KAROŃ, Łukasz Mikołaj, ZYGMUNT, Anna, KAROŃ, Karolina, GRABOWSKI, Wojciech, DRAPAŁA, Grzegorz, PEDRYCZ, Emilia and PEDRYCZ, Daria. Metabolic Reprogramming via Ketogenic Diet: A Novel Approach to Combating Neurological Diseases. Journal of Education, Health and Sport. 2024;70:55722. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.70.55722
https://apcz.umk.pl/JEHS/article/view/55722

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received:20.09.2024. Revised: 21.10.2024. Accepted: 25.10.2024. Published: 28.10.2024.

Metabolic Reprogramming via Ketogenic Diet: A Novel Approach to Combating Neurological Diseases

Authors:

1. Łukasz Karoń

- affiliation: Department of Pathology and Molecular Diagnostics, Medical University of Silesia in Katowice

- ORCID: 0009-0009-5083-8307

2. Anna Zygmunt

- affiliation: Department of Pathology and Molecular Diagnostics, Medical University of Silesia in Katowice

- ORCID: 0009-0002-5849-6347

- corresponding author: e-mail: zyginana@icloud.com

3. Karolina Karoń

- affiliation: Municipal Hospital in Zabrze

- ORCID: 0009-0005-0356-8907

4. Wojciech Grabowski

- affiliation: Municipal Hospital in Zabrze

- ORCID: 0009-0006-9238-1411

5. Grzegorz Drapała

- affiliation: Wojewodzki Szpital Zespolony w Kielcach

- ORCID: 0009-0008-1492-1544

6. Emilia Pedrycz
- affiliation: Wojewodzki Szpital Zespolony w Kielcach
- ORCID: 0009-0006-2751-2227
7. Daria Pedrycz
- affiliation: Department of Family Medicine, Medical University of Białystok
- ORCID: 0009-0001-4988-5992

Keywords: epilepsy, ketogenic diet, drug-resistant epilepsy, non-pharmacological therapy, ketosis, Atkins diet.

Abstract

Epilepsy is a chronic neurological disorder characterized by a persistent tendency for the brain to generate seizures, affecting approximately 0.5–1% of the global population. Despite advances in pharmacological treatments and surgical interventions, around 30% of individuals with epilepsy continue to experience seizures, leading to significant impacts on quality of life. Among these individuals, many suffer from drug-resistant epilepsy (DRE), where seizures persist despite optimal drug therapy or surgical interventions.

In recent years, the ketogenic diet (KD)—a high-fat, low-carbohydrate dietary regimen—has emerged as an effective non-pharmacological strategy for managing DRE. The KD works by inducing ketosis, a metabolic state where the body uses fat as the primary energy source instead of carbohydrates, which has been associated with neuroprotective effects and significant seizure reduction. Variants of the KD, such as the Modified Atkins Diet (MAD) and Low Glycemic Index Treatment (LGIT), offer less restrictive alternatives that have shown similar efficacy in reducing seizure frequency.

This review explores the cellular and molecular mechanisms of the KD, evaluates its safety and tolerability across different age groups, and assesses its efficacy in treating epilepsy, particularly DRE. The findings underscore the potential of personalized dietary interventions to serve as effective adjunctive therapies in the management of epilepsy, offering new hope for individuals who do not respond to conventional treatments.

Introduction

Epilepsy stands as a chronic and debilitating neurological disorder marked by the enduring predisposition of the brain to generate seizures—a condition affecting a global populace with

a prevalence rate of 0.5–1% and a lifetime incidence of 1–3% (1). Despite advancements in pharmacological treatments and surgical interventions, approximately 30% of individuals living with epilepsy continue to suffer from seizures throughout their lives, underscoring a substantial impact on both societal and global health scales. Among these individuals, a significant proportion is categorized under the umbrella of drug-resistant epilepsy (DRE)—a condition wherein seizures persist in spite of the administration of optimal drug therapy or after surgical interventions have been attempted (2).

In recent years, the ketogenic diet (KD)—a high-fat, low-carbohydrate regimen—has emerged as an efficacious non-pharmacological strategy for managing DRE. Endorsed by accumulating clinical data, KD and its variations, including the modified Atkins diet, have demonstrated considerable potential in mitigating epileptogenesis through the biochemical cascade triggered by physiological ketosis. Furthermore, these dietary manipulations have proven both safe and tolerable across diverse demographic groups, including both pediatric and adult populations (3)(1).

The ketogenic diet operates on the premise of inducing a state of ketosis, where the body utilizes fat as the primary energy source instead of carbohydrates. This metabolic shift has been credited with neuroprotective properties, presenting a viable therapeutic avenue for individuals struggling with epilepsy. Given the pressing need to address the limitations of current therapeutic strategies and the rising prevalence of DRE, a comprehensive exploration of dietary interventions offers a promising adjunctive therapeutic pathway.

