

KETOGENIC DIETARY TREATMENT OF REFRACTORY EPILEPSY IN CHILDREN: NARRATIVE REVIEW

Yasmin Czervenny Schoemberger

Universidade Positivo

Curitiba - Paraná

<http://lattes.cnpq.br/0231091652621727>

Luiza Maria Pereira

Universidade Positivo

Curitiba - Paraná

<http://lattes.cnpq.br/3518544281420836>

Maria Augusta Pacheco Jacobsen

Universidade Positivo

Curitiba - Paraná

<https://lattes.cnpq.br/8799169327334427>

Beatriz Vicenzi Rocha

Universidade Positivo

Curitiba - Paraná

<https://lattes.cnpq.br/0266938159839537>

Rafaella Smaniotto Santana

Universidade Positivo

Curitiba - Paraná

<https://lattes.cnpq.br/7455253571613079>

Luísa Garbossa

Universidade Positivo

Curitiba - Paraná

<http://lattes.cnpq.br/8322556400375156>

Ana Luisa Trentini Bittencourt

Universidade Positivo

Curitiba - Paraná

<http://lattes.cnpq.br/8556501076131907>

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Sophia Lugarini

Universidade Positivo

Curitiba - Paraná

<https://lattes.cnpq.br/6052806719822866>

Lorenzo De Santiago Biesuz

Universidade Positivo

Curitiba - Paraná

<https://lattes.cnpq.br/4652290080975076>

Selton Eliezer Steniski

Universidade Positivo

Curitiba - Paraná

<https://lattes.cnpq.br/2328790850296377>

Rafael Schmid Scapini

Universidade Positivo

Curitiba - Paraná

<https://lattes.cnpq.br/6541941718437594>

João Victor Hertel Fiates

Universidade Positivo

Curitiba - Paraná

<https://lattes.cnpq.br/2397682725289440>

Isabelli Zeitz de Castro

Universidade Positivo

Curitiba - Paraná

<http://lattes.cnpq.br/9699695660736416>

Abstract: Epilepsy is a neurological condition resulting from a genetic abnormality or acquired brain damage, characterized by regular and disparate convulsive episodes. Refractory epilepsy, a drug-resistant category, is very common in children and lacks alternative treatments. Therefore, the ketogenic diet - a diet rich in lipids, moderate in proteins and low in carbohydrates - appears as a nutritious and less invasive alternative for pediatric patients with this condition. The objective of this article was to evaluate and discuss the functionality of ketogenic dietary treatment in children with refractory epilepsy, as well as its mechanism of action.

To this end, a narrative review of studies was carried out in the *PubMed/Medline* and *SciELO* public and open access databases, using the indexing terms Ketogenic Diet, Refractory Epilepsia and Children, associated with the Boolean connectors AND, OR and NOT, among the years from 2002 to 2020, restricted to Portuguese and English languages. Abstracts of presentations and meetings, editorials, review articles and studies without sufficient data and other articles that did not meet the inclusion criteria were excluded: articles that included in their primary resolution the effectiveness of ketogenic dietary treatment in children, from 1 year to 13 years, with refractory epilepsy. When carrying out the advanced search, 675 articles were identified in *PUBMED/Medline* and 13 in *SciELO*. Then, 11 articles were selected according to the established inclusion and exclusion criteria. Analyzing the selected studies, 8 positive results and 7 adverse effects were found in pediatric patients undergoing ketogenic dietary treatment. It was concluded, from this research, that the ketogenic diet is a therapy used in the treatment of children with refractory epilepsy. Its function is to modulate neurotransmitters through the production of ketone bodies, controlling epileptic seizures

and proving beneficial to children who do not respond adequately to conventional medications, despite the existence of reversible adverse effects.

Keywords: Refractory Epilepsy. Convulsive Crisis. Alternative Therapy. Diet therapy. Pediatric Patients.

INTRODUCTION

Epilepsy is a neurological condition resulting from a genetic pathology or an acquired brain injury, characterized by the occurrence of frequent convulsive episodes - synchronous or excessive activity of neurons in the brain - causing transient abnormal signs or symptoms, such as changes in consciousness, involuntary movements, autonomic or psychiatric events. (FISHER et al, 2010). This chronic disease affects 0.5% to 1% of the world's population and 60% of cases begin during childhood, becoming serious at this early stage of life, as it influences the child's growth and development process (ZUBERI et al, 2015).

