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USE OF KETOGENIC DIET THERAPY IN EPILEPSY WITH MITOCHONDRIAL DYSFUNCTION: A SYSTEMATIC AND CRITICAL REVIEW

R. R. KOCATÜRK[1, 2], A. TEMİZYÜREK[3], E. REIS[1], S. TUR[1], S. YILMAZ[1], HA. DEMIRKAYA[1], Ö. Ö. ÖZCAN[4], M. KARAHAN[1, 5]

[1]Nutrition and Dietetics, Faculty of Health Sciences, Üsküdar University, Istanbul, Turkey
[2]Molecular Biology, Institute of Science, Üsküdar University, Istanbul, Turkey
[3]Physiology, Faculty of Medicine, Altinbas University, Istanbul, Turkey,
[4]Molecular Neuroscience, Health Sciences Institute, Üsküdar University, Istanbul, Turkey
[5]Biomedical Device Technology, Vocational School of Health Sciences, Istanbul, Turkey, Üsküdar University

E-mail: mesut.karahan@uskudar.edu.tr

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Background. With the development of molecular techniques over time more than 60% of epilepsy has associated with mitochondrial (mt) dysfunction. Ketogenic diet (KD) has been used in the treatment of epilepsy since the 1920s.

Aim. To evaluate the evidence behind KD in mt dysfunction in epilepsy.

Methods. Databases PubMed, Google Scholar and MEDLINE were searched in an umbrella approach to 12 March 2021 in English. To identify relevant studies specific search strategies were devised for the following topics: (1) mitochondrial dysfunction (2) epilepsy (3) KD treatment.

Results. From 1794 papers, 36 articles were included in analysis: 16 (44.44%) preclinical studies, 11 (30.55%) case reports, 9 (25%) clinical studies. In all the preclinic studies, KD regulated the number of mt profiles, transcripts of metabolic enzymes and encoding mt proteins, protected the mice against to seizures and had an anticonvulsant mechanism. Case reports and clinical trials have reported patients with good results in seizure control and mt functions, although not all of them give good results as well as preclinical.

Conclusion. Healthcare institutions, researchers, neurologists, health promotion organizations, and dietitians should consider these results to improve KD programs and disease outcomes for mt dysfunction in epilepsy.

Key words: epilepsy; ketogenic diet; mitochondrial dysfunction; treatment.

Epilepsy is a neurological disorder characterized by epileptic seizures and unusual behavior that happens because of very harmful damage to neuronal cells in the brain especially in the lateral and temporal lobes [1]. According to the latest data of the World Health Organization (WHO), globally, an estimated five million people are diagnosed with epilepsy each year. In high-income countries, there are estimated to be 49 per 100 000 people diagnosed with epilepsy each year. In low- and middle-income countries, this can be as high as 139 per 100 000 [2].

Mitochondrial DNA (mtDNA) or genomic DNA mutations and mt dysfunction cause various diseases such as Lactic Acidosis, and Stroke-like Episodes (MELAS), Myoclonic Epilepsy and Ragged Red Fibers (MERRF), Progressive External Ophthalmoplegia, Leber Hereditary Optic Neuropathy, Kearns-Sayre Syndrome, and Leigh Syndrome (LS) etc. which can be diagnosed clinically [3–6]. In general, epileptic seizures are currently

controlled by nutrition therapies, antiepileptic drugs (AEDs) (Valproic acid, Carbamazepine, Phenobarbital, Phenytoin, Lamotrigine, Zonisamide, Topiramate and Levetiracetam), vagus nerve stimulations (VNS) and surgery [7, 8]. Although surgery seems to be the last solution in general, the most common treatment methods are AEDs and dietary approaches (i.e., ketogenic diet (KD) and Atkins Diet). KD is a high-fat, low-carb, and protein-rich diet and designed to mimic the anticonvulsant effects of fasting, which is known to suppress seizures [9]. Many studies have reported that KD is a safe, effective, and anti-seizure treatment for many types of epilepsy (especially for infantile epilepsies) [10, 11].