This paper aims to better understand how diets, especially the ketogenic diet, could change the way epilepsy is treated. By looking at how these diets work at the cellular level, checking their safety for different age groups, and seeing how effective they are, the goal is to develop more personalized dietary treatments.

Classic ketogenic diet (KD)

The classical ketogenic diet is a rigorous, carefully calculated, high-fat, low-carbohydrate diet that has been used effectively in the treatment of epilepsy and other neurological disorders. Its principle hinges on inducing a physiological state of ketosis, where the body transitions from utilizing glucose as its primary energy source to burning fats, leading to the production of ketones. The diet's efficacy in controlling seizures has been well-documented across various studies, highlighting its benefits especially for those with drug-resistant epilepsy. One variant of the ketogenic diet, known as the classical ketogenic diet, maintains a strict 4:1 ratio of fats

to carbohydrates and proteins. This regimen has shown promise in reducing seizure frequency and improving the quality of life for patients with pharmacoresistant epilepsy, notwithstanding concerns regarding potential long-term cardiovascular risks owing to its high-fat content (4).

Despite its challenges and strict dietary restrictions, the classical ketogenic diet, alongside other variants like the modified Atkins diet and medium-chain triglyceride ketogenic diet, provides a viable alternative to traditional seizure medications, particularly for pediatric populations and, with growing evidence, for adults as well (5)(6). Long-term adherence to this diet has been associated with significant control over seizures, although it poses certain risks such as slowed growth, kidney stones, and potential cardiovascular impacts requiring careful monitoring (7). The diet's implementation requires meticulous planning and monitoring by healthcare professionals to mitigate adverse effects and ensure patient safety, thereby improving compliance and maintaining its therapeutic efficacy (1).

Modified Atkins Diet (MAD)

The Modified Atkins Diet (MAD) is a less restrictive variant of the classical ketogenic diet, designed to induce ketosis through a high-fat, low-carbohydrate regimen, offering an alternative therapeutic option for managing epilepsy in both children and adults. Unlike the classical ketogenic diet that requires a strict ratio of fats to carbohydrates and protein, MAD allows for a more flexible eating plan, emphasizing fat intake while limiting carbohydrates to a set amount per day without strict calorie or fluid intake restrictions (8)(9). This approach has gained popularity due to its efficacy in seizure control and its improved palatability and tolerability compared to more restrictive diets (10).

MAD has demonstrated significant efficacy in reducing seizure frequency, with various studies reporting substantial reductions in adult and adolescent populations (10). Its implementation has shown that it can be a successful management strategy for drug-resistant epilepsy, with fewer side effects and potential health benefits beyond seizure control, such as weight management and improved metabolic profiles (8). Despite its benefits, successful application of MAD, similar to other ketogenic dietary therapies, requires careful planning and monitoring to mitigate potential side effects and ensure dietary adherence and effectiveness (1)(11).

Low glycemic index treatment (LGIT)

Low Glycemic Index Treatment (LGIT) is a dietary approach specifically designed for managing epilepsy, characterized by the consumption of foods that have a low glycemic index (GI). This method focuses on controlling seizures by modulating blood glucose levels and promoting a mild state of ketosis, without the strict fat-to-carbohydrate ratios inherent in the classical ketogenic diet or the Modified Atkins Diet. LGIT encourages the intake of carbohydrates that result in a slower and more gradual increase in blood glucose levels, thereby potentially reducing the frequency of epileptic seizures. Although LGIT is less restrictive and may offer a more palatable and feasible option for long-term adherence, it maintains the principle of limiting glucose intake to influence the metabolic changes associated with seizure control (4).

The efficacy and tolerability of LGIT have been explored in various studies, suggesting that this diet can be a beneficial alternative therapy for patients with drug-resistant epilepsy, including both children and adults. Research has demonstrated that LGIT can lead to significant reductions in seizure frequency, with the advantage of being associated with milder side effects compared to more restrictive ketogenic diets (12)(2). Given its emphasis on low-GI foods, LGIT may also present a more manageable and sustainable diet for patients with intractable epilepsy, promoting better long-term compliance while optimizing seizure control (1).

Medium-chain triglyceride diet (MCTD)

The Medium-Chain Triglyceride (MCT) diet is a specialized form of ketogenic diet therapy that emphasizes the consumption of fats in the medium-chain triglyceride form, rather than the long-chain fats predominantly found in typical diets. This approach allows for a greater proportion of carbohydrates and proteins than traditional ketogenic diets while still maintaining the body in a state of ketosis, where it burns fat for energy instead of carbohydrates. The MCT diet's distinct advantage lies in the metabolism of medium-chain triglycerides, which are rapidly absorbed and metabolized by the liver, leading to efficient ketone production. This can be especially beneficial in managing epilepsy, offering an alternative for those who may find the restrictions of classical ketogenic diets challenging to maintain over time.