Refractory epilepsy arises when the disease is resistant to treatment using traditional medicines. This drug resistance is a multicausal phenomenon and the use of alternative therapies, such as the ketogenic diet, may be an appropriate choice to improve outcomes in the pediatric patient population. (PEREIRA et al, 2010).

Ketogenic dietary treatment, developed by researcher Rollin Woodyatt in 1921, is recommended mainly for children, as it is less invasive than traditional medicines and consists of a therapeutic diet abundant in oils and lipids, moderate in proteins and low in carbohydrates (PEREIRA et al, 2010). The foods recommended for intake during the therapy period are indicated in the following table, by Lima et al, 2018.

Taking the aforementioned foods into consideration, the treatment of refractory

epilepsy becomes lighter and tastier, expanding its access to a larger group of people (SAMPAIO et al, 2016). And, in addition, as one of its effects is to reduce the frequency of seizures, it provides a better quality of life for the individual (MARTIN-MCGILL et al, 2020).

The ketogenic diet is referred to as diet therapy, which, due to its composition, is capable of subjecting the individual to a ketogenic state of human metabolism. Depending on the disorder being treated, there are different diet therapies that have been developed in order to increase retention and palatability, which, synchronously, imitate the effects produced by the Original Ketogenic Diet. They are: Classic Ketogenic Diet (cKD), Medium Chain Triglyceride Ketogenic (MCTKD), Modified Atkins (MAD) and low glycemic index treatment (LGIT). (WELLS et al, 2020).

When carrying out research on individuals undergoing the Classic Ketogenic Diet, Woodyatt found the presence of Acetoacetate, Beta-Hydroxybutyrate and Acetone, compounds that affect the body's oxidative stress, consequently improving human neuronal functions and, simultaneously, refractory epilepsy. (WHELESS et al, 2015).

At the same time, according to clinical observations carried out by Doctor Wildner, from the Mayo Clinic, in Minnesota, in the United States, it was observed in practice that the increase in lipid intake in the diet of epileptic children caused a reduction of around 50% of convulsive episodes in those children. who had the disease in its incurable aspect, opposing old theories that predicted prolonged fasting as a possible solution, which, in addition to reducing children's quality of life, did little to reduce the occurrence of nervous disorders. (PEREIRA et al, 2010).

Given what was described, the present work aimed to evaluate and discuss the

FATS GROUP	MEAT GROUP	GROUP OF VEGETABLES	GROUP OF TUBERS	GROUP OF FRUITS	BEVERAGE GROUP
Vegetable oil, dairy-free butter/margarine and mayonnaise.	Beef, pork, fish, sausages and processed meats.	Carrot, eggplant, pumpkin, tomato and green leaves.	Potatoes, beets, cassava, yams and yams.	Avocado, strawberry, papaya and mango. Except bananas and oranges.	Unsweetened teas, natural lemon juice and almond milk.

Table 1: List of foods recommended for intake during ketogenic dietary treatment

Source: (LIMA et al, 2014)

functionality of ketogenic dietary treatment in children with refractory epilepsy, as well as its mechanism of action.

METHODOLOGY

For this narrative review, a search was carried out in the databases *Medical Literature Analysis and Retrieval System Online (Pubmed/Medline)* and SciELO, with public and open access, between 2002 and 2020, restricted to Portuguese and English languages. The following indexing terms were used to search for articles: *Ketogenic Diet, Refractory Epilepsy and Children*, as well as the combination and correlation of these words and expressions. The search was performed using the indexing terms associated with the Boolean connectors *AND, OR and NOT*.

The titles and abstracts of all studies identified by the search on electronic platforms were selected according to the following inclusion criteria: articles that included in their primary resolution the effectiveness and use of ketogenic dietary treatment in children, from 1 year to 13 years, carriers of refractory epilepsy.

All articles that evaluated the applicability of the ketogenic diet in children with any pathology or chronic disease other than refractory epilepsy were excluded, as well as those that did not evaluate the effect of ketosis on lipid metabolism after dietary intervention. In addition, abstracts of presentations and meetings, editorials, review articles and studies without sufficient data were excluded.

