

Role of ketogenic diet in pediatric epilepsy

Abstract

Pediatric epileptic seizures occupy a significant place in the current nosology of neurological syndromes. Most effected population with seizures is children and elderly and less affected are adults. Role of diet is plays an important part in reducing the severity of symptoms, most significant diet is ketogenic, which has been used from 1921 as a best treatment option. Composition of ketogenic diet (KD) includes highest ratio of fat, moderate ratio of protein and lowest ratio of carbohydrates. Combination of energy giving nutrients in this ratio induces the ketosis which leads to reduction in the initiation of seizures. Ketogenic diet participates in various mechanisms i.e. regulation of neurotransmitters, limiting glycolysis pathway, tri-carboxylic-acid cycle and oxidation of polyunsaturated fatty acid; induces the anti-seizures responses. Numerous nutrients also showing the positive potential against epileptic seizures. But continues and very strict adherence to ketogenic diet causes some adverse effects on human body disrupting the normal mechanism of body. The focus of this review is on the pediatric epilepsy and modification in symptoms with the application of the ketogenic diet.

Keywords: epilepsy, neurons, brain, seizures, ketogenic diet, low carbohydrate diet

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Pathophysiology of prevalence epilepsy

Epileptic seizures are the abnormal electrical activity of neurons situated in the cerebral cortex. At cell level, neurons of the cerebral cortex work in patterns that facilitate memory, sensory functioning, learning and behavioral output of defined neural circuits. An area of brain capable of generating seizures contains millions of neurons, all of which can fire synchronously. During electroencephalography (EEG), the recording electrodes on the scalp detect the synchronous firing of at least a 1-2cm of brain region as a spike and slow wave called epileptic-form activity.¹ Seizures are common with their occurrence rate of 0.5-1.6 % in the overall population. The prevalence of epilepsy in children ranges between 43-188 per 100,000. Nearly 160,000 children and teenagers face their 1st unprovoked seizure and about 31,000 of them are identified with epileptic. Recent study assessed that the global incidence of seizures estimated in 2015 was 6.8 per thousand children and the rate approximation 105 per 100,000 for pediatric population.^{2,3} Epilepsy is a brain ailment categorized by durable disposition to produce epileptic seizures.⁴ Pediatricians not feel comfortable to deal with children who are suffering from epilepsy. The objective of presenting this review is to shed some light on the important points of the evaluation of children presented with an epileptic seizure.

Types of seizures

Most common form of seizures in children from six months to five years of age. Almost 3-6 % of the children have faced at least 1 febrile seizure by five years of age. Most of the febrile seizures are of shorter duration, simple and with the duration of less than 15 minutes. Complex febrile seizures typically have numerous recurrences in twenty-four hours and can be of longer duration.^{5,6} The risk of incidence of epilepsy in children with febrile seizures is 1.9-3.9 %.⁷ Benign epilepsy seizures have occurred with the incidence rate of 21.9-24.9 %. These seizures categorized by hemi-facial motor seizures and may be preceded by somato-sensory symptoms involving the lips, inner cheek and tongue.⁸⁻¹⁰ Results of recent studies exhibited

that an important percentage of children with temporal spikes have neurological problems such as learning and attention difficulties.^{11,12}

Importance of ketogenic diet in controlling seizures

Seizures control procedure has been documented by scientist many centuries ago which is fasting especially deliberate fasting.¹³ Later studies revealed the importance of ketogenic diet which shows the similar results as fasting for longer duration. Basic purpose of ketogenic diet is to increase the production of ketone bodies by providing high fatty food as the chief energy nutrient, whereas limiting carbohydrates and proteins. In normal metabolic condition body derived glucose from carbohydrates and is the key nutrient of energy for brain. On the other hand, in the absence of major energy source called carbohydrate, mitochondrial beta-oxidation of fatty acids which occurs in liver produces huge amounts of ketone bodies; aceto-acetate and β -hydroxy-butryate (BHB), and the brain easily use them as energy source.^{14,15}

Provision of ketogenic diet is based on accurate measurements of calories to avoid rapid increase in weight. High fat ratio used for children of the age of 2 to 3 in which four gram of fat combined with one gram of carbohydrates and proteins. On the other hand, three gram of fat for every one gram of protein used for older children because of the presence of much higher body mass index so required more protein for the proper functioning of human body.^{16,17} Six children study results demonstrated that, who were receiving the medium chain triglycerides (MCT oil) diet with coconut oil (which contains 45% MCTs), that coconut oil was equally beneficial in maintaining ketosis, providing the same anti-seizure benefits and was more cheap and then alone MCT oil.¹⁸