While the MCT diet has been primarily considered in pediatric epilepsy management, recent research and interest have expanded its application to adults, recognizing its potential benefits in managing drug-resistant seizures and other neurological conditions. The efficacy of the

MCT diet, along with patient compliance rates, has been encouraging, indicating that it can offer a promising complementary therapy for intractable epilepsy in adults, potentially with fewer dietary restrictions and more flexibility than classical ketogenic or Atkins diets (6) (13). However, adherence to such dietary therapies remains a challenge, underscoring the need for effective support and educational strategies to help patients and their families navigate the treatment (14). Moreover, the specialized nature of dietary treatment for epilepsy, including the MCT diet, requires strong motivation from patients, relatives, and careful follow-up from healthcare providers to ensure success and mitigate potential adverse effects (15).

Pathophysiology of the ketogenic diet and epilepsy

The pathophysiology of the ketogenic diet (KD) in epilepsy involves multiple complex mechanisms, reflecting its multifaceted impact on the brain's function and energy metabolism. The core principle of the KD, a high-fat and low-carbohydrate regimen, induces a state of ketosis, where ketone bodies become the primary source of energy instead of glucose, mimicking the metabolic effects of fasting on the brain. This metabolic shift is thought to enhance mitochondrial function and energy production, potentially stabilizing neuronal membranes and reducing neuronal excitability (1).

Furthermore, the diet's influence extends to altering the expression and function of neurotransmitters, such as gamma-aminobutyric acid (GABA) and glutamate, which are critical in the regulation of neuronal excitability. The ketogenic state is believed to increase the synthesis of GABA, a major inhibitory neurotransmitter in the brain, thereby exerting an antiepileptic effect through the suppression of neural overactivity (4).

The efficacy of KD in reducing seizures has been well documented across various age groups, seizure types, and epilepsy syndromes, with studies reporting significant seizure reduction and even seizure freedom in some cases. Meta-analyses and randomized controlled trials have highlighted the diet's effectiveness, revealing that patients on KD show a higher likelihood of achieving more than a 50% reduction in seizure frequency compared to those discontinuing the diet (16)(17).

While the precise mechanisms through which KD exerts its antiepileptic effects remain incompletely understood, the diet's impact on enhancing brain energy metabolism, altering neurotransmitter levels, and modulating neuroinflammation are considered key factors. Despite its proven efficacy, the KD's restrictiveness, potential side effects, and the need for

close medical supervision limit its widespread use, with patient compliance playing a crucial role in its clinical effectiveness (18).

Indications for the use of the ketogenic diet in epilepsies

The utility of the ketogenic diet (KD) as a treatment modality spans a growing array of indications in the realm of epilepsies, particularly for those forms resistant to pharmacological treatments. Initially devised as a means to mimic the metabolic state of fasting, KD has re-emerged as a vital intervention for managing drug-resistant epilepsy in both children and adults, demonstrating success in reducing the frequency and severity of seizures (19). Even more, considerations have expanded towards the feasibility and safety of this dietary approach in mitigating acute status epilepticus when conventional antiseizure medications or anesthetic agents prove ineffective.

Scientific inquiries have elucidated the KD's effects across different versions and ratios in managing epilepsy, underscoring its adaptability and potential for tailored treatment strategies (20). Whether for children or adults, the diet's adjustment to individual needs—be it through classical formulations or less restrictive variants—emphasizes the significance of patient-centric interventions to enhance efficacy and tolerability (21).

The underpinning mechanisms, ranging from impacts on neurotransmission and neuro-inflammation to modulation of oxidative stress, align with the positive outcomes observed in seizure control and cognitive benefits. This underlies the KD’s application not only in epilepsy management but also its exploratory use in other neurological disorders, accentuating a neuroprotective profile that could transcend traditional seizure-related outcomes (22).

Clinical efficacy in the treatment of epilepsy

The clinical efficacy of the ketogenic diet (KD) in treating epilepsy has been well-documented across multiple research studies, showcasing its significant impact in reducing seizure frequencies in both pediatric and adult populations dealing with drug-resistant epilepsy. The KD, characterized by its high-fat and low-carbohydrate composition, is designed to mimic the metabolic state of fasting, leading to a reduction in seizure occurrences

through various proposed mechanisms including alterations in neurotransmitter levels and energy metabolism optimization (1)(22).

Clinical trials and studies have indicated that the adoption of KD and its variants, such as the modified Atkins diet (MAD) and the classical ketogenic diet (cKD), can result in substantial improvements in seizure control. This has been evidenced by reductions in weekly seizure rates and improved tolerability among patients with pharmacoresistant epilepsy (4)(23)(24).

