The effectiveness of the ketogenic diet in reducing the frequency of seizures in children diagnosed with refractory epilepsy

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Abstract: Refractory epilepsy in children is defined as not responding to anti-epileptic drugs and has many adverse effects on children's quality and life, and it may even result in risks of sudden death. Therefore, it is significant to find an alternative and effective treatment to reduce the frequency of seizures and improve the quality of life of children diagnosed with refractory epilepsy. The purpose of this paper is to critically review the past studies and determine the effectiveness of the ketogenic diet in the reduction of seizures in children with refractory epilepsy. The secondary outcome of this paper is to consider the drastic effects the KD has on the quality of life, including adverse side effects, the restrictiveness of the diet, and other implications. In conclusion, it is determined that the ketogenic diet is a viable, safe, and overall tolerable treatment for children with refractory epilepsy; however long-term efficacy of the diet is extremely difficult and is likely a more viable option for short-term treatment.

1. Introduction

More than 70 million individuals worldwide have epilepsy, which is defined as a neurological disorder characterized by at least two unprovoked seizures [1]. Epilepsy in children and adolescents is a devastating disorder in which people are prone to recurring epileptic seizures or abnormalities in behavior or movement [2]. The ketogenic diet (KD) was developed in the 1920s to treat epilepsy in children [3]. The KD is widely recognized and used across over 60 countries all over the world [4]. The KD, characterized as high in fat and low in carbohydrates, is now widely used to treat children with refractory or intractable epilepsy [5]. The KD is intended to imitate the effects of fasting on the body, in which fat is converted to ketones in the body and used as an energy source [6]. When glucose supply is inadequate, the brain utilizes ketones to compensate for the lack of glucose availability and as the sole substantial backup fuel for glucose [7]. The main idea behind the KD for seizure treatment is that ketones are used as an alternative fuel source for the brain to reduce the incidence of seizures caused by deficiencies in glucose metabolism [8].

The classical ketogenic diet has a ratio of 4:1 or 3:1 grams of fat for every gram of carbohydrate/protein, creating a high fat provided by long-chain triglycerides, moderate protein, and low carbohydrate diet [9]. Aside from classical KD, its modified alternatives, such as the modified Atkins diet and low-glycemic-index treatments, have gained foundations for improving palatableness and compliance [10]. The modified Atkins diet is less restrictive than the classical ketogenic diet due to its relatively fewer dietary restrictions [11]. In addition, because of the liberalization of carbohydrates and reduction in fat content, low-glycemic-index treatments are more palatable than the classical KD [12].

While many anti-epileptic drugs (AED) exist and can be effective treatments for seizure reduction, one-third of children with epilepsy suffer seizures that are refractory to AED, and several children suffer catastrophic epilepsy [13]. It is critical not to rely solely on pharmaceutical therapies when treating drug-resistant epilepsy because uncontrolled seizures negatively affect the quality of life, and uncontrolled tonic-clonic seizures are considered one of the most significant risk factors for sudden death epilepsy [14]. When two or three suitable AED fail to respond, patients with refractory epilepsy

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should consider the KD [15]. The ketogenic diet is used as an alternative treatment to reduce seizure frequency in children with refractory epilepsy if AED and surgery are not viable options for treatment [3].

Various research studies have implemented KD and found significant evidence on reducing seizures and positive effects on refractory epilepsy. However, side effects and the restrictive nature of the diet raise concerns over the quality of life of children on the diet. Being unable to consume a typical childhood diet can negatively affect epileptic children and their families and make the diet challenging to maintain in the long term [16].

The purpose of this paper is to critically review the past studies and determine the effectiveness of the ketogenic diet in the reduction of seizures in children with refractory epilepsy. The secondary outcome of this paper is to consider the drastic effects the KD has on the quality of life, including adverse side effects, the restrictiveness of the diet, and other implications. The topic of this paper is significant to determine as epilepsy causes adverse effects on the quality of life of children and their families, and alternative treatments could improve the lives of many individuals through seizure reduction or complete seizure elimination in some cases.

A common theme evident throughout each paper selected was the significant levels of positive effects that were seen throughout interventions that resulted in >50%, >90% and seizure-free changes for many children with refractory epilepsy. This result of KD intervention is a very positive indication of the efficacy of the ketogenic diet, and consistent data reflected the positive treatment results. Numerous individuals reported that their seizures had been wholly eliminated once placed on the KD, which is a significant improvement and motivation for using the KD. The safety of the KD was evaluated, and Lambrechts et al. evaluated and determined that the KD was a safe and tolerable treatment alternative [17-19].