Articles considered relevant were read in

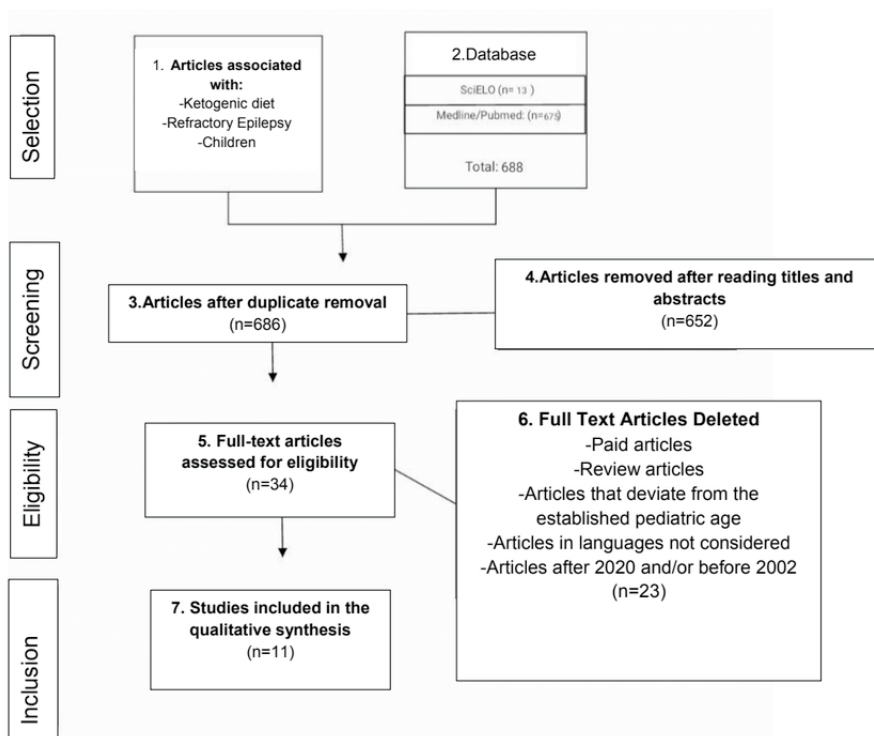
full for evaluation following the inclusion and exclusion criteria. Furthermore, other articles were added to this narrative review, with the aim of contextualizing and complementing the debate on the topic.

RESULTS

In isolation, when searching for the index term *Ketogenic Diet and Ketogenic Diet*, 4,668 articles were identified in PUBMED/Medline and 50 in Scielo. The search term *Refractory Epilepsy and Refractory Epilepsia* found 17,356 articles in PUBMED/Medline and 269 in Scielo. Finally, the search term *Children and Children* found 3,096,192 articles in PUBMED/Medline and 47,531 in Scielo. When carrying out the advanced search, using Boolean operators, combining the terms *Ketogenic Diet AND Refractory Epilepsy AND Children* and their correlates in Portuguese, 675 articles were identified in PUBMED/Medline [2] and 13 in Scielo [2].

Next, 652 articles were excluded, as shown in the study selection flow diagram [4], namely: articles that are repeated, paid articles that make it impossible to read the entire article for free, review articles, documents that do not address the effects of the ketogenic diet on refractory epilepsy in children aged 1 to 13 years, texts written in languages other than Portuguese and English and studies from years before 2002 and after 2020.

Finally, 11 articles were selected [7], which met the pre-specified eligibility criteria [6]. It is possible that there are other articles that have not been published by the date of the



Flowchart: Articles consulted

SOURCE: The authors (2023)