Interestingly, the implementation of KD therapies has also been linked to potential cardiometabolic benefits, further suggesting a multifaceted impact beyond seizure control. Despite concerns regarding the diet's high-fat content, the assessment of lipid profiles and other biomarkers in adults has generally showcased a manageable risk profile, underpinning the importance of careful monitoring and adjustments to maximise efficacy and safety (4).

Ketogenic Diet Therapies for Drug-Resistant Epilepsy

Ketogenic diet therapies (KDT) are increasingly recognized as effective treatment options for patients with drug-resistant epilepsy, offering potential benefits across diverse age groups and epilepsy types. For adult patients with pharmacoresistant epilepsy, the ketogenic diet (KD) stands out as a promising treatment alternative. Characterized by high fat and low carbohydrate content, KD aims to induce a state of ketosis, mimicking the metabolic effects of fasting, which has been associated with a reduction in seizure frequency. This therapeutic approach encompasses various diet formulations such as the classical KD, modified Atkins diet (MAD), medium-chain triglycerides KD, and low glycemic index KD, each tailored to enhance patient compliance and minimize side effects (4). However, the implementation of KD in adults presents unique challenges, including poor dietary adherence and concerns about potential cardiometabolic risks due to its high-fat content.

Furthermore, evidence from the literature suggests that while both KD and MAD have shown efficacy in reducing seizure frequency in adults with refractory epilepsy, these dietary interventions often face barriers to long-term adherence. Despite the potential for significant seizure reduction, many patients discontinue the diet due to its restrictive nature and the complexity of dietary management (25)(26). The feasibility and willingness of patients to participate in randomized control trials (RCTs) for KD further illustrate the need for tailored approaches that consider dietary preferences, potential side effects, and individual patient needs (26).

Despite these challenges, the effectiveness of KD in reducing episodes of seizures in patients with refractory epilepsy cannot be overlooked. Systematic reviews and clinical trials have provided evidence supporting its use, particularly when comparing the classical ketogenic diet to other dietary approaches like the medium-chain triglyceride diet and the gradual modification of KD ratios (27). It's imperative that future research addresses the limitations associated with KD, exploring strategies to improve compliance, minimize side effects, and ultimately increase the number of patients who can benefit from this dietary therapy (28).

Ketogenic Diet Therapies for status epilepticus and neurological disorders

The ketogenic diet (KD), a high-fat, low-carbohydrate regimen, has broadened its scope of efficacy beyond treating drug-resistant epilepsy to include a variety of adult neurological disorders. Originally developed for seizure management, KD therapies have evolved over the past century, with significant clinical trials conducted in the last three decades highlighting their role in both pediatric and adult epilepsy, as well as in the management of acute status epilepticus (SE) in critical care settings (29). Moreover, KD's therapeutic potential has been expanding, showing promise in managing adult epilepsy, adult malignant glioma, Alzheimer's disease, migraines, motor neuron diseases, and other neurological conditions, attributed to its effects on neurotransmission, oxidative stress, and neuroinflammation (22)(30).

The effectiveness of KD in acute management of SE, a medical emergency characterized by prolonged seizures, reflects a significant advancement, offering a safe and potential therapeutic option when standard antiseizure medications fail. Systematic reviews have underscored KD's safety and efficacy, with an 82% success rate in ceasing SE among observed patients, though these findings necessitate further validation through rigorous controlled trials due to inherent study limitations (31). Beyond epilepsy, the role of KD in cases of refractory status epilepticus (RSE) reveals its capacity to not only reduce seizure frequency significantly but also to allow tapering of antiepileptic drugs and mechanical ventilation withdrawal, despite associated adverse events such as aspiration pneumonia and hypertriglyceridemia (32).

Ketogenic diet in the treatment of various diseases

The ketogenic diet (KD) has been extensively studied for its effectiveness in treating various conditions, demonstrating a broad spectrum of responses among different populations. For

instance, KD and its variants, such as the modified Atkins diet (MAD), have established roles in managing drug-resistant epilepsy, showing potential in reducing seizure frequency and improving the quality of life in both pediatric and adult populations (1)(3). Beyond epilepsy, KD has also been investigated for its impacts on psychiatric comorbidities in adults with epilepsy, where a longer duration on the diet correlated with fewer symptoms of anxiety and depression, signifying a positive psychiatric effect (33). Moreover, various forms of KD, including MAD and medium-chain triglyceride (MCT) diets, show promise in treating central nervous system diseases beyond epilepsy, such as Alzheimer's and Parkinson's disease, with reported improvements in memory and motor functions (34).