2. The effectiveness of the KD for children suffering from refractory epilepsy

Sourbron et al.'s systematic review has a primary objective of determining the effectiveness of the ketogenic diet for children who have refractory epilepsy, with a success measurement of >50% reduction in seizures [3]. All studies included had 4:1 or 3:1 ketogenic diet intervention on children (ages 1-18) and were published after 1970. Two main criteria had to be fulfilled to include the studies; records of treatment outcomes after the KD and a ratio of either 4:1 or 3:1, resulting in a total of 11 studies being included [3].

The results of this systemic review concluded that 50% of children with refractory epilepsy would experience a significant positive effect from the KD and see a reduction in seizure frequency, signifying that more than >50% of seizure incidences were reduced. Table 1 represents the seizure reduction in each of the studies included. In 6 of the 11 studies reviewed, >90% seizure reduction was reported, while >50% seizure reduction was found in 9 studies. In addition, the systematic review conducted a statistical analysis using a confidence interval (CI) of 95% and found that 15.8% of patients became seizure-free. Strengths of this systemic review include using randomized control trials (RCT) to reduce bias and increase the quality of evidence, measurement of quality of life, adherence and side effects, and control group comparison [3].

Limitations of this review must be acknowledged. While many studies are RCT, there is a gap of evidence when comparing the effectiveness of the KD to the traditional treatment methods of surgery and AED. Another limitation that Sourbron et al. acknowledged is the lack of scientific understanding as to why the KD has the potential to reduce seizure frequency. Many of the studies recorded side effects, and compliance levels yet struggled to determine what "compliance" was defined as and provided somewhat limited evidence on the side effects. While the review was completed in 2020, evidence was compiled from the 1970s-present and that medical advancements could provide a better understanding of the mechanisms as to how the KD reduces seizures [3].

Regardless of the limitations, this review concluded that the KD could be an effective treatment for refractory epilepsy in children and provides a conclusion that the KD can have a positive effect on children. Not only did this review provide conclusive evidence about seizure reduction, but it also

factored in secondary outcomes to their conclusion. This review had an in-depth overview of the KD effectiveness and motivated future researchers to discover more clinically detailed reviews regarding the side effects and their causes [3].

Lambrechts et al. conducted a RCT with a primary outcome of determining the effectiveness of the KD on the reduction of seizures in children [19]. This RCT involved a modified cross-over treatment by utilizing a control group and a KD intervention group and concluded blood tests, measured state of ketosis, seizure severity, and reported side effects. The KD ratio utilized was 4:1 or 3:1. KD group intervention outcomes were assessed at baseline and 4, 7, 10, 13 and 16 months after the baseline period. In addition, Care-as-usual (CAU) group patients received the anti-epileptic drug as prescribed, and their outcomes were assessed at baseline and after four months [19].

The results of this RCT are documented in Table 2 and Table 3, which represent the changes in seizure frequency within each study participant, with a significant improvement in seizure reductions (in the intervention group) at both six weeks (57.7%) and four months (65.2%). It is also essential to recognize that a few individuals within the control group experienced a decrease in seizure frequency, with six-week and four-month markers being 18.2% and 36.8%, respectively. This RCT could cause concerns with the effectiveness of the KD treatment for seizure reduction as some seizure frequency saw improvement without the diet; however, most patients in the control group did not experience this and seizure improvement was drastically more significant in the KD group. Researchers acknowledged this is a typical result of many similar trials as seizure frequency can be reduced by many other unknown factors and through ageing [19]. Side effects and quality of life (QoL) results showed no significant differences within the nine categories reported in each group, except for abdominal symptoms in the KD group, with the 6-week check-in reporting increased symptoms and 4-month check-in reporting a slight decreased, but higher than baseline amount of GI symptoms [19].

