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«Ο ρόλος της Κετογονικής δίαιτας στη φαρμακοανθεκτική επιληψία στα παιδιά: συστηματική ανασκόπηση»

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“The role of ketogenic diet in drug-resistant epilepsy in children: a systematic review”

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ABBREVIATIONS

AED(s)……. Anti-epileptic Drugs

ASD(s)…….Anti-seizure Drugs

BDNF……..Brain-Derived Neurotrophic Factor

GI……..Gastrointestinal

KD…….Ketogenic Diet

LGIT……...Low Glycemic Index Treatment

MAD……...Modified Atkins Diet

MCT…….....Medium Chain Triglycerides

NADH……Nicotinamide Adenine Dinucleotide Phosphate

RCT(s)…….Randomized Controlled Trial(s)

A. Abstract

Introduction: Drug resistant epilepsy affects about 25-30% of people worldwide. Ketogenic diet (KD) is used for refractory epilepsy since 1921, with an explosion in its use over the past 15 years.
Objective: The aim of this study is to review all evidence from Randomized Controlled Trials (RCTs) regarding the efficacy of ketogenic diet in drug-resistant childhood epilepsy.
Methods: An online literature search was performed in the databases of Pubmed, Cohrane library, Scopus, Clinical Trials.gov and Google Scholar. Predefined criteria were implemented regarding data extraction and study quality.
Results: Data were extracted from 11 RCTs with totally 787 children (6 months-8 years). In 5 studies children had >50% seizure reduction with a statistically significant difference between the KD group and the control group after 3-4 months. Classic KD proved to be slightly more efficacious than MAD but with no statistically significance. Secondary outcomes were adverse events, seizure severity, quality of life and behavior. Gastrointestinal symptoms were the most frequent adverse events. Serious adverse events were rare.
Conclusion: Ketogenic diet is an effective treatment for drug-resistant epilepsy in children. The mechanisms of action have not been verified yet and scientists focus on the potential beneficial role of altered gut microbiota. Treatment targeting the gut microbiota may be the future solution.

A. Περίληψη

Εισαγωγή: Η φαρμακοανθεκτική επιληψία απαντάται περίπου στο 25-30% των ανθρώπων παγκοσμίως. Η χρήση της κετογονικής δίαιτας άρχεται από το 1921, με μια αύξηση της χρήσης της τα τελευταία 15 χρόνια.
Στόχος: Ο στόχος της παρούσας μελέτης είναι η ανασκόπηση όλων αποδεδειγμένων δεδομένων από Τυχαιποιημένες Κλινικές δοκιμές που αφορούν την αποτελεσματικότητα της κετογονικής δίαιτας στην φαρμακοανθεκτική επιληψία στα παιδιά.
Μέθοδοι: Πραγματοποιήθηκε μια διαδικτυακή αναζήτηση σε βάσεις δεδομένων όπως Pubmed, Cohrane library, Scopus, Clinical Trials.gov και Google Scholar. Εφαρμόστηκαν προκαθορισμένα κριτήρια αποκλεισμού των μελετών και κριτήρια σχετικά με την ποιότητα της μελέτης.
Αποτελέσματα: Δεδομένα εξήχθησαν από 11 Τυχαιποιημένες Κλινικές δοκιμές που περιελάμβαναν συνολικά 787 παιδία ηλικίας 6 μηνών-8 ετών. Σε 5 μελέτες τα παιδιά παρουσίασαν >50% μείωση των σπασμών μετά από 3-4 μήνες, με κλινικά σημαντική διαφορά μεταξύ της ομάδας που έλαβε κετογονική δίαιτα και της ομάδας που έλαβε τη συνήθη θεραπευτική αγωγή. Η κλασική κετογονική δίαιτα αποδείχθηκε πως ήταν ελάχιστα περισσότερο αποτελεσματική από την τροποποιημένη δίαιτα Άτκινς, αλλά όχι με στατιστικά σημαντική διαφορά. Δευτερεύοντα αποτελέσματα ήταν οι ανεπιθύμητες ενέργειες της κετογονικής δίαιτας, η σοβαρότητα των σπασμών, η ποιότητα ζωής και η επίπτωση στη συμπεριφορά. Οι συχνότερες ανεπιθύμητες αντιδράσεις ήταν τα συμπτώματα από το γαστρεντερικό. Σοβαρές ανεπιθύμητες ενέργειες ήταν σπάνιες.
Συμπέρασμα: Η κετογονική δίαιτα αποτελεί αποτελεσματική θεραπεία για την ανθεκτική στα φάρμακα επιληψία στα παιδιά. Οι μηχανισμοί δράσης δεν έχουν ακόμη αποσαφηνιστεί και οι ερευνητές επικεντρώνονται στον πιθανό ευνοϊκό ρόλο της τροποποιημένης από την κετογονική δίαιτα εντερικής μικροβιακής χλωρίδας. Μια θεραπεία που στοχεύει στην εντερική χλωρίδα θα μπορούσε να είναι η μελλοντική λύση στο πρόβλημα.