Anti-seizure mechanisms of ketogenic diet

Ketogenic diet participates in altered the levels of neurotransmitters. Basically, long chain fatty acids in high fat diet are converted into ketone bodies in liver by excessive acetyl CoA, and these ketone bodies are involved in the production of gamma-aminobutyric-

acid.¹⁹ Mechanism of its production as; first of all, the conversion in glutamine from glutamate is by the enzymes produced by specialized glial cells which are present in brain and spinal regions. After that glutamine is transferred to neurons, which involves in its chemical modification and produces the gamma-aminobutyric-acid. In this way, the ketone bodies play an important role to modify the mechanism of glutamate by enhancing the activity of gamma-aminobutyric-acid.²⁰ Dhalin et al.²¹ study demonstrated that children contain the high levels of gamma-aminobutyric-acid as compared to adults.²¹ Melo et al.²² demonstrated that when ketogenic diet has been fed to the rats for the duration of 4 weeks it showed significant reduction in glutamate by increasing the level of gamma-aminobutyric-acid.²² Another study demonstrated that ketogenic diet is more efficient in showing the anti-seizures effects in children as compared to adults.

Another important anti-seizures mechanism of ketogenic diet is to limit the pathway of glycolysis and enhances the ketone bodies production by beta oxidation of fatty acids. Mantis et al. study results exhibited that caloric restrictions in rats especially by carbohydrates induces the process of inhibiting or reducing the epileptic seizures.^{23,24} Not only the restrictions in glycolysis pathway enhances the positive response in body but also the usage of glycolytic inhibitor *i.e.* phosphoglucose isomerase which participates in maintaining or regulating the frequency of seizures.²⁵ Another substance fructose 1,6 biphosphate which play a significant role in indirectly inhibiting glucose pathway by transferring it towards pentose phosphate pathway and enhances

the activity of ketone bodies by decreasing the efficiency of seizures.²⁶ Divers studies indicated that ketogenic diet increase the formation of energy in the form of ATP (Adenosine-tri-phosphate) particularly in neurons by replenishing the tri-carboxylic-acid cycle with the help of ketone bodies which produces acetyl-CoA (act as intermediate of tri-carboxylic-acid cycle) in abundance and this process significantly decreases the seizures.^{27,28}

Polyunsaturated fatty acids mechanism is also important in seizures reduction due to its attractive neuron protection properties. Study results of Fraser et al. indicated that administration of ketogenic diet to pediatric patients for one month can surely be elevate the levels of ketone bodies, fatty acids especially essential which includes arachidonic acid, linoleic acid and docosahexaenoic acid, in this way polyunsaturated fatty acids participates in the significant decline of seizure episodes.^{29,30} Schlanger et al. research findings showed that ingestion of 6 grams of polyunsaturated fatty acids for the period of six months appeared to lessen the epileptic seizures in pediatrics. A three months randomized study in epileptic individuals exhibited that the provision of docosahexaenoic acid in amount of 0.8 gram per day suppresses the seizures pathway effectively.^{31,32} Bromfield et al.³³ demonstrated that administration of 2.5milligram combination of docosahexaenoic acid and eicosapentaenoic acid per day for four months in patients with continues episodes of seizures showed efficient results as compared to control group.³³ Anti-seizure mechanisms of ketogenic diet are summarized in Table 1.

Table 1 Anti-seizure mechanisms of ketogenic diet

Mechanisms	Mode of action	References
Regulation of neurotransmitters	Conversion of glutamate to glutamine Transfer of glutamine to neurons By enzymatic action, production of gamma-aminobutyric-acid Anti-seizures effects	Cendes et al. ¹⁹ , Yudkoff et al. ²⁰ & Melo et al. ²²
Limiting glycolysis pathway	Restrict glycolysis and induce beta-oxidation Enhance ketone bodies production Positive effective of Glycolytic inhibitor Contributes in seizures control	Mantis et al. ²³ , Huttenlocher et al. ²⁴ & Stafstrom et al. ²⁵
Tri-carboxylic-acid cycle	Intermediate acetyl-CoA participates in ATP formation Especially in neurons Enhances ketone bodies and reduce epileptic seizures	Lian et al. ²⁶ , Hadera et al. ²⁷ & Kovac et al. ²⁸
Oxidation of polyunsaturated fatty acids	Neuron protective properties Oxidation produces docosahexaenoic acid, linoleic acid, eicosapentaenoic acid Reduces the episodes of seizures effectively	Michael et al. ³⁰ Yuen et al. ³² Bromfield et al. ³³