Strengths of this study conducted by Lambrechts et al. include using an RCT study design, initial recording of both groups at baseline (no treatment), and blood tests to record levels of lipids of state of ketosis. Researchers in Lambrechts et al.'s RCT noted a limitation to their study conclusions was that a 4-month period was relatively short in terms of determining the long-term tolerability of the KD, and potentially follow-up study could extend the trial for the KD and determine the long-term side effects > 4 months [19]. Nevertheless, the conclusion within this RCT determined that the use of the KD was an effective and safe method of reducing seizure frequency in children with refractory epilepsy. Abdominal side effects could be adequately managed through diet reconfiguration, and the significant reduction of seizures was a compelling argument for this diet [19]. This RCT was unique and provided a comprehensive KD trial that provided highly relevant and detailed evidence in the efficacy and safety of the KD in children with refractory epilepsy while building upon information obtained in Sourbron et al.'s systemic review [3].

Table 1. Seizure reduction and elimination reported during KD intervention.

Study	Seizure free (% of total)	>90% reduction (% of total)	>50% reduction (% of total)
Hopkins & Lynch. 1970	8.8%	N/A	N/A
Huttenlocher et al. 1971	33%	N/A	N/A
Janaki et al. 1976	20%	N/A	100%
Huttenlocher. 1976	22%	56%	89%
Berman. 1978	25% (KD) & 5.6% (MCT)	N/A	50% (KD) & 33% (MCT)
Trauner. 1985	29%	N/A	29%
Sills et al. 1989	16%	24%	44%
Schwartz et al. 1989	N/A	41%	81%
Kinsman et al. 1992	N/A	29%	38%
Vining et al.	10% (12 months)	22% (12 month)	40% (12 month)
Freeman et al. (unpublished)	7% (12 months)	27% (12 months)	50% (12 months)

Note: All data within Table 1 was obtained from Table 2 in Sourbron et al.'s systemic review [3].

Table 2. Seizure frequency changes throughout RCT for the Ketogenic Diet group.

Time	# who experience reduced seizures	# who did not see reduction in seizures
6 weeks	15 or 57.7%	11 or 42.3%
4 months	15 or 65.2%	8 or 34.8%

Note: All data within Table 2 was obtained from Table 4 in Lambrechts et al.'s RCT [19].

Table 3. Seizure frequency changes throughout RCT for the CAU group.

Time	# who experience reduced seizures	# who did not see reduction in seizures
6 weeks	4 of 18.2%	7 or 36.8%
4 months	18 or 81.8%	12 of 63.2%

Note: All data within Table 3 was obtained from Table 4 in Lambrechts et al.'s RCT [19].

3. Quality of life of epilepsy patients who were undergoing the KD

Poelzer et al.'s systematic review provided a unique perspective about the effectiveness of KD in children with refractory epilepsy as its primary objective was to determine the quality of life of epilepsy patients who were undergoing the KD [16]. The studies included within this review were selected from a wide range of databases and were a variety of study types (RCT, observation, retrospective etc.) that all analyzed the efficacy of the KD (4:1 ratio) in terms of QoL [16]. The strengths of this systematic review included the use of study designs that were selected based on nine high-quality standards (clear statement of aims, appropriate methodology etc.). Data were obtained internationally and included many children's ages that provided both qualitative and quantitative data. A fundamental limitation within this systemic review was the lack of definition as to what is "Quality of life". There are numerous different definitions and measurements of quality of life, and while lack of definition raises concerns, it will always be a subjective measurement. An event or change that negatively impacts an individual should be recorded and trusted, as QoL is up to each individual and it is vital to recognize this when concluding the overall tolerability of the KD [16].

The data and conclusions drawn from this systemic review will be highly beneficial and significant because sweeping conclusions about the QoL of patients on the KD can be drawn from this systemic review. This review focused on a significant area within the effectiveness of KD in children with refractory epilepsy because it is significant to determine if the KD is effective, what the consequences will be for patients on the diet, and how their overall quality of life will change. Discussion within this systemic review highlighted that the KD is difficult for children to maintain and drastically affects both their psychological and metabolic health and this is concerning. In addition, many children had reported side effects, the family's difficulties, and difficulty ensuring proper nutrient intake [16]. This review compliments and explores secondary outcomes of many other studies and provides an in-depth understanding of the QoL effects.