B. 1. Introduction

Epilepsy is the most frequent neurological disease affecting about 1% of the population. The prevalence of epilepsy in children is consistently higher and ranges from 3.2-5.5/1,000 in developed countries and 3.6-44/1,000 in underdeveloped countries. Prevalence also seems highest in the rural areas and first year of life and declines to adult level[1].

Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition [2]. There are many causes that contribute to epilepsy but the most studied include cerebrovascular diseases (21%), tumours (11%), traumatic brain injuries (7%), and others like toxic and infectious disorders, congenital malformations, and genetic alternations [3, 4].

The treatment options of epilepsy vary from classic anti-epileptic drugs to surgery and vagus nerve stimulation, whereas there is a significant proportion of non-responsiveness in 25% of children that are non-responders. The International League Against Epilepsy supports that "Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [5]. Using a more practical definition "Drug-resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [6].

Several theories have been developed in order to explain the mechanisms leading to resistance in anticonvulsant medication. Transporter hypothesis which states that overexpression of the multi-drug resistant transporters leads to resistance because these transporters throw the drugs out of the cell; hence, keeping them away from their site of action. The target hypothesis states that alteration or modification in the target cellular regions (ion-channels or receptors) leads to the development of resistance against the antiepileptic effect of the target drug. Gene variant hypothesis suggested that changes in genes that regulate either pharmacokinetic or pharmacodynamics behavior of the drug cause or show resistance to the antiseizure drugs (ASDs). Moreover, the neural network hypothesis assumes that seizure-induced neuro-modulation also triggers the remodeling of the neuronal networks. As a result, there is down regulation of the physiological anti-seizure system which hinders the ASDs from reaching the target neuronal region [7].

Ketogenic dietary therapies (KDTs) are widely used by children and adults with refractory epilepsy. Fasting and other dietary treatments have been used to treat epilepsy since at least 500 BC. To mimic the metabolism of fasting, the classic ketogenic diet (KD) was introduced by modern physicians as a treatment for epilepsy in the 1920s. Over the past 15 years, there has been an explosion in the use, and scientific interest in the KD [8,9].

There are 4 types of KDTs: the classic KD, the modified Atkins diet (MAD), the low glycemic index treatment (LGIT) and the medium chain triglyceride diet (MCT) [10]. The original classical KD is based on a ratio of fat to carbohydrate and protein, usually 3:1 or 4:1. Fat is provided as long-chain triglycerides. Protein is kept to minimum requirements for growth, and carbohydrate sources are mostly limited to small portions of vegetables or fruit. The modified Atkins diet (MAD) consists of a nearly balanced diet (60% fat, 30% protein, and 10% carbohydrates by weight), without any restriction of recommended daily calories according to patient age. The Low Glycemic Index Treatment (LGIT) is based on a balanced caloric intake to maintain growth and nutrition. In the current reports, this diet is implemented in an outpatient basis. Fat contributes to 60% of calories while proteins represent 20–30%. The carbohydrates intake is 40–60 g per day, representing a larger intake than the KD or the MAD. But the carbohydrates are restricted to foods with a glycemic index < 50. The glycemic index is a measure that reflects the tendency to elevate blood glucose. The LGIT diet is similar to a 1:1 KD ratio [10].

Patients with refractory epilepsy experience many difficulties in their lives. They are in risk of life-threatening events, often spend a huge part of their lives in hospitals and depend largerly on their families. The aim of this systematic review is to assess all evidence concerning the efficacy of ketogenic diet therapies in children with drug-resistant epilepsy.

2. Methods

A literature advanced search was performed in the databases of Pubmed, Cochrane Library, Scopus, Clinical Trials.gov and Google Scholar. The terms used where ((((ketogenic diet) AND (children OR infants)) AND (drug resistant OR refractory)) AND (epilepsy OR convulsion OR seizures)) AND (randomized controlled trial). There were no date limits; the study language was English; and the studies were included in the systematic review according to the relevance of the subject.

Study selection and quality

Only randomized controlled trials with children between 1-18 years were included. Children were eligible if they experience at least 1 seizure per week despite receiving two or more antiepileptic drugs. The study quality was assessed according to the Oxford Quality Scoring System.

The primary outcome was the proportion of children with seizure reduction>50% after a follow-up period in dietary therapies. The secondary outcomes were seizure severity, side effects, tolerance, rate of withdrawals, quality of life and socio-economic parameters.

3. Results

Studies identified through database searching were 79; two more were identified through references and after removal of duplicates the records were 62. Thirty-eight studies were excluded because they did not meet the eligibility criteria (included adults, compared anti-epileptic drugs, the subjects were animals, were not available in free texts) and 13 were excluded because they were not RCTs. The search was based on the PRISMA guidelines flowchart, which is presented in the Figure 1.

3.1. Study characteristics

Only two RCT included children whose seizures were not controlled by at least three antiepileptic drugs (AEDs) [11,12]. The inclusion criteria regarding seizure frequency varied from > 1 seizure daily or 7 seizures per week [13] to at least 2 seizures per month [14]. The types of ketogenic diet analyzed in the studies were Classic ketogenic diet (CKD) and Modified Atkins diet (MAD) .