Relationship of mt Function, OS and Seizure

Epileptogenesis can be initiated by a range of brain lesions, including those due to tumors, infections, status epilepticus, childhood febrile seizures, stroke, hypoxia, traumatic brain injuries, and neurodegenerative diseases [5]. The frequency and severity of seizures occurring in the pathogenesis of epilepsy increases oxidative stress (OS) [4, 13–16]. AEDs are used in the clinic for seizure control in epilepsy due to mt dysfunction. However, some of AEDs (i.e., carbamazepine, phenobarbital, primidone, or oxcarbazepine) may cause OS by creating mt toxicity [17, 18]. Myoclonic and tonic seizures can coexist in situations that cause stress, as seen in Epilepsia Partialis Continua (EPC) [19, 20]. Status epilepticus is also well-known presentation feature of epilepsy with OS status in mt Respiratory Chain Complex (RCC) defects [21]. Mt dysfunction is related to epilepsy and can diagnosed by genetic or spectroscopic analyses, include neonatal epileptic encephalopathies with burst suppression due to mutation of the mt glutamate *SLC25A22* gene, neonatal onset epilepsy due to Lipoic Acid Synthetase *(LIAS)* deficiency associated with mutation c.7464A (p.Arg249His) in the *LIAS* gene, parieto-occipital epilepsy caused by a DNA Polymerase Subunit Gamma *(POLG) 1* gene compound heterozygous A467T/W748S genotype, intractable epilepsy due to *POLG* gene mutations, epilepsy with sensorineural hearing impairment, or diabetes mellitus due to a variant m.15218 A4G mutation, and Dravet Syndrome (DS) with comorbid gene mutations (c.3734 G4A and c. e733 C4T), and mt RCC I, II, III and IV dysfunction [8].

Effect of KD on mt Dysfunction and Brain Energy Metabolism

Neuronal cells under the effect of KD become more resistant to metabolic stress and epileptic seizure thresholds increase. Aggravation of seizure sensitivity increases the frequency and severity of seizures. KD is important in preventing OS that occurs in mitochondria due to increased ROS activity in neural cells. Ketone body (KB) are the metabolite of KD such as Acetoacetic Acid, beta-hydroxybutyric Acid and stimulates mt biogenesis, which reduces OS in mt and mtDNA mutation and improve mt function [12, 22]. KB reduces OS by clearing free radicals and increasing antioxidant levels [15]. Dutton et al. reported that KD reduced ROS activity in the mt of mice treated with 10–12 KD ($P < 0.05$) [23]. In addition, KD increased the endogenous antioxidant Glutathione (GSH) levels in mt, improved the mt redox state ($P < 0.01$), KD regulated GSH biosynthesis, increases the mt antioxidant status, protects mtDNA from oxidant-induced damage ($P < 0.05$) and provided seizure control [24, 25].

Direct neuronal effects induced by the KD may involve ATP-sensitive potassium (K_{ATP}) channel modulation, enhanced purinergic (i.e., adenosine) and Gamma Aminobutyric Acid (GABA)ergic neurotransmission, increased brain-derived neurotrophic factor expression consequent to glycolytic restriction, attenuation of neuroinflammation, as well as an expansion in bioenergetic reserves and stabilization of the neuronal membrane potential through improved mt function [27]. Glucose is the most preferred energy source in the brain in neuronal stimulation and sudden seizures. The KD's low carbohydrate content reduces the amount of glycolysis in the blood. KD mimics the metabolic state of starvation, forcing the body to utilize fat as its primary source of energy instead of carbohydrates. Glucose expenditure gets very high in neurons, but ATP deficit is provided by oxidation of KD during the epileptic seizures [28]. ATP is providing from KB that turn into the basic energy source for neurons by β-oxidation [26, 29]. KD increases the seizure threshold by increasing the amount of ATP with the change in glycolysis and mt function. Long-term KD therapy coordinates several genes involved in energy metabolism, provides increased energy stores such as mt biogenesis and phosphocreatine. This improves the function of neurons and causes fewer neurons to die under OS conditions [30].

KD also regulates neurotransmitter release due to energy use in neurons. Clanton et al. found that Glutamate is a mediator molecule between the neuronal and astrocytic compartments in the regulation of the GABAergic inhibiting tone. Glutamine synthetase deficiency is pathogenic process for the production of seizures both in the brain slice model and in the human neuropathological study [31–33]. In a contrast study, Chan et al. found that although KD treatment increased the GABA and agmatine levels but did not change glutamate levels in the hippocampus of rats [33]. Similarly, Calderón et al. found that KD has no effect on glutamate release [34]. Another study demonstrated that mt Dihydroorotate Dehydrogenase (DHODH) as a regulator of activity set points in hippocampal networks and DHODH inhibition is known to reduce susceptibility to seizures in the intractable epilepsy model [35]. KD can regulate to mt protein transcripts [36] so it may have a connection with DHODH. KD may help to inhibit DHODH and the seizures in epilepsy but there is no evidence.