4. Comparison of the efficacy and tolerability of the 2.5:1 versus classical 4:1 (KD)

Raju et al.'s randomized open-labelled study had the primary objective to compare the efficacy and tolerability of the 2.5:1 versus classical 4:1 (KD) in children with refractory epilepsy [20]. In addition, this study provided a comparison between 2 KD ratios and their relative efficacy. This study was a randomized open-label trial with 38 participants (ages 6 months-5 years) who had two seizures/month despite the use of at least 2 AED. The outcomes assessed to evaluate efficacy were seizure frequency, adverse effects, and biochemical profiles (liver and kidney function, fasting lipid protein and urinary calcium and creatinine ratios). Before the intervention, baseline measurements and a non-fasting gradual KD initiation protocol were done by having each randomized group start with a 1:1 ratio, then increased to 2.1:1 or 4:1 ratio. Recipes were planned and calculated based on preferences, cultural values, and locally available food [20].

As seen in Table 4, 58% of children in the 4:1 group and 63% in the 2.5:1 group saw seizure reduction greater than 50%. The 4:1 and 2.5:1 group saw 26% and 21% of children become seizure-free, respectively. Side effects reported a high incidence of constipation, and a total of 3 children were hospitalized for lower respiratory tract infections in which KD continued during and after discharge. The biochemical test revealed that children in the 4:1 group had a ketone level of 80-160mg/dl (large ketosis). The 2.5:1 group also reported large ketosis, except for one child with moderate ketosis (40mg/dl). Attrition occurred (3 per group) due to unsatisfactory seizure control, food refusal, and family contradictions [20].

Strengths of this randomized open-labelled study include randomization to reduce confounding variables, and the ability to compare impacts and efficacy of 2 types of KD treatments. In addition, the use of clinical measurements to document a significant biochemical change and level of ketosis is a significant strength that can confirm whether or not the patient is experiencing true ketosis. This randomized open-labelled study is also the first study to be looking at the 2.5:1 ratio compared to the classic KD. Limitations of this study include having a small sample size that was not determined using statistical sample size calculation, making it difficult to generalize for the average population. In addition, blinding was impossible in dietary intervention, and there could have been concerns about bias within the results [20].

Conclusions drawn show that the ketogenic diet effectively reduces the seizure frequency of children with refractory epilepsy; however, this randomized open-labelled study highlights that the 2.5:1 ratio may be more effective in seizure reduction with fewer adverse effects as the biochemical profile of the two groups are comparable. Nevertheless, this is a significant contribution to the effectiveness of KD in children with refractory epilepsy as it clearly shows the effectiveness of the KD and raises questions as to how it can become a more tolerable option [20].

In Coppola et al.'s paper, the primary objective was to examine the efficacy and safety of the classic 4:1 ketogenic diet as a supplemental treatment for children & young adults with refractory epilepsy [18]. Thus, this study evaluated the efficacy through considerations on seizure type, epilepsy form, and age-related factors while the tolerability and practicality were measured for safety.

Coppola et al. conducted a prospective cohort study with 56 patients (ages 1-23) with drug-resistant epilepsy who had a minimum of two seizures/week and never had KD treatment. The gradual introduction of high-fat meals occurred, and each patient consumed 0.8-1.2 g of protein/kg of weight. Calories and the diet were individually adjusted to avoid weight loss or gain. The study measured seizure type, frequency, compliance to diet, and adverse side effects. Monthly follow-up evaluations and every 7-15 days of phone check-in were conducted, with a total treatment time between 1 and 18 months [18].

Table 5 highlights the main findings, and it is essential to note that 21.4% of patients had poor compliance to the KD, raising similar concerns seen in other studies. At 1-month, 42.8% of individuals had greater than 50% seizure reduction. At three months, 75% of individuals continued the diet, and 50% of participants saw benefits, either >50% reduction or became seizure-free. Participation continued to decrease, yet seizure reduction continued to be present. Over time (as seen in table 5), dietary compliance drastically decreased; by the 1-year mark, only 8.9% of initial enrollment remained on the KD. Side effects were minimal and often could be remedied through diet adjustment in the long term, and patients under eight years had a better response to the diet. This data represents both the positive and negative effects of the KD and clearly indicates that long-term dietary maintenance is difficult, even if seizure reduction occurs [18].

Strengths include a multicentered prospective cohort study, allowing greater generalizability with the results, decreasing bias and confounding variables through intervention control. Weekly and bi-weekly check-ins decrease recall bias and monitor the progression of the diet efficacy. Limitations of this study would be a small participant group; despite it being multicenter, it is a small cohort in which it is difficult to generalize to larger populations. Even without the minor compliance issue, it is not uncommon for high attrition rates in prospective studies, raising concern for the long-term implementation of the diet. QoL was not measured, and this is a limitation as it would provide insight into why participants dropped out and how the KD affected their QoL [18].