The baseline characteristics of the treatment group and the control group were similar (gender, age, nationality, type of epilepsy, epilepsy syndromes, age of the diagnosis of epilepsy) in all RCTs. Patients with comorbidities such as diabetes, hyperinsulinemia, hyperlipidemia, metabolic disorders, previous treatements with ketogenic diet, renal calculi or other medical contraindications were excluded. In one study [15], patients with behavioral or motivational problems that affect the compliance with the diet were not eligible. In one RCT, the inclusion criteria were more strict including patients who achieved seizure free outcomes and showed improvement in hypsarrythmic patterns and whose parents agreed to be enrolled in the study[17].

The adverse events were also marked for each type of diet and the most frequent included constipation and other gastrointestinal disorders, hunger, anorexia, central nervous system disorders such as headaches or lethargy and lower respiratory infections. The attrition rate varied between 8% and 33% for a time period 3-6 months. The differential drop-out rate at endpoint was lower than 15%. Only in one study [16] the drop out was 42% in a time period of 16 months.

The study characteristics are presented in the Table 1. The name, number of participants with age range, seizure type and epilepsy syndromes, duration, retention rate and the proportion of seizure reduction in 3, 6 months in both treatment and control group are analyzed for each study.

Figure 1. Prisma flowchart 2019

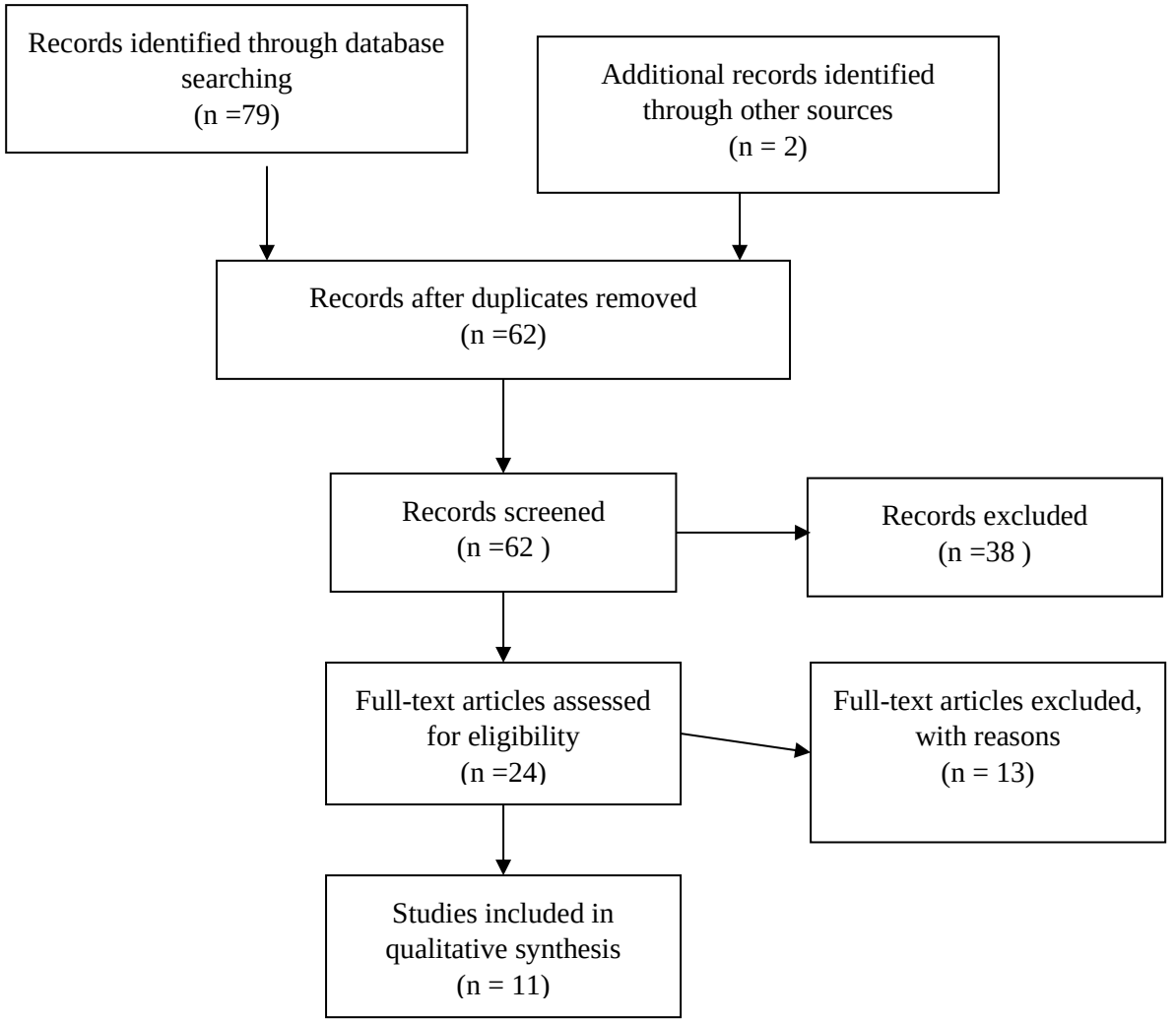


Table 1.

