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Review Article

Ketogenic Diet in Seizure Management

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Abstract

Introduction: The ketogenic diet contains high-fat, low-carbohydrate, and normal-protein that can be used for the treatment of epilepsy and are in use for many decades. The classic ketogenic diet contains 90% of lipid (fat) and low carbohydrate and protein. The ketogenic diet is can be used as a dietary treatment for obesity since it produces similar effects as fasting. For the patients who are resistant to pharmacotherapy and require a non-surgical option, a ketogenic diet is found to be a good alternative option for the treatment of epileptic patients. The diet planned for the patient should not be very restrictive, and palate friendly to be continued for a longer period of time. Although with the increase in treatment options for seizure management, such as the introduction of anticonvulsant medication, the use of the keto diet became less frequent. But the keto diet has regained its popularity in the past 2 decades. The healthcare providers do not endorse the diet, and hence, there is no particular protocol followed. Different clinical centers have different guideline, which makes it difficult to compare and evaluate diets efficacy.

Aim of the Study: The review aims is to understand the role of the keto diet in seizure management.

Methodology: The review is comprehensive research of PUBMED since the year 1921 to 2019.

Conclusion: The ketogenic diet and its variant is considered as an alternative option to non-surgical patients and those resistant to pharmacological therapy. Every patient is unique in their need; thus, the diet should be planned accordingly. Prior to treatment, it is essential to inform the patient about the efficacy of anti-epileptic therapy in comparison to the ketogenic diet. They can be educated regarding the same using websites and videos.

Keywords: *Ketogenic Diet; Seizure Management; Epilepsy*

Background of Keto Diet

Epilepsy is one disabling and common neurological disease that is mostly treated and controlled successfully with antiepileptic drugs. 30% of patients show refractory epilepsy and have shown the failure of treatment by antiepileptic drugs. Many of the epileptic patients are not fit candidates for surgery, so alternative option such as diet modification (ketogenic diet), palliative surgery, neuromodulation can be beneficial [1].

Dietary treatments as an alternative for diseases have been used for the past 2000 years. Fasting as a therapeutic measure for epilepsy was first recorded in Hippocratic collection. G G Guelpa and A Marie recorded the first modern use of fasting as a treatment for epilepsy in 1911. In the early 1920s, the modern use of this therapy began. A study done in Harvard medical school observed the effects of starvation as a treatment for epilepsy; the result showed improvement in seizure activity after 2 - 3 days [2-4].

A similar study done by a physician in Minnesota suggested that a particular diet could produce similar action and benefits as fasting, such a diet produce ketonemia. Several epileptic patients were studied, which showed results similar to fasting [2-4].

Methodology

We did a systematic search for ketogenic diet in seizure management using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Ketogenic diet, seizure management, epilepsy.

Classic ketogenic diet

A high fat and low protein and carbohydrate with restricted calories and fluids are known as a classic ketogenic diet. This diet alters metabolism and use fat instead of carbohydrate as the primary fuel. The catabolic product of fatty acids is the ketone body produced by the liver also includes urinary ketosis [5].

It is a rigid diet which is mathematically and individually calculated as well as medically monitored; thus, there can be a deficiency of vitamins and minerals, which should be separately provided. The anticonvulsant mechanism of the KD is by the shift in the energy metabolism from glycolytic energy production to energy generation through oxidative phosphorylation (fatty acid b-oxidation and ketone-body production). This is further described in more detail in the section on the mechanism of action [6,7].

Mechanism of action

There is no incomplete understanding of the mechanism of action of KD, but some theories have been proposed, which shows how it modifies the neuronal metabolism and excitability to reduce the seizure frequency. Possibly, the actual mechanism of reduction of cortical hyperexcitability includes multiple factors. This involves various systems involved in seizure reduction are related to metabolic changes in the blood and cerebrospinal fluid (CSF), a decrease in glucose levels and an increase in ketone bodies. The function of mitochondria and its energy reserve may also play a vital role in the mechanism of the ketogenic diet, resulting in synapse stabilization and excitatory decrease [8].

Anticonvulsant effects of ketone bodies

The by-product of fatty acid oxidation in the mitochondrial matrix of hepatocytes are ketone bodies, acetoacetate, and beta-hydroxybutyrate (βOHB). There are many theories which show the role of ketone bodies, but the existence of an anticonvulsant effect is controversial. Some studies have found no relationship between ketone bodies and synaptic transmission and seizure control [9,10].

Animal experimental studies were done on the (rats) which was exposed to ketone bodies demonstrated no variation or change in synaptic plasticity. A similar study did conduct did not detect any anticonvulsant effects in either. Ketone bodies were supplemented in spontaneously epileptic kcna1-null mice; the result showed attenuation of electrographic seizure-like events. An inhibitory effect of ketone bodies on mitochondrial permeability transition has also been observed related to apoptotic and necrotic death. A broad spectrum of anticonvulsant effects was seen associated with acetoacetate in a study [5,10].