This study concluded that KD was effective in seizure reductions for refractory epilepsy; however, the long-term dietary commitment was a major barrier. Conclusions draw highlight that while the KD is an effective and safe treatment, it cannot be considered a viable long-term solution to refractory epilepsy treatment [18].

Table 4. Seizure reduction and elimination at 3 months.

Group	% with >50% reduction	% with 100% seizure elimination
4:1	58%	26%
2.5:1	63%	21%

Note: All data within Table 4 was obtained from Raju et al.'s randomized open-labelled study [20].

Table 5. Seizure reduction and elimination reported at 1, 3, 6 and 12 months.

Time	% >50-90% seizure reduction	% elimination of seizures
1 month	42.8%	Not reported
3 months	27%	11%
6 months	20%	7%
12 months	100%	0%

Note: All data within Table 5 was obtained from Coppola et al.'s paper [18].

5. Safety and Tolerability of the KD

Cai et al.'s systemic review aimed to determine if the KD was a safe and acceptable treatment for refractory epilepsy in children (0-18 years) [17]. A comprehensive search narrowed down 45 studies that had documented adverse effects (AE) on KD interventions on the target population, and each study was throughout analyzed to ensure high-quality data was obtained. KD ratios ranged from 2.5-4:1, and study designs included RCTs and prospective studies. The studies included combined to form a highly diverse population as they were from various places in the world. Unfortunately, 24 deaths occurred throughout the included studies; however, all were determined to be uncorrelated to the implementation of KD [17].

Conclusions and results drawn from this systemic review in Tables 6 and 7 highlight that most common AEs after consuming KD were gastrointestinal disturbances, dyslipidemia, hyperuricemia, lethargy and infectious disease; severe AE was a rare occurrence [17]. This systematic review provided the evidence to understand whether the KD is an effective treatment in children with refractory epilepsy while taking account of the negative perspective of KD (impact of AEs) [17].

Strengths of this review include analyzing data from a variety of study designs and KD regimens and providing high-quality evidence about the safety and tolerability of the KD. In addition, researchers considered many relevant factors affecting the efficacy of ketogenic diet, including AE, attrition, diet composition etc., creating a comprehensive overview and analysis of the diet. A key strength of this review was the analysis of both short- and long-term effects and retention rates of KD on children of all ages from an international perspective. This systematic review also has strength in paying attention to particular groups of vulnerable patients with profound disabilities, suggesting that these fragile patients should be under careful medical supervision during KD treatment [17].

Limitations include lack of information about determining the impact of KD on growth rate as this is very controversial, and data obtained within the review was inconclusive as long-term growth effects were not measured. A significant limitation was determining whether AEs result from treatment or other conditions. Elevated triglyceride levels resulting from KD could lead to CVD later in life, and this study did not account for this risk; however, it could be a follow-up study focus [17].

This systemic review concluded that KD is a safe and tolerable treatment given with proper implementation and monitoring of ketosis levels, especially for children receiving long-term KD therapy. This review is beneficial as it indicated that the restrictive nature of KD is a major challenge for compliance, yet the diet is effective in seizure reduction and safe for epileptic children. Vulnerable

patients (comorbidities etc.) require medical supervision during KD to reduce severe AE, critical information to understand how to ensure effective and safe KD treatment for patients with special needs [17].

Table 6. Commonly reported gastrointestinal adverse effects throughout treatment.

Adverse effect reported	% of study population
Gastrointestinal disturbances	9.6%
Constipation	13.2%
Vomiting	9.1%
Diarrhea	3.8%
Hunger	2.4%
Abdominal pain	1.7%
Gastroesophageal reflux	0.7%
Fatty diarrhea	0.1%

Note: All data within Table 6 was obtained from Cai et al.'s systemic review [17].

Table 7. Commonly reported non-gastrointestinal adverse effects throughout treatment

Adverse effect reported	% of study population
Hyperlipidemia	4.6%
Hypercholesterolemia	3.8%
Hypertriglyceridemia	3.2%
Hyperuricemia	4.4%
Lethargy	4.1%
Infectious diseases	3.8%

Note: All data within Table 7 was obtained from Cai et al.'s systemic review [17].