However, not all responses to KD are beneficial or universally effective. The diet's adherence is challenged by its restrictiveness and potential side effects, which could influence its long-term sustainability and user compliance. Furthermore, while evidence suggests improvements in conditions such as Type 2 diabetes and nonmotor Parkinson's symptoms, inconsistencies and the need for further research highlight a gap in understanding the full extent of KD's applicability (35).

Short- and long-term adverse events

The ketogenic diet (KD), a high-fat, low-carbohydrate diet, has been historically used for the treatment of refractory epilepsy in children and adults. While it is effective in reducing seizure frequency and achieving seizure freedom in certain patient populations, its adoption comes with potential short- and long-term adverse events. Studies examining the modified Atkins diet (MAD), a variant of the KD, reported constipation (17%), lethargy (11%), and anorexia (12%) as common short-term adverse events among patients with drug-resistant epilepsy (36). In terms of long-term compliance and adverse effects, implementation among adults has shown significant challenges, including increased LDL cholesterol levels, which may pose a cardiovascular risk (37). In a prospective open-label pilot study, common adverse effects included gastrointestinal symptoms like nausea, vomiting, diarrhea, constipation, and significant weight loss (38). Despite these setbacks, patient adherence varied, and a substantial proportion of subjects experienced a notable reduction in seizure frequency, indicating a balance between efficacy and the manageable nature of most adverse effects (38).

Deaths, retention rates and reasons for stopping the ketogenic diet

The ketogenic diet (KD), utilized in managing drug-resistant epilepsy, presents with variability in retention rates and reasons for discontinuation, though specific data on deaths directly attributed to the KD remain scant within the selected literature. Verrotti et al. (2020) provide an overview of various dietary regimens, including the KD and its modifications, emphasizing their efficacy and safety in both pediatric and adult populations with epilepsy. The review underlines the therapeutic potential of these diets in managing refractory epilepsy, focusing broadly on safety and tolerability without delving into mortality rates or specific discontinuation reasons related to adverse effects (1). Similarly, Neves et al. (2020) discuss the utility and metabolic impacts of the KD in adult patients with pharmacoresistant epilepsy, highlighting concerns related to its cardiovascular risks due to high fat and cholesterol intake but not detailing retention rates, reasons for discontinuation, or deaths associated with the diet (4).

Exclusion criteria for the ketogenic diet

The efficacy of the Ketogenic Diet (KD) as a treatment for drug-resistant epilepsy has been widely recognized, supporting its role in managing refractory seizures across various age groups. Despite its therapeutic potential, specific exclusion criteria limit its applicability.

According to Verrotti et al. (2020), while detailing the role of dietary regimens in epilepsy treatment, exclusionary conditions are not explicitly outlined but emphasize the necessity for personalized dietary protocols (1). McDonald and Cervenka (2020) also provide an extensive review of KD therapies for seizures and status epilepticus, highlighting its history, utility, and potential safety in managing drug-resistant epilepsy without directly specifying exclusion criteria (29). Similarly, van Berkel et al. (2018) focus on the cognitive benefits of the KD in epilepsy patients, contributing to understanding its positive effects beyond seizure control, without detailing specific exclusions for diet initiation (39). Chan et al. (2023) systematically reviews the economic evaluations of nonpharmacological treatments for drug-resistant epilepsy, including KD, yet specific exclusion criteria for the KD application are not described (40). Lastly, Murphy (2005) traces the KD's development and investigates its clinical and animal research effects, providing a historical context rather than current clinical practice exclusion criteria (41).

Conclusion

The ketogenic diet (KD), with its variants like the classical ketogenic diet, modified Atkins diet (MAD), low glycemic index treatment (LGIT), and medium-chain triglyceride (MCT) diet, has demonstrated substantial efficacy in managing drug-resistant epilepsy across diverse populations. These dietary therapies induce a state of ketosis, shifting the body's energy source from glucose to ketones, which has been linked to significant reductions in seizure frequency and improvements in patient quality of life. Despite its proven benefits, the ketogenic diet requires rigorous planning and monitoring due to potential side effects such as cardiovascular risks, slowed growth, and gastrointestinal issues.

Long-term adherence remains a challenge due to the diet's restrictive nature, with patient compliance being a critical factor in its effectiveness. However, alternative approaches like MAD and LGIT offer more flexibility and better palatability, potentially enhancing adherence and expanding the applicability of ketogenic therapies. The pathophysiological mechanisms behind KD's antiepileptic effects, including alterations in neurotransmitter levels and energy metabolism, highlight its multifaceted impact on brain function.

While KD therapies have shown remarkable success in reducing seizures, their implementation necessitates careful patient selection, monitoring, and support to mitigate adverse effects and ensure safety. Future research should focus on improving dietary adherence, exploring personalized dietary protocols, and addressing the long-term cardiovascular implications to maximize the therapeutic potential of ketogenic diets in epilepsy treatment.

