Role of dietary therapy in managing epilepsy in children


INTRODUCTION

Although many drugs have been validated for the management of epilepsy, many children that administer these treatment modalities have been associated with drug-resistant events and recurrent seizures. 1-3 Besides, many adverse events and complications have been associated with the administration of these treatment modalities. As a result, there is an urgent need to develop better management approaches. Accordingly, around 44% of children with epilepsy tend to use alternative and complementary therapeutic approaches to enhance the frequency of seizures to improve their life’s quality. 3 Ketogenic diets have been proposed as effective management approaches that have been validated by many studies in the literature.
infantile spasms, GLUT-1 deficiency and Dravet syndrome. As a result, it has been noticed that observable favorable outcomes within the first three months from starting the administration of these treatment regimens.\textsuperscript{4,7} The aim of the study was to discuss the dietary therapeutic approaches for the management of epilepsy in children.

METHODS

We performed an extensive literature search of the Medline, Cochrane, and EMBASE databases on 10\textsuperscript{th} July 2021 using the medical subject headings (MeSH) or a combination of all possible related terms. This was followed by the manual search for papers in Google Scholar and the reference lists of the initially included papers. Papers discussing dietary therapy in managing epilepsy in children were screened for relevant information. We did not pose any limits on date, language, age of participants, or publication type.

DISCUSSION

Ketogenic diets

These dietary supplementations are now commonly used to treat epilepsy in children because of their potential events on reducing convulsions and the associated inflammatory responses.\textsuperscript{8} Moreover, ketogenic diets are mainly composed of various dietary components, including huge amounts of fats with very little carbohydrate levels and sufficient amounts of proteins (Figure 1).

![Ketogenic Diet](image)

**Figure 1: Components of the ketogenic diet for epilepsy.**

These regimens can significantly induce a metabolic shift from glycolysis to beta-oxidation. Furthermore, to estimate the adequate amounts of the dietary supplements that are used in the ketogenic diets, the ketogenic ratio has been used to describe the ratio between fats to proteins and carbohydrates. However, it was previously demonstrated that maintaining the administration of ketogenic diets have a difficult process. In this context, in 1971, a significant modification to the ketogenic diet was introduced, and the potential anti-epileptic drug is now termed the medium-chain triglycerides, which are mainly reached in medium-chain fatty acids.\textsuperscript{8} As a result of this modification to the dietary regimen, increased ketogenesis has been reported with many favorable events that are discussed later on within this article. In a similar context, many dietary regimens have been developed similar to the medium-chain triglycerides, including the low glycemic index diet and the modified Atkins diet.\textsuperscript{8,9}

Additionally, many previous studies have assessed the potential efficacy of these regimens as antiepileptic approaches. Most of the current studies also recruited children populations. Evidence from these studies indicates that children that administered ketogenic diets showed a 50% reduction in their epilepsy status, in 33-56% of them while around 16% of children have recovered from epilepsy.\textsuperscript{8} This was furtherly indicated in a randomized controlled trial that showed that more than two-thirds of them included children had more than 50% reduction in seizures and convulsions.\textsuperscript{10} Further randomized controlled trials also compared the efficacy of the ketogenic diets as compared to the routine administration of drugs in children that were pharmaco-resistant to epileptic therapy. In addition, Neal et al has indicated that dietary management was significantly more efficient in reducing the frequency of seizures in their included patients, as compared to the control group.\textsuperscript{11} A previous trial was also conducted in India and recruited 52 children to continue their drug-based treatment for epilepsy and another 50 children to administer a modified Atkins diet. The authors reported that 30% of children receiving the dietary management showed more than a 90% reduction in the frequency of seizures as compared to only 7.7%, and the difference was statistically significant. A huge difference was furtherly noticed in children that achieved more than 50% reduction in the frequency of seizures.\textsuperscript{12} Another Dutch comparative investigation also has shown that around 50% of the group of children receiving dietary management were associated with more than 50% reduction in the frequency of seizures, as compared to 18.2% only within the control group.\textsuperscript{13}