6. Long-term clinical outcomes and economic evaluation of the KD versus care as usual

Wijnen et al.'s RCT had an objective of documenting and analyzing the financial outcomes and clinical effects of the KD on children (48 total, 1-18yrs) with refractory epilepsy through control (care as usual, CAU) and intervention (KD) [21]. This RCT builds upon Lambrechts et al.'s RCT [19] and follows similar study design methods yet provides in-depth economic evaluations of the KD through assessing seizure frequency, severity, quality-adjusted life years, side-effects, health care costs, production losses, patient and family costs at baseline and at 16-month follow-up [21].

Results are highlighted in Tables 8 and 9 and clearly indicate that the KD group had a 50% reduction in seizures and severity in 34.6% of individuals, with the CAU group reporting 18.2%. Side effects reported at baseline (as seen in table 10) often decreased in incidence while on the KD at both 4 and 16 months. It is important to note that the majority of participants remained on AEDs throughout treatment, making the CAU seizure reduction somewhat expected. The resulting cost per QALY (quality-adjusted life year) ratios were inconclusive due to insignificant differences between KD and CAU groups. The cost of the KD was considered and found that there was a higher cost associated when compared to the CAU group; however, KD required a hospital stay (as seen in table 11). This data determined the efficacy, side effects, family implications, and compliance issues of the KD while considering the economic implications to create an overall conclusion on whether or not this is a viable and obtainable treatment [21].

Strengths of Wijnen et al.'s paper include high-quality evidence through an RCT to reduce confounding factors, building upon Lambrechts et al.'s systemic review [19] for economic analysis and comprehensive data about the efficacy of the KD for seizure treatment [21]. This study utilized randomization and evaluated outcomes multiple times, enabling a broader comparison of long-term clinical outcomes and cost-effectiveness. The use of EQ-5D to assess the quality of life of parents was proactive; however, the EQ-5D may limit included relevant factors and was limited to <50% of

patients, requiring future studies to develop accurate measurements to assess the quality of life of parents, which is an important factor affecting the retention rate of KD. Patients in this study were only given an MCT diet, limiting the comparison to classical KD. Future studies could explore different KD regimens to optimally prescribe KD type with individual patients [21].

The CAU group data was only obtained until four months, then extrapolated to 16 months, raising concerns about the accuracy of the data comparison. CAU group costs may be underestimated and did not account for surgery, vagus nerve stimulator, and AED. This study performed a logistic regression analysis, which did not show a significant influence of the etiology of epilepsy on the likelihood of becoming a responder in both groups. Future studies could focus on biological mechanisms and provide more insight into the efficacy of KD. This study is significant to conclude the efficacy of the ketogenic diet for treating refractory childhood epilepsy when taking account of its long-term clinical outcomes and economic evaluation compared to CAU [21].

Table 8. Seizure reduction reported in the ketogenic diet group.

Time	% of >50% seizure reduction	% of >90% seizure reduction	% Seizure free
4 months	27.0%	11.5%	11.5%
16 months	15.4%	7.7%	11.5%

Note: All data within Table 8 was obtained from Wijnen et al.'s paper [21].

Table 9. Seizure reduction reported in the care as usual group.

Time	% of >50% seizure reduction	% of >90% seizure reduction	% Seizure free
4 months	4.55%	4.55%	9.1%
16 months	4.55%	4.55%	9.1%

Note: All data within Table 9 was obtained from Wijnen et al.'s paper [21].

Table 10. Side effects reported at baseline and throughout treatment in the KD group.

Side effect & severity	Baseline	4 months	16 months
General CNS	5.36	2.07	3.67
Behaviour (increased irritability)	3.23	0.57	2.45
Depressive symptoms	2.12	1.07	2.00
Changes in cognitive function	10.21	5.31	7.71
Motor problems and coordination	1.26	0.31	1.50
Visual complaints	0.00	0.00	0.00
Headache	1.00	0.14	0.45
Cosmetic and dermatological complaints	1.58	0.50	2.55
Gastrointestinal complaints	3.00	1.36	2.05

Note: All data within Table 10 was obtained from Wijnen et al.'s paper [21].

Table 11. Cost associated with CAU and KD groups.