Study	Participants	Type of seizure/syndrome	Type of ketogenic diet	Time period	Seizure reduction%	Retention rate %
Jeon A Kim et al. 2016	N=104 (1-18yrs)	Tonic(n=16), myoclonic(n=8), tonic-myoclonic(n=8), atonic(n=4),epileptic spasms(n=24), focal(n=41)	Classic KD(n=51) MAD (n=53)	6 months	-After 3 months: CKD group >90% reduction in 19% of children, >50% reduction in 22% of children, Seizure free in 33% of children MAD group >90% reduction in 32% of children, >50% reduction in 42 % of children, Seizure free in 25% of children After 6 months: CKD group >90% reduction in 37 % of children, >50% reduction in 39% of children, Seizure free in 31% of children MAD group >90% reduction in 30% of children, >50% reduction in 36% of children, Seizure free in 23% of children p-value>0.05	66.6% in the KD group 14% drop-outs for life threatening or disabling events (metabolic acidosis, serious infection, osteoporosis, renal calculi formation), other reasons (intolerance, negative efficacy) 68% in the MAD group 3% drop-out for serious side effects (infection,allergic reaction), other reasons (intolerance, negative efficacy)

Lambrechts DAJE et al. 2016	N=57 (1-18yrs)	West s. (n=3), Lennox Gastaut(n=1), Doose s.(n=3), Dravet s.(n=1), childhood absence epilepsy(n=1), myoclonic absences (n=1), generalized epilepsies(n=4), localization related epilepsies(n=12)	CKD (n=7) MCT (n=18) Mix (n=6)	4 months	-After 1 month: **KD group** >90% reduction in 0 children, >50% reduction in 26.9% of children, Seizure free in 7.7% of children **Control group** >90% reduction in 4.5% of children, >50% reduction in 13.7% of children, Seizure free in 4.5% of children After 4 months: **KD group** >90% reduction in 11.5 % of children, >50% reduction in 27% of children, Seizure free in 11.5 % of children **Control group** >90% reduction in 4.5% of children, >50% reduction in 4.5% of children, Seizure free in 9.2% of children	89.6% in KD group reasons for discontinuation : GI side effects, spontaneous seizure reduction 78.6% in control group Reasons for discontinuation: Dissatisfaction with randomization result
Elizabeth G. Neal et al. 2008	N=145 (2-16yrs)	Lennox gastaut(n=14), West s.(n=11), myoclonic absence epilepsy(n=7), unspecified myoclonic absence epilepsy(n=8), myoclonic astatic epilepsy(n=8), atypical absence seizure(n=3), continuous spike wave of low sleep(n=2),childhood absence epilepsy(n=2), myoclonic encephalopathy(n=1), non specific syndrome diagnosis(n=22), focal epilepsy(n=57)	CKD (2:1 ratio and gradually 3:1, 4:1) , MCT diet , non-fasting initiation protocol	3 months	-After 3 months: **KD group (n=73)** >90% reduction in 7% of children (p-value=0.0582) >50% reduction in 38% of children (p-value=0.0001) <50% reduction in 62% of children (p-value=0.001) **Control group (n=72)** >90% in 0% of children >50% reduction in 6% of children <50% reduction in 94% of children	73% in KD group Reasons for discontinuation: Parents' unsatisfaction, GI side effects, intolerance, negative efficacy 68% in control group reasons for drop-out: change mind, die, inadequate data, diagnosis changed, improvement in seizures

Suvasini Sharma et al. 2013	N=102 (2-14yrs)	Tonic (n=48) Myoclonic (n=47) Atonic (n=27) Absence (n=20) Tonic–clonic (n=16) Partial (n=19) Epileptic Spasms (n=19) Lennox-Gastaut s. (n=47) West s. (n=19) Myoclonic astatic epilepsy (n=5) Partial epilepsy secondary to structural lesions (n=5) Others (n=4) Unclassified(n=22)	MAD group (n=50)	3 months	After 3 months MAD group(n=50) >90% reduction in 30% of children >50% reduction in 52% of children Control group (n=52) >90% reduction in 77% of children >50% reduction in 11.5% of children p-value<0.05	<u>87.8 % in MAD group</u> Reasons for discontinuation: Lost to follow up, unknown reasons <u>97.5% in control group</u> Lost to follow up
Ben F.M. Wijnen et al. 2017	N=48 (1-18yrs)	Not referred	MCT (n=18) Classical(n= 2) Mixture(n= 1) Percutaneous gastrostomy tube (n=6)	16 months	After 4 months Ketogenic diet(n=26) Seizure-free in 3 children ≥ 90% seizure reduction 3 % of children ≥ 50% seizure reduction in 7% of children Control group (n=22) Seizure-free in 2% of children ≥ 90% seizure reduction 1 % of children ≥ 50% seizure reduction in 1% of children	<u>58% in KD group</u> Reasons for discontinuation: Side effects, incompliance, change mind
K.N. Vykunta Raju et al. 2011	N=38 (6m-5yrs)	West s. (n=16) Lennox—Gastaut s.(n=17) Doose s.(n=2) Unclassified(n=3) Myoclonic(n=22) Atypical absence(n=18) Atonic(n=8) Generalized tonic(n=17) Infantile spasms(n=16) Partial(n=3)	4:1 classic KD (n=19) 2.5:1 KD (n=19)	3 months	After 3 months 4:1 group >50% reduction in 58% of children Seizure free in 26% of children 2.5:1 group >50% reduction in 63% of children Seizure free in 21% of children	<u>84.2% in 4:1 diet group</u> reasons for discontinuation : unsatisfactory seizure control and intolerance <u>84.2% in 2.5:1 diet group</u> same reasons with 4:1 group