According to a study, injection of ketone bodies led to the reduction of seizure susceptibility. In a section of mouse tissue, a decrease of the spontaneous firing rate was found, eliminated by the absence of ATP-sensitive potassium channels (KATP). Ketone bodies can exert a direct inhibitory effect on vesicular glutamate transport. From this divergent result, it can be said that ketone bodies of different concentrations have been used in these studies along with the diversity in seizure thresholds of the animal models used. The diet composition can also explain these conflicting results obtained from an experimental study [11].

Synaptic functional and neuronal metabolism

The change in neuronal metabolism, mitochondrial function, and energy reserve and the environment explain the neuronal mechanism of ketone bodies. The usual substrate for neurons is glucose under normal circumstances, and its diffusion through the brain-blood barrier is facilitated by glucose transports present in the brain capillary endothelial layer. The presence of glucose metabolism produces the rapidly available energy that is necessary for seizure activity. Therefore, in patients on the keto diet, due to blood glucose energy levels, the brain begins to use ketone bodies instead of glucose energy. The anaerobic metabolism also slows the energy availability, which in turn reduces seizures [12].

In an experimental model's the administration 2-Deoxy-D-glucose showed anticonvulsant propriety of a decrease in glucose metabolism and elevated the seizure threshold. After glucose infusion, the anticonvulsant effect of the ketone bodies can be quickly reversed. These data obtained from several studies not only postulate the influence of ketone body but also the reduction in glucose level as a mechanism of action for a ketone diet [13].

Chronic ketosis can play a vital role in anticonvulsant properties of keto diet since chronic ketosis elevates brain energy and reserve via stabilization and reduction of the excitability of synapses. This energy reserve is directly associated with mitochondria, which is an important element to consider in the antiepileptic effect of ketone diet. There is an increase in mitochondrial activity leads to increase in ATP production, which activates KATP which in turn attenuates neuronal excitability [14].

Role of gut microbes, inflammation, and genetics

The gut microorganism has been recent studies for its effect on many diseases, especially in inflammatory cause since many metabolic pathways are known to be modulated by gut microbiota. The anti-seizure effects of gut microbiota were demonstrated by Olson, according to which the keto diet modifies the gut microbiota with decrease in alpha-diversity and an increase in putatively beneficial bacteria *Akkermansia muciniphila* and *Parabacteroides* spp. This leads to changes in colonic luminal metabolome with a decrease in gamma-glutamyl amino acids, which in turn increases the GABA/glutamate content in the brain by decreasing gamma-glutamyl amino acids in the blood. A study model reported that keto diet confers protection against seizures. Moreover, the keto diet decreases the frequency of spontaneous seizures in Kcna1 knockout mice. Therefore, changes in the gut microbiota are found to be an important factor for keto diet mediated seizure protection [15].

The role of inflammatory mediators like cytokines in epilepsy is well known, and there is evidence that the keto diet also interferes with a pro-inflammatory cytokine. A study showed a reduction of interleukin 1β and other pro-inflammatory cytokines in rats treated with KD in the LPS model [16].

A study showed that beta-hydroxybutyrate inhibits class I histone deacetylases. During the keto diet, the elevation of beta-hydroxybutyrate leads to change in gene transcription on a large scale but particularly those linked to resistance factors of oxidative stress. This result showed that the keto diet has a potential role as a disease-modifying treatment in epilepsy [17].

Neurotransmitter function

There is synaptic stabilization related to changed in critical amino acids as a result of ketone metabolism, which is induced by the keto diet. It is proposed that the keto diet interferes with the gamma-aminobutyric acid (GABA) concentration, which is the major inhibitory neurotransmitter. Ketone body also promotes the decrease in aspartate levels lead to the synthesis of GABA. The conversion of glutamate to glutamine in astrocytes and inhibitory effect of aspartate on glutamate decarboxylase explains this action. Not only the increase in GABA but the other neurotransmitters such as adenosine A1 can also be implicated in the anti-seizure effect also in the keto diet. However, this is still controversial and more evidence is required [18].

Indication

The keto diet has more frequently been used and considered as the gold standard for the treatment of various metabolic diseases such as Glucose Transporter Protein 1 (GLUT-1) deficiency syndrome and Pyruvate Dehydrogenase Deficiency. Recently, the keto diet has been consistently reported to be beneficial in nearly 70% of patients with positive responses, as opposed to the average 50% response in several conditions such as infantile spasms. The keto diet has proven to be beneficial for other conditions but with less evidence and possible benefits. Additionally, the keto diet is an important alternative treatment for patients with refractory epilepsy that are not surgical candidates. Following are some indication [19].