Administration of the ketogenic diet

For proper administration of ketogenic diet patient firstly examined by neurologist. Antiepileptic drugs and biochemical tests should be carried out in addition to other tests to figure out the disorders in fatty acid oxidation. To begin the diet, fasting is not considered essential. In a study, two randomized clinical trials were carried out between fasting and steadily eating of ketogenic diet. Results of study exhibited that epileptic individuals shown significant reduction in chronic seizure at the duration of three months. Retching and hypoglycemia shown to be less problematical for the individuals that were not on fasting.^{34,35} When the diet is started, the child is monitored by the members of the ketogenic diet team in an outpatient clinic. Regular appointments are very important to observe the nutritional status, growth, and seizures of children during the sequence of ketogenic therapy. Integration of medium-chain-triglyceride oil or coconut oil in the normal diet is a good way to increase ketosis and having the laxative properties which are helpful in reducing the adverse effect of this diet that is constipation.³⁶

Seizures also happen due to disturbances in the diet, like a mistake in preparing or in the weight of the food, drinking or eating a non-ketogenic food, or when introduced or changed a medication. Sleep deprivation, or illness may be some of the causative factors that may have triggered the child's temporary breakthrough seizures.³⁷ Supplementation of vitamin and minerals is vital due to the insufficient sources from the diet. Vitamin D, calcium, and phosphorus levels are alarming due to these decreased levels; fractures, osteomalacia and rickets appeared in children especially in those who were on anti-epileptic drug for longer duration.³⁸

More activeness shown in the children who have controlled seizures, for this purpose enhancement in calories must be recommended. Make ketogenic diet more pleasant so it will be easily chosen by children. Some children enjoy eating fatty food in the form of butter while others prefer high fatty meals through cream instead of butter or margarine. Some children cannot be able to digest the exceeded amounts of fat *i.e.* 4:1; however, they can be able to digest 3:1 diet in which fat contents slightly lesser than former ones and it also provides adequate quantities of carbohydrates and proteins. Consuming 100% of the diet is the initial goal. It may take many weeks, and the dietitian should make creative meals to increase approval by the child. Following to maintain a state of ketosis which helps to halt seizures. Ketosis is checked at home with urine testing. Urine ketone levels are a basic guess of serum ketone levels but they can do for simple monitoring purposes.^{39,40}

Anti-seizures potential of nutrients

Taurine is inhibitory amino acid in the brain and may causes hyperpolarization of neuron and inhibition of neuronal firing. The increase level of taurine is linked with reduced seizure susceptibility while decrease in level with more spontaneous seizure activity. The mechanism by which taurine could decrease seizure susceptibility may be by inhibiting the release of D-aspartate (analogue of L-glutamate), decreasing the intracellular level of free Ca^{2+} and by its effect on chloride channels (activating GABAA receptors). It has been searched that about one-third of human beings suffering from epilepsy have shown significant relief of seizure by taurine administration. However, the major issue with taurine treatment is decreased efficacy with time as body adapts to the therapy by causing its excretion through urine. Numbers of taurine derivatives have been developed

so far but none of them were proved to be very effective.⁴¹ Taurine has been given at a wide range of doses (200mg/day to 21g/day) for variable periods of time to the patients with severe, intractable epilepsy. There are so many benefits of taking taurine to different body organs including maintaining proper hydration and electrolyte stability in cells, forming bile salts, which play very important role in digestion, regulating minerals such as calcium within cells, it may also support the general function of central nervous system and eyes, regulating immune system health and antioxidant function. The main dietary sources of taurine are animal foods, like meat, fish and dairy. Smaller amounts occur in some plant foods. It may also have added to many energy drinks. Taurine is very effective against partial epilepsy but has very little effect on generalized epilepsy.⁴²

Manganese is essential trace element which is required for proper development and functioning of the central nervous system. It has been stated that manganese is necessary for activity of glutamine synthetase which converts glutamate to glutamine, however deficiency of manganese causes accumulation of glutamate which may leads to generation of seizure. Lupine was used in the treatment of epilepsy; the anticonvulsant activity of lupine could be because of exceptionally high concentration of manganese.⁴³ Manganese is considered an essential nutrient and can be found especially in seeds and whole grains, as well as in smaller amounts in legumes, beans, nuts and leafy green vegetables.⁴⁴