		Generalized tonic clonic(n=9)				
Joo Hee Seo et al. 2007	N=76 (8m-8yrs)	Infantile spasms(n=30) Lennox-Gastaut s. (n=21) Partial seizure(n=17) Generalized seizure(n=8)	4:1 Classic KD 3:1 KD	6 months	After 3 months 4:1 group seizure free in 55% of children >90% reduction in 5% of children >50% reduction in 25% of children <50% in 15% of children 3:1 group seizure free in 30.5% of children >90% reduction in 5.6 % of children >50% reduction in 36.1% of children <50% in 27.8 % of children	<u>87.5% in 4:1 diet group</u> Main reason for drop out was intolerance <u>83.3% in 3:1 diet group</u> Main reason for drop out was intolerance, 1 patient discontinued because of acute pancreatitis
Suvasini Sharma et al. 2016	N=81 (2-14 yrs)	Generalized tonic clonic (n=5) Tonic(n=27) Myoclonic (n=14) Atonic (n=8) Focal(n=3) Epileptic Spasms(n=40) Focal(n=5) West s. (42) Lennox Gastaut s. (n=17) Myoclonic astatic epilepsy(n=1) Unclassified(n=7)	MAD (n=41)	3 months	After 3 months MAD group(n=41) >90% reduction in 19.5% of children (p value=0.09) >50% reduction in 56.1% of children (p-value<0.0001) Seizure free in 14.6% of children (p-value=0.26) Control group (n=40) >90% reduction in 5% of children >50% reduction in 7.5% of children Seizure free in 5% of children	<u>90.2% in MAD group</u> Reasons for discontinuation: Side effects, intolerance <u>94.2% in control group</u> Reasons for discontinuation: lost to follow up
Yoon J-R et al. 2014	N=108 (2-16yrs)	Not referred	Classic KD(n=42) MAD(n=35)	6 months	After 6 months CKD >90% reduction in 40% of children >50% reduction in 61% of children MAD group >90% reduction in 37% of children >50% reduction in 40% of children p-value=0.829	<u>92.8% in KD group</u> Reasons for discontinuation: adverse events 100% in MAD group

Karimzadeh P et al. 2019	N=45 (12-36m)	Infantile spasm and myoclonus , others	CKD, Formula based CKD	6 months	50% seizure reduction was higher in children who were in formula based group than in CKD only group (Odds ratio: 7.32, Confidence Interval: 2.27-23.58, P<0.05)	0% in CKD group Reasons for discontinuation: Adverse events (urolithiasis, decrease cognition, intolerability) 38.3% in formula based group Reasons for discontinuation: Seizure reoccurrence, intolerability
Kang Ch. et al. 2011	N=40 (6-60m)	Hypoxic ischemic encephalopathy(n=8), malformations of cortical development(n=6), mitochondrial disease(n=1) , suspicious metabolic disease(n=5), cryptogenic(n=15)	CKD	2 years	2 patients in the short trial group had seizure relapsed with clusters of spasms and one patient had reccurrence of occasional focal seizures Two patients in the long term trial group progressed to Lennox-Gastaut s. and one patient experienced recurrence of occasional focal seizures with secondary generalization	79.1% in the long-term trial group Reasons for discontinuation: Ureteral stones, intolerance, aspiration pneumonia 100% in the short-term group

3.2. Study quality

Children were randomly assigned to the ketogenic diet therapy group and the control group receiving the usual therapy. In 10 out of 11 RCTs, there was not blinding except in the study by Jeong Kim et al study, where participants, providers and investigators were blinded to the treatment group assignments. The seizure records were assessed at baseline and after 3 to 16 months after KD. The duration of the follow-up varied between 3 to 6 months in 9 out of 10 studies. The primary outcome in all studies was proportion of reduction in seizure frequency and in most studies secondary outcomes were seizure severity, adverse events, quality of life and behavioral changes.

