

Review Article

Role of dietary therapy in managing epilepsy in children

Mohammed Saeed Babonji^{1*}, Zahra Abdullah Alkhatir², Adel Abed Alharbi³,
Buthaynah Abdullah Alghasham⁴, Ola Lateef Abumansour⁵, Majed Hassan Ali⁶,
Walaa Mohamed Ali⁷, Nermeen Nasser Alrajhi⁸, Abdulaziz Ali Al Mohammed⁹,
Mutasim Hassan Alhasani¹⁰, Saad Shaker Algethami¹⁰, Salah Mohammed Alzanbagi¹

¹Department of Pediatrics, Al Aziziyah Children Hospital, Jeddah, Saudi Arabia

²Department of Pediatrics, Maternity Children Hospital, Dammam, Saudi Arabia

³Department of Pediatrics, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia

⁴King Khalid Primary Health Center, Ministry of Health, Unizah, Saudi Arabia

⁵College of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia

⁶College of Pharmacy, Almaarefa University, Riyadh, Saudi Arabia

⁷College of Medicine, Mansoura University, Mansoura, Egypt

⁸College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

⁹College of Medicine, King Saud University, Riyadh, Saudi Arabia

¹⁰Department of Pediatrics, King Fahad Hospital, Al Baha, Saudi Arabia

Received: 22 July 2021

Accepted: 07 August 2021

*Correspondence:

Dr. Mohammed Saeed Babonji,

E-mail: Dr.mohammed_babonji1406@hotmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Ketogenic diets have been proposed as effective management approaches that have been validated by many studies in the literature. The efficacy of administering these treatment modalities has been validated by many studies within epilepsy-related syndromes as Rett syndrome, 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. In this literature review, we have discussed the dietary therapeutic approaches for managing epilepsy in children. The findings have been combined from different studies in the literature. Many of them are comparative investigations that 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 pharmaco-resistant cases.

Keywords: Epilepsy, Management, Alternative medicine, Ketogenic diet, Pediatrics

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.^{1,2} 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. The efficacy of administering these treatment modalities has been validated by many studies within epilepsy-related syndromes as Rett syndrome,

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.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 10th 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.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).

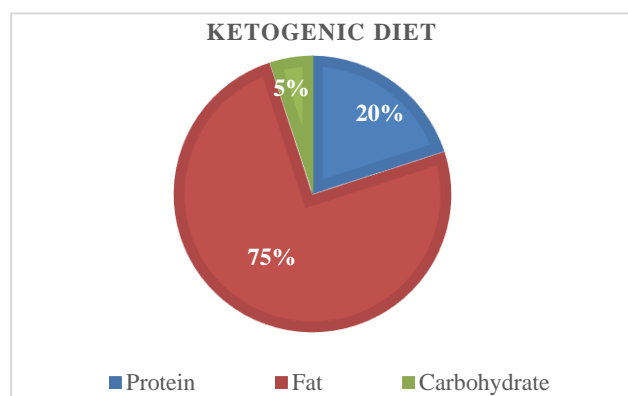


Figure 1: Components of the ketogenic diet for epilepsy.

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.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.^{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.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.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.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.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.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.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.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.^{16,17} Furthermore, Hallbook et al.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.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.^{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.¹⁰ Bone demineralization and mental retardation were also reported among some children. However, the evidence regarding these events is still controversial.^{8,16} Disrupted menstrual cycles and an increased number of bruises are also reported among some children that administered these treatment regimens.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.²¹ In such situations, prophylactic calcium citrate might be indicated.^{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 anti-epileptic 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.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.^{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 measure 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.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.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.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.²⁷ Accordingly, the administration of ketogenic diets has been linked with a significant improvement in the O_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_{ATP}). Within the ingested dietary supplements, the wide availability of the ketone bodies can significantly lead to the opening of the K_{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_{ATP} channels are activated. Activated K_{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_{ATP} .^{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.^{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.²⁸ Enhanced transcriptional activities of peroxisome proliferator-activated receptors (PPAR) have been reported as a result of the sequence of these acetylation activities leading to reduced anti-inflammatory effects through upregulation of the antioxidant endogenous genes.³¹ 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 PPAR α leading to favorable events through inhibition of the pro-inflammatory transcription factor nuclear factor-kappa β , leading to enhanced anti-inflammatory response.³²

In the same context, Medium-chain triglyceride diets were also reported to have abundant amounts of decanoic acid leading to significant activation of PPAR γ .³³ 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 PPAR γ is that these might act directly on the decanoic acid through inhibition of the excitatory ionotropic glutamate AMPA receptors, being competitive antagonists.^{33,34} 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.³⁴

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 pharmaco-resistant cases.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