Cost category (averages in Euros)	Ketogenic diet cost	Care as usual cost
Intervention costs	6571.31	1548.60
Diet costs	9483.28	N/A
Total health care costs	34,180.21	23,927.80
Total costs	61,018.81	53,366.63

Note: All data within Table 11 was obtained from Wijnen et al.'s paper [21].

7. Short-term and long-term efficacy of classical KD and modified Atkins diet

Rezaei et al.'s systematic review and meta-analysis has the primary objective of determining short and long-term effects of the KD (4:1) and modified Atkins diet (MAD, 1:1 or 2:1) in children with refractory epilepsy through documenting effects at 1-24 months [22]. Conclusive research utilized multiple high-level databases and resulted in a total of 70 research papers to be included. All studies included had to involve the target population, utilize KD or MAD, designs of intervention and observational, and report >50% seizure reduction [22].

This systemic review was, at the time, the first high-level evidence publication comparing the efficacy of the KD and MAD diets for both short- and long-term use. They reported that MAD had an efficacy of 34% and KD with 52% when results from all monthly reports were combined. However, they discovered that the efficacy of the KD decreased in many studies over time, yet still has significant efficacy rates. A key difference noted between the two diets was that KD required an initial hospital stay, whereas MAD did not, making it more accessible for all families. The results of this systemic review concluded that both the KD and MAD had positive results for the treatment of refractory epilepsy; however, there was no significant difference between the two diets in relation to seizure control. However, MAD is less restrictive for children and families and could be a different alternative to the traditional KD that is more accommodating [22].

Strengths of this systemic review include every type of study conducted to examine the effects of KD vs. MAD and high-level evidence utilized through RCT, prospective, and observational studies to reduce confounding factors. As well, multiple databases were searched, ensuring validity and reliability of data collected. Measuring both diets' efficacy at multiple times and in multiple populations is a major strength as it creates a comprehensive set of data to determine the primary objective. Limitations within this study were recognized by the researchers as follows; unable to separate children and adolescence due to study designs, unable to determine the effects of KD and MAD on individual types of epilepsy; beneficial to determine if a specific type of refractory epilepsy benefited the most from dietary intervention [22].

This review compared and contrasted the difference between KD and MAD, contributing to both the primary and secondary outcomes of determining the efficacy and tolerability of the KD in the treatment of refractory epilepsy in children [22]. It is a critical component to determine the effectiveness and tolerability of the KD because compliance is a major issue (seen within all studies). In addition, this systemic review determined if there is a more tolerable alternative to the use of KD as a treatment for refractory epilepsy, sparking further research and discussion.

8. Conclusions

Throughout in-depth research and analysis of the use of the ketogenic diet for the treatment of refractory epilepsy, numerous positive benefits were discovered, and concerns raised about side effects and effects on quality of life were analyzed. In addition, numerous other factors influence an individual's response to treatment, including but not limited to: other medical conditions, family support, and financial status, and food preference, type of epilepsy, age, and subjective judgement of their own QoL. Throughout this review, data from various academic papers that included systematic reviews, meta-analysis, RCTs, prospective, observational, and case-control studies were collected to provide a variable and comprehensive understanding of the KD diet effects.

A key component to all of the research papers included was the issues with compliance and tolerability of the diet. Many studies reported that gastrointestinal systems were common. However, they could be avoided with adequate diet adjustments. Wijnen et al.'s paper provided a unique perspective of the financial implementations of supporting a child on the KD and raised concerns about the long-term viability of the treatment [21]. Aspects regarding the quality of life of children and their families were included. While there were financial barriers, restrictions on dietary consumption, and family conflicts, the ketogenic diet has significant positive effects on reducing seizures. Side effects

and QoL was the critical area that required further research as there were gaps in the literature that made it difficult to compare evidence between papers selected.

In conclusion, it is determined that the ketogenic diet is a viable, safe, and overall tolerable treatment for children with refractory epilepsy. However, the long-term efficacy of the diet is extremely difficult and is likely a more viable option for short-term treatment. Further research is required to determine and understand the mechanisms in which the ketogenic diet reduces seizures and the short- and long-term implications of a high-fat diet. Quality of life will be dependent on each individual's subjective evaluation and unique circumstances. However, based on the data collected, the overall quality of life improvements that occur with seizure reduction are greater than the restrictive nature and minor side effects of the diet.

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