Disclosure

Author’s contribution: Łukasz Karoń, Anna Zygmunt, Karolina Karoń, Wojciech Grabowski, Grzegorz Drapała, Emilia Pedrycz, Daria Pedrycz

Conceptualisation: Łukasz Karoń, Anna Zygmunt, Grzegorz Drapała

Methodology: Anna Zygmunt, Łukasz Karoń, Karolina Karoń

Software: Łukasz Karoń, Wojciech Grabowski, Grzegorz Drapała

Check: Anna Zygmunt, Karolina Karoń, Emilia Pedrycz

Formal: Łukasz Karoń, Wojciech Grabowski, Emilia Pedrycz

Investigation: Anna Zygmunt, Łukasz Karoń, Wojciech Grabowski, Daria Pedrycz

Resources: Łukasz Karoń, Wojciech Grabowski, Grzegorz Drapała

Data curation: Łukasz Karoń, Wojciech Grabowski, Anna Zygmunt, Karolina Karoń

Writing - Rough Preparation: Karolina Karoń, Daria Katarzyna Pedrycz

Writing - Review and Editing: Łukasz Karoń, Karolina Karoń, Emilia Pedrycz
Visualisation: Łukasz Karoń, Wojciech Grabowski, Grzegorz Drapała
Supervision: Łukasz Karoń, Wojciech Grabowski, Grzegorz Drapała
Project Administration: Łukasz Karoń, Wojciech Grabowski, Emilia Pedrycz

All authors have read and agreed with the published version of the manuscript.

Funding statement: The study did not receive special funding.
Institutional review board statement: Not applicable.
Informed consent statement: Not applicable.
Data availability statement: Not applicable.
Conflict of interest: The authors declare no conflict of interest.

Bibliography

1. Verrotti, A., Iapadre, G., Di Francesco, L., Zagaroli, L., & Farello, G. (2020). Diet in the treatment of epilepsy: What we know so far. *Nutrients*, *12*(9), 2645. https://doi.org/10.3390/nu12092645
2. Ułamek-Kozioł, M., Czuczwar, S. J., Januszewski, S., & Pluta, R. (2019). Ketogenic diet and epilepsy. *Nutrients*, *11*(10), 2510. https://doi.org/10.3390/nu11102510
3. Sourbron, J., Klinkenberg, S., Van Kuijk, S. M. J., Lagae, L., Lambrechts, D., Braakman, H. M. H., & Majoie, M. (2020). Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis. *Child S Nervous System*, *36*(6), 1099–1109. https://doi.org/10.1007/s00381-020-04578-7
4. Neves, G. S., Lunardi, M. S., Lin, K., Rieger, D. K., Ribeiro, L. C., & Moreira, J. D. (2020). Ketogenic diet, seizure control, and cardiometabolic risk in adult patients with pharmacoresistant epilepsy: a review. *Nutrition Reviews*, *79*(8), 931–944. https://doi.org/10.1093/nutrit/nuaa112
5. Elia, M., Klepper, J., Leiendecker, B., & Hartmann, H. (2018). Ketogenic diets in the treatment of epilepsy. *Current Pharmaceutical Design*, *23*(37), 5691–5701. https://doi.org/10.2174/1381612823666170809101517
6. Ye, F., Li, X., Jiang, W., Sun, H., & Liu, J. (2015). Efficacy of and Patient Compliance with a Ketogenic Diet in Adults with Intractable Epilepsy: A Meta-

Analysis. *Journal of Clinical Neurology*, *11*(1), 26. https://doi.org/10.3988/jcn.2015.11.1.26