Author/ Year of publication / Country of Study	Effect of ketogenic diet on refractory epilepsy
Dressler A.; Stöcklin B.; Reithofer E.; Benninger F.; Freilinger M.; Hauser E.; Reiter-Fink E.; Seidl R.; Trimmel-Schwahofer P.; Feucht M. 2010. Áustria.	It demonstrated the positive long-term results and tolerability of the ketogenic diet in patients aged approximately 4 years with drug-resistant epilepsy.
Freitas A.; Paz J. A.; Casella E. B.; Marques-Dias M. J. 2007. Brazil.	In cases of refractory epilepsy in children, the ketogenic diet is a good anti-epileptic treatment. Age-related differences were not found and there were significant reductions in antiepileptic drug use. The children also showed improvements in cognitive skills.
Karimzadeh P.; Sedighi M.; Beheshti M.; Azargashb E.; Ghofrani M.; Abdollahe-Gorgi F. 2014. Irã.	The use of the ketogenic diet reduced seizures by 50% in 71.4% of pediatric patients, after the second week of treatment. At the end of the first month, there was a reduction of 73.8% and, at the end of the second month, 77.8%.
Lima P. A.; Sampaio L. P.; Damasceno N. R. 2014. Brazil.	The main effects on the production of the ketone body are the modulation of neurotransmitters and the result of oxidant reactions in the brain, reflecting the positive consequences of using the ketogenic diet for refractory epilepsy.
Luz I. R.; Pereira C.; Garcia P.; Ferreira F.; Faria A.; Macedo C.; Diogo L.; Robalo C. 2019. Portugal.	The effects of the ketogenic diet are not limited to controlling seizures, they also include improving the child's behavior and consciousness.
Pong A. W.; Geary B. R.; Engelstad K. M.; Natarajan A.; Yang H.; De Vivo D. C. 2012. United States.	The ketogenic diet provides ketones to treat the neuroglycopenia of GLUT Deficiency Syndrome 1. More than 50% of pediatric patients had reduced epileptic episodes and 68% of them were completely seizure free.
Rebollo G. M. J.; Díaz S. M. X.; Soto R. M.; Pacheco A. J.; Witting E. S.; Daroch R. I.; Moraga M. F. 2020. Spain.	The ketogenic diet is a useful, non-pharmacological treatment. In pediatric patients with drug-resistant epilepsy, it is effective and has no nutritional impact.

Rizzutti S.; Ramos A. M.; Cintra I. P.; Muszkat M.; Gabbai A. A. 2006. Brazil.	The ketogenic diet may be a safe and effective way to treat children with refractory epilepsy. The adverse effects were reversible and the growth curve was not affected, maintaining adequate weight and height.
Rogovik A. L.; Goldman R. D. 2010. Canada.	The ketogenic diet must be considered a treatment option for children with refractory epilepsy. Strictly speaking, the diet's lack of palatability and side effects limit its use and adversely affect patient compliance and clinical efficacy.
Herrero J. R.; Villarroya C. E.; Peñas G. J.; Alcolea G. B.; Gómez F. B.; Macfarland P. L. A.; Giner P. C. 2020. Spain.	The ketogenic diet, when used to treat refractory epilepsy, has side effects that, although common, are very mild.
Herrero R. J.; Villarroya C. E.; Sebastián P. I.; Cuesta B.; Giner P. C. 2021. Spain.	Treatment with the ketogenic diet, despite its side effects, appears to be a safe and effective way to treat childhood epilepsy, especially refractory epilepsy.

Table 2: Summary of articles

Source: The Authors (2023)

research or have been published in a language not covered by this narrative review.

DISCUSSION

The current narrative review of the literature sought to identify the functionality of ketogenic dietary treatment in children with refractory epilepsy, as well as its mechanism of action.

Initially, Pereira et al. (2010) characterized refractory epilepsy as a drug-resistant aspect of epilepsy and proved that the ketogenic diet is essential for children in whom traditional epilepsy treatment does not produce effective changes in frequent seizures. Meanwhile, Rebollo et al. (2020) added that the ketogenic diet is a useful and non-pharmacological, therefore non-invasive, treatment for children aged 2 to 12 years. Martin-McGill et al. (2020), in addition to adding the same, considered the ease of ketogenic dietary treatment in children, as it is tasty and easy to implement.

In contrast, Luz et al. (2019), Karimzadeh et al. (2014) and Rogovik et al. (2010) argued that there is a lack of food attractiveness in the ketogenic diet, which reduces children's adherence to treatment. Furthermore, Luz et al. (2019) summarized that the diet not only acts to improve epileptic seizures, but also promotes positive actions in the child's

behavior and consciousness. Luz et al. (2019) concluded that the ketogenic diet is an effective and safe therapeutic option for pediatric patients with refractory epilepsy, but it must be approached in a more attractive way to increase treatment adherence.

Furthermore, Freitas et al. (2007) proved that the ketogenic diet is effective for children with difficult-to-control epilepsy, observing fewer harmful effects when compared to other alternatives for controlling seizures.

When verifying the mechanism of action of the ketogenic diet in children, Lima et al. (2014) demonstrated that the main effects on the production of the ketone body are the modulation of excitatory and inhibitory neurotransmitters, such as glutamate and gamma-aminobutyric acid (GABA), stimulating them in their formation, helping to control convulsive crises and also as a result of oxidizing reactions in the brain. Lima et al. (2014) determined that these effects reflect the positive consequences of using the ketogenic diet for refractory epilepsy in children up to 2 years old, where the transport of monocarboxylic acids is still consistent, without the maturation of the adult brain. Furthermore, Pong et al. (2012) highlighted that dietary metabolism provides ketones to treat neuroglycopenia - symptoms triggered

by insufficient glucose supply to the brain - helping with GLUT 1 syndrome, a genetic disorder that affects brain metabolism, being one of the reasons why a epilepsy is characterized as refractory.