3.3. Study outcomes

Primary outcome

Data were extracted from 11 RCTs with totally 787 participants aged between 6 months to 8 years. In five out of eleven studies, children had >50% seizure reduction with a statistically significant difference between the group receiving ketogenic diet therapy and the group treated with usual care in a time follow-up between 3-4 months. If the follow-up was extended to 16 months, the difference was not significant [16]. In nine out of eleven studies the proportion of children in ketogenic diet group that had >50% seizure reduction after at least 3 months was 22-63%. In two studies comparing classic ketogenic diet group and Modified Atkins diet, the classic ketogenic diet appeared to be slightly more efficacious than MAD but with no statistically significance. Regarding the lipid ratio of the ketogenic diet, two RCTs showed the effectiveness of a 2.5:1 or 3:1 ratio instead of a 4:1 ratio. The proportion of children in the 2.5:1 or 3:1 diet group with >50% reduction was higher and the tolerability was better from 4:1 diet group.

Secondary outcomes

Adverse effects

All studies reported gastrointestinal symptoms and a mild increase in total cholesterol as the most recurrent side effects of the ketogenic diet. Constipation, vomiting, anorexia, diarrhea occurred at the fisrt 3 months of the diet and tended to be reduced in frequency in the follow-up visits. Most of them were faced by dietary adjustments or conservative treatment, including H2 blockers and anti-emetics. In two studies with longer follow-up [15,16], a clinically relevant decrease in height and weight was reported after 6-12 months receiving ketogenic diet. Lower respiratory infections, metabolic acidosis, symptomatic hypoglycemia were tolerable with conservative treatment. Acute pancreatitis in one children, hyperammonemic encephalopathy in another and frequent chest infections in two children where reasons for discontinuation of the diet [12,18]. Urolithiasis and microscopic hematuria were asymptomatic and were reported in some cases after 3 months yet more frequently after 6 months of diet. In two studies, osteopenia was reported in children after 8 months of diet.

Behavior and cognitive outcomes

In one RCT [16], after 16 months of ketogenic diet, patients had significantly fewer behavior and motor/coordination problems in comparison with the control arm. In two studies [18,21] the majority of parents referred improvement in alertness, activity level, social interaction and behavior.

Seizure severity

In two studies [15,16], the seizure severity was decreased in the KD group. Lambrechts et al.[15] reported that children in the KD group had twice as many reduction in seizure severity after 4 months compared with the control group. In the other 9 studies, seizure severity was not reported.

Quality of life-cost

Only in one study [16] the quality of life was assessed. Quality of life was measured by using questionnaires for children's quality of life. The questionnaires were answered by parents or carers to calculate cost per Quality-Adjusted Life Year (QALY) for the patients. Due to the high cost of follow-up in the KD group, cost per QALY ratios were inconclusive.

Retention rate

All studies experienced withdrawals. The retention rate varied between 58% and 92.8%. The lower retention rate was observed in the study by Wijnen et al.[16] where the follow-up was 16 months. The most common reasons for patients' drop-outs were adverse events, intolerance, lack of seizure reduction and negative efficacy. In the study by Karimzadeh et al.[11] he total drop-out of patients under 2 years was 100% in the classic ketogenic diet group. The use of formula based ketogenic diet in this study showed a better compliance and tolerability from infants and small children (1-3 years old). Comparing modified Atkins diet and classic ketogenic diet, two studies [17,18] reported better retention rates in the MAD groups. One study [12] revealed lower rates of discontinuation in the 4:1 group compared to the 3:1 group (see table 1).

4. Discussion

This systematic review has shown that ketogenic diet therapies could be an effective treatment for children with refractory epilepsy. Many studies have suggested that ketogenic diet is an evidence-based treatment for drug-resistant epilepsy. Regarding to the mechanism of action, diets force the body to adapt to alternative intakes in order to provide adequate energy for the daily functioning requiring medical and trained dietician assistance [10].

In all 11 RCTs the proportion of children with >50% reduction in seizures were higher in the KD group than that in control group. This proportion ranges between 7-63% and depends from the duration of follow-up, the type of ketogenic diet and was adjusted in most RCTs for patients' characteristics. The above findings are compatible with previous studies. Soubron et al. [22] suggest that seizure frequency reduction ≥50% occurs in 35-56.1% in participants in the KD group, compared with 6-18.2% in the control group. In the study by In Lyons et al.[23] systematic review and meta-analysis the proportion of infants that achieved ≥50% seizure reduction was 59% (95%CI, 53-65) and 33% were seizure free (95% CI, 26-43). Another observational study including 29 adult and adolescent patients (mean age 32 years, range 11–51) showed that 45% of patients had ≥ 50% reduction in seizure frequency after.

With regards to the attrition rate, Soubron et al concluded that drop-outs ranged between 10-26% during a period of 3-6 months and the higher drop-out was reported when the follow-up was extended in 16 months [16,17]. Lyons et al. cited retention rates 84%, 68% , 43%, 27% at 3,6,12 and 24 months respectively. The reasons for discontinuation were similar including inefficacy, adverse events and reviewed extra intercurrent enterocolitis and seizure free [23]. In the study by Nei et al.[24] at 3 months 62% remained on the diet and this declined to 38% by 6 months. The main reasons for discontinuation were intolerance and lack of efficacy.