7. Groesbeck, D. K., Bluml, R. M., & Kossoff, E. H. (2006). Long-term use of the ketogenic diet in the treatment of epilepsy. *Developmental Medicine & Child Neurology*, *48*(12), 978. https://doi.org/10.1017/s0012162206002143
8. Williams, T. J., & Cervenka, M. C. (2017). The role for ketogenic diets in epilepsy and status epilepticus in adults. *Clinical Neurophysiology Practice*, *2*, 154–160. https://doi.org/10.1016/j.cnp.2017.06.001
9. Meira, I. D., Romão, T. T., Prado, H. J. P. D., Krüger, L. T., Pires, M. E. P., & Da Conceição, P. O. (2019). Ketogenic diet and epilepsy: What we know so far. *Frontiers in Neuroscience*, *13*. https://doi.org/10.3389/fnins.2019.00005
10. Nei, M., Ngo, L., Sirven, J. I., & Sperling, M. R. (2014). Ketogenic diet in adolescents and adults with epilepsy. *Seizure*, *23*(6), 439–442. https://doi.org/10.1016/j.seizure.2014.02.015
11. De Giorgis, V., Tagliabue, A., Bisulli, F., Brambilla, I., Camerini, A., Cusmai, R., Darra, F., Dianin, A., Domenica, E., Lodi, M. a. M., Matricardi, S., Messana, T., Operto, F., Ragona, F., Russo, E., Varesio, C., Volpi, L., Zanaboni, M. P., Pasca, L., & Veggiotti, P. (2023). Ketogenic dietary therapies in epilepsy: recommendations of the Italian League against Epilepsy Dietary Therapy Study Group. *Frontiers in Neurology*, *14*. https://doi.org/10.3389/fneur.2023.1215618
12. Liu, H., Yang, Y., Wang, Y., Tang, H., Zhang, F., Zhang, Y., & Zhao, Y. (2018). Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. *Epilepsia Open*, *3*(1), 9–17. https://doi.org/10.1002/epi4.12098
13. Husari, K. S., & Cervenka, M. C. (2020). The ketogenic diet all grown up—Ketogenic diet therapies for adults. *Epilepsy Research*, *162*, 106319. https://doi.org/10.1016/j.eplepsyres.2020.106319
14. De Cassya Lopes Neri, L., Guglielmetti, M., Fiorini, S., Pasca, L., Zanaboni, M. P., De Giorgis, V., Tagliabue, A., & Ferraris, C. (2024). Adherence to ketogenic dietary therapies in epilepsy: A systematic review of literature. *Nutrition Research*, *126*, 67–87. https://doi.org/10.1016/j.nutres.2024.03.009
15. Kverneland, M., Molteberg, E., Haavardsholm, K. C., Pedersen, S., Ramm-Pettersen, A., & Nakken, K. O. (2017). Diettbehandling av epilepsi. *Tidsskrift for Den Norske Legeforening*. https://doi.org/10.4045/tidsskr.16.0486

16. Henderson, C. B., Filloux, F. M., Alder, S. C., Lyon, J. L., & Caplin, D. A. (2006). Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. *Journal of Child Neurology*, *21*(3), 193–198. https://doi.org/10.2310/7010.2006.00044
17. Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD001903. Accessed 27 August 2024. https://doi.org/10.1002/14651858.cd001903.pub3
18. Rogovik AL, Goldman RD. Ketogenic diet for treatment of epilepsy. Can Fam Physician. 2010 Jun;56(6):540-2. PMID: 20547519; PMCID: PMC2902940.
1. https://pubmed.ncbi.nlm.nih.gov/20547519/
19. McDonald, T. J. W., & Cervenka, M. C. (2020). Ketogenic diet therapies for seizures and status epilepticus. *Seminars in Neurology*, *40*(06), 719–729. https://doi.org/10.1055/s-0040-1719077
20. Kishk, N. A., Yousof, H. Z., Ebraheim, A. M., Elkholy, T. a. F. A., Soliman, S. H., Mohammed, R. A., & Shamloul, R. M. (2021). The effect of ketogenic diet escalation in adolescents and adults with drug-resistant epilepsy: a prospective study. *Nutritional Neuroscience*, *25*(10), 2023–2032. https://doi.org/10.1080/1028415x.2021.1927604
21. He, F., Qiu, J., Li, H., Guo, H., Wang, S., Ding, Y., Xu, S., Wang, Z., Feng, J., Zhang, P., Ding, M., & Wang, S. (2022). Efficacy of the ketogenic diet in Chinese adults versus children with drug-resistant epilepsy: A pilot study. *Epilepsy & Behavior*, *134*, 108820. https://doi.org/10.1016/j.yebeh.2022.108820
22. McDonald, T. J., & Cervenka, M. C. (2018). Ketogenic diets for adult neurological disorders. *Neurotherapeutics*, *15*(4), 1018–1031. https://doi.org/10.1007/s13311-018-0666-8
23. Martin-McGill, K. J., Bresnahan, R., Levy, R. G., & Cooper, P. N. (2020). Ketogenic diets for drug-resistant epilepsy. *Cochrane Library*, *2020*(6). https://doi.org/10.1002/14651858.cd001903.pub5
24. Tapias, J. K. B., Hurtado, D. I. C., Castaño, L. H., & Pérez, A. M. (2024). Ketogenic diet therapies as a non-pharmacological adjuvant in resistant epilepsy: retrospective analysis of adult outpatients in Colombia. *Nutritional Neuroscience*, 1–7. https://doi.org/10.1080/1028415x.2024.2336716