In the same context, another Scandanavian investigation also showed that 16% of their include population were associated with a complete recovery from epilepsy, and around 50% also achieved more than 50% reduction in the frequency of seizures.\textsuperscript{14} Besides, it was also previously reported that maintaining the ketogenic diet in these children was significantly associated with enhanced maintenance favorable outcomes of the antiepileptic effects.\textsuperscript{15} A previous study also mentioned that stopping the dietary management over 2-3 years was also associated with favorable events in these children with no recurrence of seizures.\textsuperscript{16,17} Furthermore, Hallbook et al.\textsuperscript{18} also mentioned that the administration of the ketogenic diets was significantly associated with enhanced sleeping, reduced seizures, enhanced quality of life, and attention. Cognitive functions also improved following the administration of dietary supplementations to manage children who suffered from epilepsy.\textsuperscript{19}
However, it should be noted that some adverse events might develop as a result of the administration of these treatment regimens. Vomiting, constipation or diarrhea, weight loss, hunger, and reduced energy are the most common adverse events that have been frequently reported in these children within the first three months from initiating the management with a modified ketogenic diet or the classic ketogenic dietary supplementations.\textsuperscript{10,11}

Sepsis, pneumonia, gallstones, acute pancreatitis, status epilepticus, fatty liver, acidosis, abdominal pain, dehydration, hyperammonaemia encephalopathy, and tachycardia were also rarely reported in such situations.\textsuperscript{10} Bone demineralization and mental retardation were also reported among some children. However, the evidence regarding these events is still controversial.\textsuperscript{8,16} Disrupted menstrual cycles and an increased number of bruises are also reported among some children that administered these treatment regimens.\textsuperscript{20} Furthermore, it was previously demonstrated that the associated incidence of kidney stones development in these children might be primarily attributable to the reduced ingestion of adequate amounts of fluids due to previous wrong habits.\textsuperscript{8,16} In such situations, prophylactic calcium citrate might be indicated.\textsuperscript{11,14,21}

**How dietary therapy works?**

Studies in the literature have previously demonstrated some of the mechanisms by which the different dietary regimens are commonly used to treat epilepsy. Nevertheless, we think that many of these mechanisms are not adequately discussed in the literature. Therefore, we would like to shed more light on them in the current section of this manuscript. Some authors indicated that the antiepileptic functions of these regimens are mainly attributable to the ketone bodies that are usually present in these foods, and usually result from fatty acids oxidation. Alternations and changes in the mitochondrial functions and genetic expressions were also reported to be potential mechanisms for these food regimens. In the same context, glutamate recycling was also reported among some studies in the literature as a potential event secondary to the administration of dietary regimens for the management of epilepsy.

Within the Krebs cycle, consuming oxaloacetate can significantly lead to an efficient metabolism of acetyl-CoA that usually results from the ingested diets that are rich in fat.\textsuperscript{22} Consequently, this will eventually lead to the increased utilization of oxaloacetate and will significantly lead to increased levels of α-ketoglutarate within the cells of the body. This will significantly increase the levels of glutamate and reduce the levels of aspartate. Therefore, it has been demonstrated that increased glutamate levels will finally boost the levels of γ-aminobutyric acid (GABA) by increased activation of glutamic acid decarboxylase.\textsuperscript{22,23} GABA is a common and powerful neurotransmitter according to many studies in the literature that has a high potential capability for reducing epilepsy. In a previous investigation that recruited children with epilepsy and aimed to measures the levels of the different neurotransmitters, the authors reported increased GABA levels in the cerebrospinal fluids of these children within the respondents to the dietary plan management than children that did not respond to it.\textsuperscript{24}

Many mechanisms have been proposed for the development of various neurological disorders that are associated with intracellular mitochondrial dysfunction. Enhanced functions of the mitochondria have been associated with the administration of ketogenic diets by upregulation of the transcripts that encode the mitochondrial proteins and reduced creatine/phosphocreatine ratio, and elevated levels of glutamate, as previously demonstrated in an animal investigation.\textsuperscript{25}