- Golyala A, Kwan P. Drug development for refractory epilepsy: The past 25 years and beyond. *Seizure*. 2017;44:147-56.
- Kwan P, Schachter S, Brodie M. Drug-Resistant Epilepsy. *New England J Med*. 2011;365:919-26.
- Sirven JI, Drazkowski JF, Zimmerman RS, Bortz JJ, Shulman DL, Macleish M. Complementary/alternative medicine for epilepsy in Arizona. *Neurology*. 2003;61(4):576-7.
- Eun SH, Kang HC, Kim DW, Kim HD. Ketogenic diet for treatment of infantile spasms. *Brain Dev*. 2006;28(9):566-71.
- Liebhaber GM, Riemann E, Baumeister FA. Ketogenic diet in Rett syndrome. *J Child Neurol*. 2003;18(1):74-5.
- Caraballo RH, Cersosimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. Ketogenic diet in patients with Dravet syndrome. *Epilepsia*. 2005;46(9):1539-44.
- Klepper J, Scheffer H, Leidencker B, Gertsen E, Binder S, Leferink M, Hertzberg C, et al. Seizure control and acceptance of the ketogenic diet in GLUT1 deficiency syndrome: a 2- to 5-year follow-up of 15 children enrolled prospectively. *Neuropediatrics*. 2005;36(5):302-8.
- Kossoff EH, Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. *J Child Neurol*. 2009;24(8):979-88.
- Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr*. 2002;76(1):5-56.
- Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. *Cochrane Database System Rev*. 2016;2:1903.
- Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol*. 2008;7(6):500-6.
- Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. *Epilepsia*. 2013;54(3):481-6.
- Lambrechts DA, Kinderen RJ, Vles JS, Louw AJ, Aldenkamp AP, Majoie HJ. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. *Acta Neurol Scand*. 2017;135(2):231-9.
- Hallbook T, Sjolander A, Amark P, Miranda M, Bjurulf B, Dahlin M. Effectiveness of the ketogenic diet used to treat resistant childhood epilepsy in Scandinavia. *Eur J Paediatr Neurol*. 2015;19(1):29-36.
- Klein P, Tyrlikova I, Mathews GC. Dietary treatment in adults with refractory epilepsy: a review. *Neurology*. 2014;83(21):1978-85.
- Groesbeck DK, Bluml RM, Kossoff EH. Long-term use of the ketogenic diet in the treatment of epilepsy. *Dev Med Child Neurol*. 2006;48(12):978-81.

17. Martinez CC, Pyzik PL, Kossoff EH. Discontinuing the ketogenic diet in seizure-free children: recurrence and risk factors. *Epilepsia*. 2007;48(1):187-90.
18. Hallbook T, Lundgren J, Rosén I. Ketogenic diet improves sleep quality in children with therapy-resistant epilepsy. *Epilepsia*. 2007;48(1):59-65.
19. IJff DM, Postular D, Lambrechts DAJE, Majoie MHJM, Kinderen RJA, Hendriksen JGM, et al. Cognitive and behavioral impact of the ketogenic diet in children and adolescents with refractory epilepsy: A randomized controlled trial. *Epilepsy Behav*. 2016;60:153-7.
20. Mady MA, Kossoff EH, McGregor AL, Wheless JW, Pyzik PL, Freeman JM. The ketogenic diet: adolescents can do it, too. *Epilepsia*. 2003;44(6):847-51.
21. Kossoff EH, Kania BA, Amark PE, Gil KR, Christina BAG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia*. 2009;50(2):304-17.
22. Hartman AL, Gasior M, Vining EP, Rogawski MA. The neuropharmacology of the ketogenic diet. *Pediatr Neurol*. 2007;36(5):281-92.
23. Yudkoff M, Daikhin Y, Melo TM, Nissim I, Sonnewald U, Nissim I. The ketogenic diet and brain metabolism of amino acids: relationship to the anticonvulsant effect. *Annual review of nutrition*. 2007;27:415-30.
24. Dahlin M, Elfving A, Ungerstedt U, Amark P. The ketogenic diet influences the levels of excitatory and inhibitory amino acids in the CSF in children with refractory epilepsy. *Epilepsy Res*. 2005;64(3):115-25.
25. Bough K. Energy metabolism as part of the anticonvulsant mechanism of the ketogenic diet. *Epilepsia*. 2008;49(8):9.
26. Lima PA, Sampaio LP, Damasceno NR. Neurobiochemical mechanisms of a ketogenic diet in refractory epilepsy. *Clinics*. 2014;69(10):699-705.
27. Boison D. New insights into the mechanisms of the ketogenic diet. *Current Opinion Neurol*. 2017;30(2):187-92.
28. Simeone TA, Simeone KA, Rho JM. Ketone Bodies as Anti-Seizure Agents. *Neurochem Res*. 2017;42(7):2011-18.
29. Ma W, Berg J, Yellen G. Ketogenic diet metabolites reduce firing in central neurons by opening K(ATP) channels. *J Neurosci*. 2007;27(14):3618-25.
30. Yellen G. Ketone bodies, glycolysis, and KATP channels in the mechanism of the ketogenic diet. *Epilepsia*. 2008;49(8):80-2.
31. Jeong EA, Jeon BT, Shin HJ, Kim N, Lee DH, Kim HJ, et al. Ketogenic diet-induced peroxisome proliferator-activated receptor- γ activation decreases neuroinflammation in the mouse hippocampus after kainic acid-induced seizures. *Exp Neurol*. 2011;232(2):195-202.
32. Donald TJW, Cervenka MC. Ketogenic Diets for Adult Neurological Disorders. *Neurotherapeutics*. 2018;15(4):1018-31.
33. Knowles S, Budney S, Deodhar M, Matthews SA, Simeone KA, Simeone TA. Ketogenic diet regulates the antioxidant catalase via the transcription factor PPAR γ 2. *Epilepsy Res*. 2018;147:71-4.
34. Chang P, Augustin K, Boddum K, Williams S, Sun M, Terschak JA, et al. Seizure control by decanoic acid through direct AMPA receptor inhibition. *Brain*. 2016;139(2):431-43.

Cite this article as: Babonji MS, Alkhatir ZA, Alharbi AA, Alghasham BA, Abumansour OL, Ali MH, et al. Role of dietary therapy in managing epilepsy in children. *Int J Community Med Public Health* 2021;8:4580-4.