25. Klein, P., Tyrlikova, I., & Mathews, G. C. (2014). Dietary treatment in adults with refractory epilepsy. *Neurology*, *83*(21), 1978–1985. https://doi.org/10.1212/wnl.0000000000001004
26. Martin-McGill, K. J., Jenkinson, M. D., Smith, C. T., & Marson, A. G. (2017). The modified ketogenic diet for adults with refractory epilepsy: An evaluation of a set up service. *Seizure*, *52*, 1–6. https://doi.org/10.1016/j.seizure.2017.08.013
27. Araya-Quintanilla, F., Celis-Rosati, A., Rodriguez-Leiva, C., Silva-Navarro, C., Silva-Pinto, Y., & Toro-Jeria, B. (2016). Efectividad de la dieta cetogénica en niños con epilepsia refractaria: revisión sistemática. *Revista De Neurología*, *62*(10), 439. https://doi.org/10.33588/rn.6210.2015487
28. Erkent, I., Ilgaz, F., & Dericioglu, N. (2023). Difficulties in the implementation of the ketogenic diet in adult patients with refractory epilepsy. *Epilepsy & Behavior*, *144*, 109234. https://doi.org/10.1016/j.yebeh.2023.109234
29. McDonald, T. J. W., & Cervenka, M. C. (2020c). Ketogenic diet therapies for seizures and status epilepticus. *Seminars in Neurology*, *40*(06), 719–729. https://doi.org/10.1055/s-0040-1719077
30. McDonald, T., & Cervenka, M. (2018b). The expanding role of ketogenic diets in adult neurological disorders. *Brain Sciences*, *8*(8), 148. https://doi.org/10.3390/brainsci8080148
31. Mahmoud, S. H., Ho-Huang, E., & Buhler, J. (2019). Systematic review of ketogenic diet use in adult patients with status epilepticus. *Epilepsia Open*, *5*(1), 10–21. https://doi.org/10.1002/epi4.12370
32. Nam, S. H., Lee, B. L., Lee, C. G., Yu, H. J., Joo, E. Y., Lee, J., & Lee, M. (2011). The role of ketogenic diet in the treatment of refractory status epilepticus. *Epilepsia*, *52*(11), e181–e184. https://doi.org/10.1111/j.1528-1167.2011.03289.x
33. Shegelman, A., Carson, K. A., McDonald, T. J., Henry-Barron, B. J., Diaz-Arias, L. A., & Cervenka, M. C. (2021). The psychiatric effects of ketogenic diet therapy on adults with chronic epilepsy. *Epilepsy & Behavior*, *117*, 107807. https://doi.org/10.1016/j.yebeh.2021.107807
34. Christensen, M. G., Damsgaard, J., & Fink-Jensen, A. (2020). Use of ketogenic diets in the treatment of central nervous system diseases: a systematic review. *Nordic Journal of Psychiatry*, *75*(1), 1–8. https://doi.org/10.1080/08039488.2020.1795924

35. McDonald, T. J., & Cervenka, M. C. (2019). Lessons learned from recent clinical trials of ketogenic diet therapies in adults. *Current Opinion in Clinical Nutrition & Metabolic Care*, *22*(6), 418–424. https://doi.org/10.1097/mco.0000000000000596
36. Mutarelli, A., Nogueira, A., Felix, N., Godoi, A., Dagostin, C. S., Castro, L. H. M., & Telles, J. P. M. (2023). Modified Atkins diet for drug-resistant epilepsy: A systematic review and meta-analysis of randomized controlled trials. *Seizure*, *112*, 77–83. https://doi.org/10.1016/j.seizure.2023.09.010
37. Mosek, A., Natour, H., Neufeld, M. Y., Shiff, Y., & Vaisman, N. (2009). Ketogenic diet treatment in adults with refractory epilepsy: A prospective pilot study. *Seizure*, *18*(1), 30–33. https://doi.org/10.1016/j.seizure.2008.06.001
38. Klein, P., Janousek, J., Barber, A., & Weissberger, R. (2010). Ketogenic diet treatment in adults with refractory epilepsy. *Epilepsy & Behavior*, *19*(4), 575–579. https://doi.org/10.1016/j.yebeh.2010.09.016
39. Van Berkel, A. A., IJff, D. M., & Verkuyl, J. M. (2018). Cognitive benefits of the ketogenic diet in patients with epilepsy: A systematic overview. *Epilepsy & Behavior*, *87*, 69–77. https://doi.org/10.1016/j.yebeh.2018.06.004
40. Chan, H. Y., Janssen, L. M. M., Wijnen, B. F. M., Hiligsmann, M., Majoie, M. H. J. M., & Evers, S. M. a. A. (2023). Economic evaluations of nonpharmacological treatments for drug-resistant epilepsy: A systematic review. *Epilepsia*, *64*(11), 2861–2877. https://doi.org/10.1111/epi.17742
41. Murphy, P. (2005). Use of the ketogenic diet as a treatment for epilepsy refractory to drug treatment. *Expert Review of Neurotherapeutics*, *5*(6), 769–775. https://doi.org/10.1586/14737175.5.6.769