The adverse events were similar to those reported in previous studies and include mainly gastrointestinal symptoms and dyslipidemia. These side effects two reported within 3 first months of diet [16,21]. More serious adverse events were lower respiratory infections, abdominal pain, anorexia, lethargy and hyperammonemic encephalopathy [20], that in most cases were treated with conservative medication.

There have been several systematic reviews and meta-analysis assessing the efficacy of ketogenic diet on refractory epilepsy [22,23,27,28]. In the study of Lyons et al.[23] the target group was infants (≤2 years old), Chai et al. incorporated only prospective studies, Kj McGill included adults and Soubron et al. reviewed only five RCTs. The main outcomes were congruent with the previous studies as mentioned above.

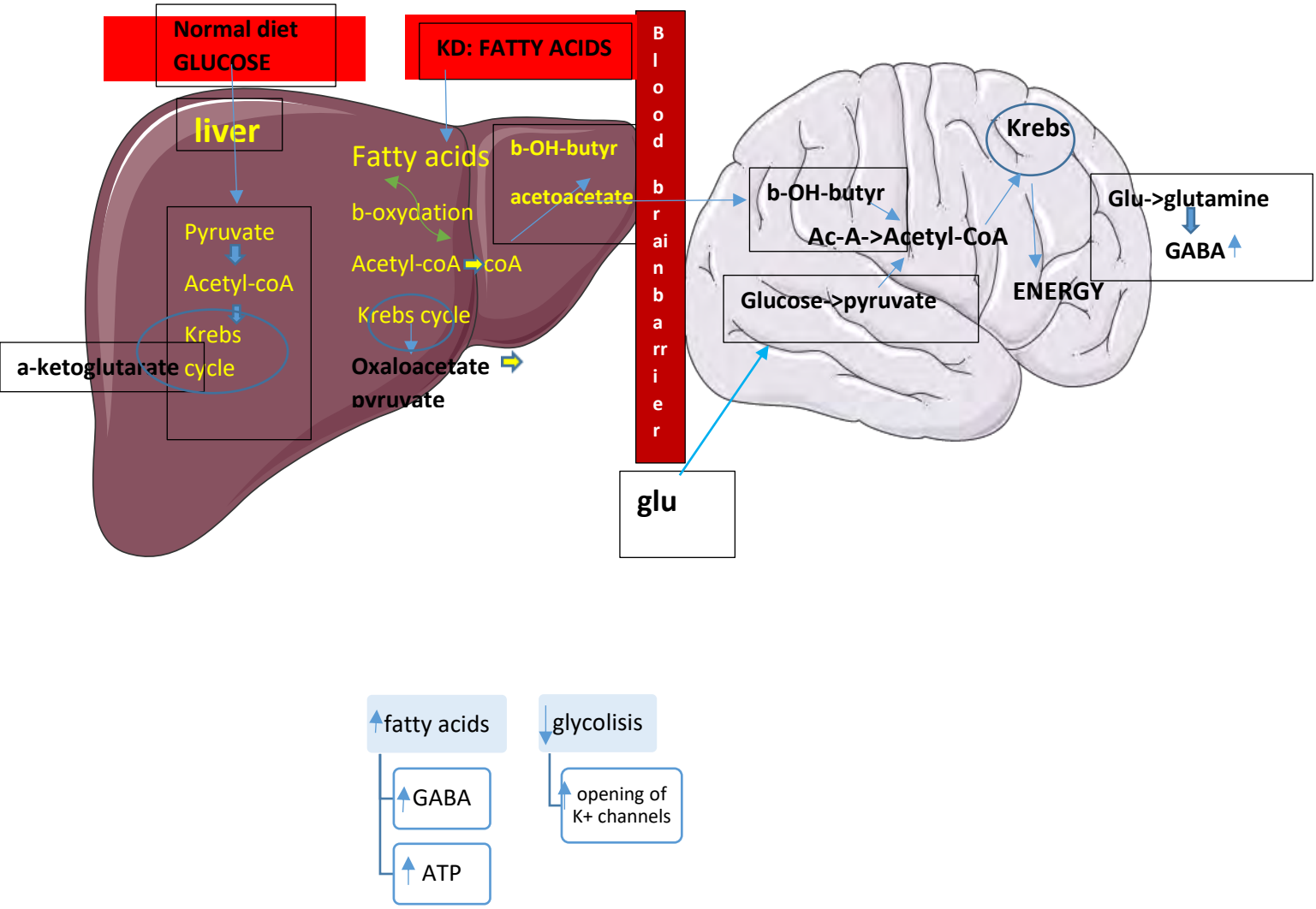
4.1. Limitations

In the majority of the studied RCTs, the main limitation was the lack of blinding. Another issue was the follow-up duration that ranged from 3 to 6 months and only in two studies the follow-up continued for 12-16 months [14,15]. In the study of Wijnen et al[16], the control group was studied for 4 months and the data were extracted from a time period of 16 months. In the same study, the control group was offered to receive the KD after the first period of 4 months, but the specific number of participants who agreed to continue the diet was not evident. The retention rates were low in the long-term trial (58% in 16 months period) and the exact reason for discontinuation was not mentioned. Data about life quality, behavior, seizure frequency were reported by parents or child carers and, therefore, there is a lack of subjectivity in the data collection.