Vitamin D is very important for the proper metabolism and functioning of calcium. Various drugs which are used to treat the seizures may inhibit vitamin D and calcium metabolism in same time. Patients taking anticonvulsants have higher risk of developing vitamin D deficiency, because these drugs induce liver enzymes which may inactivate vitamin D. Rickets, low bone mineral content, osteomalacia have been reported in drug treated epileptic patients. In patients with osteomalacia may result due to the use of phenytoin and phenobarbital, the amount of vitamin D_3 needed to achieve positive calcium balance was approximately 975IU/day. In patients with low 25-hydroxyvitamin D levels who were taking phenytoin, carbamazepine, and phenobarbitone, either alone or in combination, the amount of vitamin D_3 required to maintain a normal serum 25-hydroxyvitamin D concentration (15mg/mL or greater) ranged from 400 to 4,000IU/day, with 72 percent of patients requiring 2,400IU/day. Rich sources of vitamin D are marine water fishes and some animal foods, particularly in vitamin D fortified milk and cheese. Another excellent source of this vitamin is sunlight exposure so, expose your child towards early sunlight especially in morning. Results of a study indicated that, 23 epileptic patients who were supplemented with vitamin D shown significant. In one study, supplementing the diet of twenty-three people with epilepsy with vitamin D resulted in a significant reduction in the frequent episodes of seizures.⁴⁵

Vitamin E deficiency has been stated in patients with epilepsy. Vitamin E is important for accurate functioning of oxygen in the human body. Randomized double blind trail of 24 epileptic children showed that when vitamin E supplementation (400IU per day) given to them, symptoms of seizures decreased significantly as compared to control group who did not receive any supplementation. Results of this study demonstrated that vitamin E supplementation has positive potential on epileptic patients who feel difficulty in treatment.⁴⁶

Zinc plays an important role in blood glucose level balance, it also helps in protein synthesis, improve brain function, and the immune

system, as well as other aspects of health. Children with epilepsy have been stated to have significantly lower levels of serum zinc, especially those with West or Lennox-Gastaut syndrome. More importantly, it seems that people with epilepsy may have elevated copper-to-zinc ratio. Seizures may be prompted when zinc levels fall, as in the absence of adequate taurine. Although the main role of zinc, or the copper-to-zinc ratio, is not clearly understood, it seems that anticonvulsants may cause zinc deficiency, either by decreasing zinc absorption in the intestines or may be due to diarrhea. Therefore, zinc supplementation may be warranted. The best sources of zinc from our diet are present in seafood such as oysters and crabmeat, red meat, poultry, baked beans, pecans, milk and fortified foods such as breakfast cereals.⁴⁷ Thiamine is a vitamin, also called vitamin B1. In one study a daily oral dose of thiamine (0.05-0.3g/kg) and 750 mg in another study both confirmed significant efficacy in cases of intractable epilepsy, decreasing seizures by more than 30% in 11 of 34 patients. It can be highly significant for those patients that were unresponsive to any other anticonvulsants. A correlation of effectiveness was seen with the patients achieving the highest taurine concentrations also showing the best response of decreased seizures.⁴⁸ Food sources of thiamine include beef, liver, dried milk, nuts, oats, oranges, eggs, seeds, legumes, peas and yeast. Foods are also fortified with thiamine. Some foods that are often fortified with B1 are rice, pasta, breads, cereals and flour.⁴⁹

Adverse effects of ketogenic diet

The most common adverse effect of this diet constipation. Gastroesophageal reflux disease GERD may be exacerbated by the high fat intake, which slows gastric emptying. Kidney stones have been reported in a small percentage of patients.⁵⁰⁻⁵² Abnormality in lipid profile due to high and continues consumption of fatty meals which disturbs the functioning of liver and causes the bile stone and obstructions in biliary system pathways. Researchers revealed the drawback of this diet from the study of 151 children which showed the enhancement in the levels of bad cholesterol (LDL) and declines in the levels of good cholesterol (HDL) which further cause atherosclerosis.⁵³ Adverse effects related to nutrition include growth retardation and numerous micronutrient insufficiencies.⁵⁴

Conclusion

In conclusion, most significant diet for reducing the symptoms of seizures is ketogenic. Composition of ketogenic diet (KD) includes highest ratio of fat, moderate ratio of protein and lowest ratio of carbohydrates. Combination of energy giving nutrients in this ratio induces the ketosis which leads to reduction in the initiation of seizures. But continues and very strict adherence to ketogenic diet causes constipation, abnormality in lipid profile, stomach issues including GERD. Many nutrients also play an important role in the significant reduction of seizures when supplemented in adequate quantities with ketogenic diet. Importance of MCT and coconut oil also exhibited the positive influence in reducing pediatric epileptic seizures.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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