Cell death, which is attributable to the increased production of reactive oxygen species (ROS) and reduced production of ATP compounds, was also linked with dysfunction in complex I within the oxidative phosphorylation pathways.\textsuperscript{26} In cases with a remarkable deficiency of aspartate glutamate carrier, a significant impairment in the shuttling of aspartate to the cytosol from the mitochondria. This has been associated with a significant impact on the development of seizures and hypotonia. As a result, the nicotinamide adenine, dinucleotide-reducing equivalents transfer indirectly by the aforementioned deficiency of these compounds.\textsuperscript{27} Accordingly, the administration of ketogenic diets has been linked with a significant improvement in the O\textsubscript{2} within the mitochondria, leading to a significant improvement in oxidative stress and a significant enhancement in epilepsy-related events.

Another reported mechanism for the dietary management of epilepsy is their proven potential actions on the ATP-sensitive potassium channels (K\textsubscript{ATP}). Within the ingested dietary supplements, the wide availability of the ketone bodies can significantly lead to the opening of the K\textsubscript{ATP} channels, which have effective properties in reducing neuronal excitability. This mechanism has been initially explained by the significant reduction in the intracellular ATP that usually results from glycolysis, and therefore, K\textsubscript{ATP} channels are activated. Activated K\textsubscript{ATP} channels will then lead to significantly enhanced actions of the GABA transmitters and related neurons in the substantia nigra pars reticulata that usually involves increased levels of K\textsubscript{ATP}.\textsuperscript{24,28}

Furthermore, previous studies have indicated that the substantia nigra pars reticulata can significantly reduce the severity and frequency of seizures by acting as a gate to the convulsions by regulating the seizure threshold within the neuronal networks that are associated with hyperactivity and synchronization.\textsuperscript{29,30} Another potential mechanism is the action of the dietary products on the peroxisome proliferator-activated receptors. Hyperacetylation of the acetone bodies is induced by the ingested ketone bodies leading to increased production of acetyl-CoA, which is
commonly observed as a substrate for boosting the actions of histone acetyltransferase and decreasing the actions of histone deacetylase enzymes. Enhanced transcriptional activities of peroxisome proliferator-activated receptors (PPAR) have been reported as a result of the sequence of these acetylty activities leading to reduced anti-inflammatory effects through upregulation of the antioxidant endogenous genes. Besides, it was also observed that induce activation and boosting of the nitric acid synthase enzymes and downregulation of the levels and activation of cyclooxygenase-2 compounds are also associated with the increased levels of PPARα leading to favorable events through inhibition of the pro-inflammatory transcription factor nuclear factor-κappa β, leading to enhanced anti-inflammatory response.

In the same context, Medium-chain triglyceride diets were also reported to have abundant amounts of decanoic acid leading to significant activation of PPARγ. The latter has been associated with significantly enhanced expression of catalase products, which are commonly associated with the reduced or prevented synthesis of the ROS compounds. Therefore, this can lead to reduced levels of oxidative damage which can be significantly associated with potential effective neuroprotective roles and observable anti-seizure effects, owing to the administration of the ketogenic dietary supplementation.

Another potential role for the PPARγ is that these might act directly on the decanoic acid through inhibition of the excitatory ionotropic glutamate AMPA receptors, being competitive antagonists. Many regions with the human brain that are usually involved with the pathogenesis and physiology of epilepsy have been reported with abundant amounts of AMPA receptors. These regions might include the hippocampus and the cerebral cortex. Furthermore, it has been demonstrated that favorable in vivo and in vitro anticonvulsant events have been associated with the presence and action of AMPA receptors.

**CONCLUSION**

The different studies in the literature, with many of which being comparative investigations, have indicated the efficacy of these treatment plans in reducing both the frequency of seizures and adequately inhibiting the development of further epilepsy events. Many mechanisms have been proposed for these treatment modalities to inhibit seizures that are adequately discussed in this article. Based on the current evidence, further awareness approaches should be conducted to increase the administration of these products, especially in pharmacoresistant cases.

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**REFERENCES**