4.2. Mechanism of action

Ketogenic diet therapies for the treatment of childhood epilepsy were applied since 1921. The mechanisms of action have been studied by many researchers. The main focus has been whether ketone bodies themselves reduce neuronal excitability or is it the consequence of reduced glucose utilization. One of the proposed mechanisms is the decrease of glycolysis and the increase in the mitochondrial metabolism of ketone bodies. Ketone bodies enter nerve cells using monocarboxylate transporter (MCT) and are then directly metabolized by mitochondria in neurons. Then, mitochondria use ketone bodies to produce ATP as a source of energy for the brain. In his research, Kristopher Bough [29] has shown that KD treatment causes an increase in energy metabolism in the mitochondria of the hippocampal tissue and an elevation of the energy reserves in the hippocampus. This metabolic shift from glycolysis to mitochondrial ketone metabolism causes a decrease in glucose levels as ketone bodies become the main energy fuel in the brain. One of the candidates for the link between changes in metabolism and neuronal excitability are the ATP-sensitive potassium (KATP) channels. KATP channels are widely distributed in the brain and their increased activity has been connected with reduced neuron excitability [25]. The reduction of glycolysis results in reduction of NADH which leads to the repression of brain-derived Neurotrophic Factor (BDNF) which is connected with neuron excitability. Increased BDNF potentiates glutamatergic transmission, increasing neural activity in limbic circuits. The increased activity would lead to a secondary increase in BDNF/trkB levels and initiate further potentiation. Evidence for the latter comes from in vitro studies showing that long-term potentiation can induce BDNF[30].

Figure 2



[https://smart.servier.com]

Ketogenic diet leads to an increase in blood and hepatic fatty acids (FA). Mitochondrial fatty acids oxidation is increased raising acetyl-coA concentrations. Krebs cycle efficacy is lowered and high levels of acetyl-CoA are converted in ketone bodies (acetoacetate [Ac-A], acetone, b-hydorxybutyrate [bOH-Butyr]). B-OH butyrate is transported to the brain via the blood and induce alternative energy pathways. In the brain, ketone bodies are converted to acetyl-coA, which in turn into the Krebs cycle. Metabolic intermediates produced by Krebs cycle lead to energy production via mitochondrial respiratory complexes. The ketone bodies also enter to the glutamate-glutamine cycle leading to an increase of GABA [10].

Perspectives

Ketogenic diet and its effects have been studied in a short term basis, but long-term effect studies, especially in human subjects, need to be investigated. Animal studies have shown that cellular and biochemical alterations by ketones (such as BHB, acetone, and acetoacetate) could increase inhibitory neurotransmission (e.g., by enhancing GABAergic or ATP- sensitive potassium channels), decrease excitatory

neurotransmission (e.g., by affecting vesicular glutamate transporters), or affect mitochondrial processes [22].

The composition of the gut microbiota is influenced by environmental factors and to a lesser extent by host genetics. Diet changes the composition of the intestinal microbial community and the outcome of a dietary intervention is influenced by the composition of the gut microbiota at the time of intervention. Research has focused in part on the impact of carbohydrates where certain types of dietary fibres known as microbiota-accessible carbohydrates (MACs) present an essential energy source to a healthy intestinal microbiota. The ketogenic diet is extremely fibre-deprived and a few recent studies have investigated changes in the gut microbiota in patients with epilepsy during KD, which include diminished relative abundance of fibre-consuming bacteria such as *Bifidobacteria.* It is currently unknown whether changes in fiber intake or its effect on the gut microbiome contribute to the anti-seizure effect or whether this is only a potentially problematic consequence for the gut microbiome when increasing the dietary fat intake. More research is needed to delineate this correlation. [26].

Recent clinical trials in mice have demonstrated that ketogenic diet affects intestinal microbiota. We now need to investigate whether and how these compositional and functional shifts correlate with the anti-seizure effect of KD in patients, as it has been proved in mice [24]. A potential mechanism may include changes in the systemic metabolites that could be a target for the future development of antiepileptic drugs.

5. Conclusion

Refractory epilepsy concerns 25-30% of total pediatric epilepsies representing a global phenomenon with socio-economic consequences. Uncontrolled seizures result in cognitive and behavior problems, brain dysfunction, and are connected with an increase in hospitalizations and high mortality rates in pediatric patients. Ketogenic diet should not be considered as the last option for treatment with drug-resistant epilepsy as many studies have demonstrated the efficacy on seizure reduction, with, in most cases, minor adverse events. Recent studies have shown a potential beneficial role of altered gut microbiota caused by ketogenic diet in people with epilepsy. Therefore, treatment targeting the gut microbiota may be a promising solution.

6. References

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