• Angleman syndrome
• Complex 1 mitochondrial disorders
• Dravet syndrome
• Epilepsy with myoclonic-atonic seizures (Doose syndrome)
• Glucose transporter protein1 (Glut-1) deficiency syndrome
• Febrile infection fed children or infants
• Infantile spasms
• Ohtahara syndrome
• Pyruvate dehydrogenase deficiency
• Super-refractory status epilepticus
• Tuberous sclerosis complex

Table 1: *Indications for ketogenic diet as alternative treatment.*

Some other epileptic syndromes and conditions in which the keto diet is proven to be beneficial [19].

• Adenylosuccinate lyase deficiency
• CDKL5 encephalopathy
• Childhood absence epilepsy
• Cortical malformation
• Epilepsy of infancy and migrating focal seizure
• Juvenile myoclonic epilepsy
• Landau Kleffner syndrome
• Phosphofructokinase deficiency
• Rett syndrome

Table 2: *Epileptic syndromes where ketogenic diet is beneficial.*

Contraindication

In some pathologies the keto diet is contraindicated, following are some absolute and relative contraindication of keto diet [19].

Counseling and evaluation prior to the keto diet initiation

Since the diet is difficult to maintain, the counselors should talk with the family about the expectation clear the efficacy rate and adverse effect associated with the keto diet.

Absolute contraindication	Relative contraindication
• Carnitine deficiency (primary) • Carnitine palmitoyl transferase deficiency • Beta-oxidation defects • Medium-chain acyl dehydrogenase deficiency • Long-chain acyl dehydrogenase deficiency • Short-chain acyl dehydrogenase deficiency • Porphyria • Pyruvate carboxylase deficiency	• Inability to maintain adequate nutrition • Surgical focus identifies by neuroimaging and video EEG monitoring • The parent or caregiver non-compliance • Propofol concurrent use

The patients can be educated by mean of different media sources such as publications, videos, and websites regarding diet, videos. Before starting the diet, a seizure diary must be established to know the frequency. Kidney stones are frequently associated with the condition so a renal ultrasound should is recommended. The nutritional evaluation should be done which includes a detailed nutritional intake and food intake history of 3-days. Any particular food habit, allergies associated, intolerance and aversion due to any should be reported as well. Baseline weight, height, and the ideal weight for stature and body mass index (BMI) are needed to calculate the ketogenic ratio, calories, and fluid intake. The diet is planned and formulated according to the patient's age and compliance. The laboratory evaluation are as follow [19].

• Complete blood count (CBC) with platelets count.
• Electrolytes to include serum bicarbonate, total protein, calcium, zinc, selenium, magnesium and phosphate serum
• Liver and kidney tests (albumin, blood urea nitrogen and creatine)
• Fasting lipid profile
• Urine calcium and creatinine
• Anticonvulsant drug levels
• Serum amino acids
• Vitamin D levels

Table 3: *Laboratory evaluation prior to starting ketogenic diet.*

Diet initiation, adverse effects, and follow-up

The goal of the diet is to reach four portions of fat to one portion of protein plus carbohydrate. These approaches include diet include and exclude fasting. In the former approach, the patient must be hospitalized for 12 - 48 hrs, or when ketones are present in urine to prevent the development of hypoglycemia and dehydration, this accelerates ketosis, and when ketosis is reached, the meals are calculated to maintain a constant keto diet. While the one which exclude fasting, there is no requirement of hospitalization, and the keto diet ratio needs to be gradually increased weekly from 1:1 to 4:1. The keto diet includes a very small quantity of milk, fruits, vegetable, grains , cheese, and other vitamins so to overcome these deficiencies it should be supplemented separately. Patients are advised to follow up every 3 months, and it should be made sure that the patient and family are able to contact the diet team to resolve any problem and doubts. The adverse effects are dehydration, hypoglycemia, lethargy, metabolic acidosis, high LDL, elevated total cholesterol, and gastrointestinal symptoms.

Conclusion

The ketogenic diet can be considered as an option in epilepsy and seizure management, especially in those who use multiple antiepileptic drugs or resistant to pharmacological treatment. This is also a treatment of choice for seizures associated with glucose transporter protein deficiency and pyruvate dehydrogenase complex deficiency. Family and patient's expectations regarding the diet, its efficacy, and adverse effects should be discussed in detail with the diet team and the counsellor. A multidisciplinary team approach is required for a long term follow-up, evaluation of the patient, changes in further diet and counselling regarding the present one. Due to the strict diet, side

effects, unpalatability and patients compliance makes it difficult to evaluate the t clinical efficacy of the diet and further improvements required with the same.

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