Among the studies evaluated, Dressler et al. (2010) found that 50% of pediatric patients responded to ketogenic dietary treatment, with 48% not experiencing seizures again. In children who responded to the experiment, epileptic activity on scans improved significantly and a much lower rate of epileptic discharges was observed after 6 months, as well as a shorter duration of refractory epilepsy. Karimzadeh et al. (2014) reported that the average frequency of seizures reduced by 50% in the first weeks of pediatric treatment, 73.8% at the end of the first month and 77.8% at the end of the second month, without interference from child age, sex and type of seizure (partial or focal), proving the effectiveness of the diet in the treatment of refractory epilepsy in children. Furthermore, Freitas et al. (2007) concluded that in addition to improvement in the disease, there was also an improvement in the cognitive abilities of patients undergoing ketogenic diet treatment.

Despite the high incidence of positive results, there was a considerable incidence of side effects of the ketogenic diet in pediatric patients. Rebollo et al. (2020) and Freitas et al. (2007) described that, in a short period, some adverse reactions were observed in children, the main ones being asymptomatic hypoglycemia and gastrointestinal disorders, such as: vomiting, constipation and diarrhea. Furthermore, Rebollo et al. (2020) investigated effects when the ketogenic diet was used long-term, such as hypercalciuria and dyslipidemia. Rizzutti et al. (2006) noticed drowsiness in pediatric patients treated through ketosis. In addition to these adverse reactions, Herrero et al. (2020) highlighted electrolyte abnormalities and acidosis as a consequence

of the ketogenic diet.

However, Herrero et al. (2020) also explained that, like any treatment, it is essential to be cautious in relation to nutritional deficiencies and anthropometric disorders that may emerge due to the nutritional distribution of the ketogenic diet. In contrast, Rizzutti et al. (2006) stated that weight and height growth is not affected, with weight and height following the appropriate percentile despite dietary restriction. Herrero et al. (2020), pointed out that one of the ways to avoid these side effects is the correct distribution of foods within the regimen, so that nutrients, vitamins, carbohydrates, lipids and proteins are calculated individually for each child and, in case of the presence of side effects, recalculated.

Finally, Rebollo et al. (2020), Freitas et al. (2007), Rizzutti et al. (2006), Herrero et al. (2020) and Luz et al. (2019), concluded that treatment with a ketogenic diet causes adverse events in children that are of low severity and easy to resolve, making it an effective, safe and easy to reverse therapy, compared to the mixture of drugs used in an attempt to treat epilepsy. refractory.

Due to the results of studies that address the ketogenic diet as a treatment for refractory epilepsy presenting mostly positive results, future expectations for improving and establishing the ketogenic diet as an effective alternative therapy are high, since, by using it, it is possible reduce the exposure of pediatric patients to chemical drugs that cause drastic and irreversible side effects.

Aiming at future clinical applications of the ketogenic diet, it is necessary to carry out a more in-depth study on the adverse effects of ketogenic dietary treatment, so that they are drastically reduced and become even less relevant, compared to the positive effects and effects side effects of traditional medicines.

No studies were found that addressed

the difference between the action of the ketogenic diet on the cellular mechanism of children with refractory epilepsy and the cellular mechanism of children without this pathology. Furthermore, a low incidence of national studies and an occasional occurrence of studies with small samples were observed.

CONCLUSION

Considering all the studies evaluated, it is concluded that the ketogenic diet - an alternative treatment based on a high consumption of lipids, moderate protein and low carbohydrates - reduces oxidative reactions in the brain of epileptic children, consequently reducing their seizures. This

type of diet is particularly beneficial in cases where children do not respond adequately to conventional medications. Therefore, research has highlighted the relevance of this diet therapy to improve the quality of life of children with epilepsy, by reducing the frequency of seizures. Although some side effects have been observed in pediatric patients undergoing ketogenic dietary treatment, it is important to highlight that they are reversible, not very relevant when compared to the abundance of positive effects and adverse reactions of traditional epileptic medications, and can be the target of clinical studies. futures that aim to reduce them even further.

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