months on the diet and by 80% after a year of use. The KD provided greater control for patients with refractory epilepsy without causing any significant or growth-related side effects [4].

According to a retrospective analysis of 41 children with refractory epilepsy who had KD treatment, 10.5% experienced a 90% reduction in seizures, and 5.6% never experienced another seizure [17]. The majority of the children were started on a Radcliffe II-type diet, with an average age of 3.9 years. With no change in their anthropometric measures, less than 4% of the subjects experienced moderate and transient adverse effects, such as increased cholesterol and constipation. A modified version of the MCT diet, the Radcliffe II-type diet gets 30% of its calories from MCT oil or emulsion and 30% from LCT fats [23]. For children with refractory epilepsy, the KD is a viable therapeutic choice, which will be helpful with the earlier initiation of dietary therapy.

A further investigation looked at the efficacy and tolerability of KD in treating refractory epilepsy in eighteen children, ages two to eleven [24]. The KD was finally well tolerated by 14 out of the 18 patients and their families. Of the 14 people on the KD, seven reported an improvement in both their quality of life and frequency of seizures [24].

KD has been shown to treat refractory epilepsy, but further study is needed to identify its full advantages. There are several KD ratios, and as every patient is distinctive, each ratio is considered separately. Reducing this ratio might enhance KD adherence.

Mild metabolic abnormalities such as acidosis, hyperuricemia, hypercholesterolemia, hypocalcemia, and hypomagnesemia account for most of the adverse effects associated with KD. Since MCTs create more ketones per calorie than LCTs, people can ingest more carbohydrates and protein while using MCTs [24].

Conclusions

Studies on animals have been conducted to examine the metabolic and neurophysiological impacts of KD on refractory epilepsy [25]. Several studies, however, have shown that the KD is closely related to the seizure rate in patients with epilepsy [26].

This review showed that KD treatment for refractory epilepsy produced favorable results. Further study is necessary to determine whether the less restrictive and easier-to-consume diets, including the MAD and MCT diets, have similar effects on seizure management as the cKD.

Abbreviations

ASM: anti-seizure medication

cKD: classic ketogenic diet

GI: glycemic index

KD: ketogenic diet

LCT: long-chain triglyceride

MAD: modified Atkins diet

MCTs: medium-chain triglycerides

Declarations

Author contributions

SV, KPK, HMA, and YV: Conceptualization, Supervision. UD, SB, JBP, and SN: Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

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