An umbrella review approach was taken in recognition of the fact that a large body of literature exists on KD and epilepsy. The discovery of more than 270 identified mutations in mtDNA has further illuminated the clinical diagnosis of epilepsy and has been reported to continue to be a common feature in status epilepticus [12, 37] and previously published systematic reviews were only about epilepsy and KD outcomes and did not investigate KD effects on mt dysfunction in epilepsy groups, thus justifying the need for further research focusing on the changes that occur. This systematic review aimed to evaluate KD treatment on the mt dysfunction in epilepsy evidence with the following specific purposes: 1) to know the *in vitro and vivo*, clinical trials and case reports on mt dysfunction in epilepsy disease; 2) to verify some unanswered question about KD approach to mt dysfunction in epilepsy and 3) to evaluate the evidence of its validity and reproducibility.

Controversial Issues and Unanswered Questions

These questions were discussed with included studies in the following result sections. They can be important on the further research to be carried out in the future could lead to significant results (see Table 1).

Materials and Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were followed as a method for reporting this article [38].

Literature Search and Study Selection

Three electronic databases (PubMed, Google Scholar, MEDLINE) were searched during the period of January 1980– 12 March 2021. The review focused on the KD treatment mechanism mt dysfunction in epilepsy. Besides, only articles published in English were considered. This review focused on topics KD treatment of mt dysfunction in epilepsy, specific search strategies were devised for the following topics: (1) mt dysfunction (2) epilepsy (3) KD. To achieve the maximum sensitivity of the search strategy, we combined the terms (Ketogenic Diet) OR (Ketogenic Treatment) OR (Ketone Bodies) AND (Mitochondrial Dysfunction) OR (Mitochondrial Mutation) AND (Epilepsy) OR (Seizure) OR (Epilepticus) OR (Mitochondrial Epilepsy) as keywords. Studies including mitochondrial disorders, mitochondrial dysfunctions in epilepsy disorders or in epilepsy model and the KD were considered eligible.

Results and Discussion

34 studies were found on PubMed, 1730 studies were found on Google Scholar, 30

Table 1. **Controversial issues and unanswered questions of KD treatment for mt dysfunction in epilepsy**

1. What is the scientific fact behind the preference of a KD in mt dysfunction in epilepsy?
2. Are there other specific treatments applied with/without KD for mt dysfunction in epilepsy?
3. Do KD and AEDs treatments really help mt dysfunction in epilepsy together?
4. Can KD Prevent drug resistance due to mt dysfunction in epilepsy?
5. What are the possible seizure prevention mechanisms of KD in epilepsy due to mt dysfunction?

studies were found on MEDLINE. In this study a total of 1794 publications were identified. A total of 36 publications were finally included. The flow chart of the literature search is presented in Fig. 1. Tables 2 to 6 summarized and contained the characteristics of the included studies.

Unanswered questions (in table 1) were tried to be answered with the included studies as following.

1. What is the scientific fact behind the preference of a KD in mt dysfunction in epilepsy?

Mt dysfunction in epilepsy is a potential clinic outcome, as mt OP provides the primary source of ATP in neurons and participates in the formation of ROS, which impacts neuronal excitability and synaptic transmission strongly [13]. A decrease in ATP and an increase in AMP, ADP, lactic acid, and an increase in intracellular Ca^{+2} [10] is indicators of dysfunction in mt [13] such as Alpers-Huttenlocher syndrome, Pyruvate Dehydrogenase Complex Deficiencies, LS, MELAS, MERFF, and *POLG*-related disorders which could present with focal generalized seizures, and this means that the patient is dealing with epilepsy caused by multiple mt mutations [39]. To diagnose mt dysfunction in epilepsy, there are some ways such as presence of epileptic seizures, multi-gene panel testing, many other mutation tests on the karyotype, the sequence of mtDNA and other mt causes (i.e., mt enzyme activity) [39, 40]. Looking at some examples from the included studies, Krysko and Sundaram reported that one of the common ND3 mt mutation T10191C can lead to epileptic seizures and high m.3243A> G heteroplasmy causes mt dysfunction in neurons so that, seizures can occur and the mt disorder can lead to epilepsy on the patient [40]. Homoplasmic

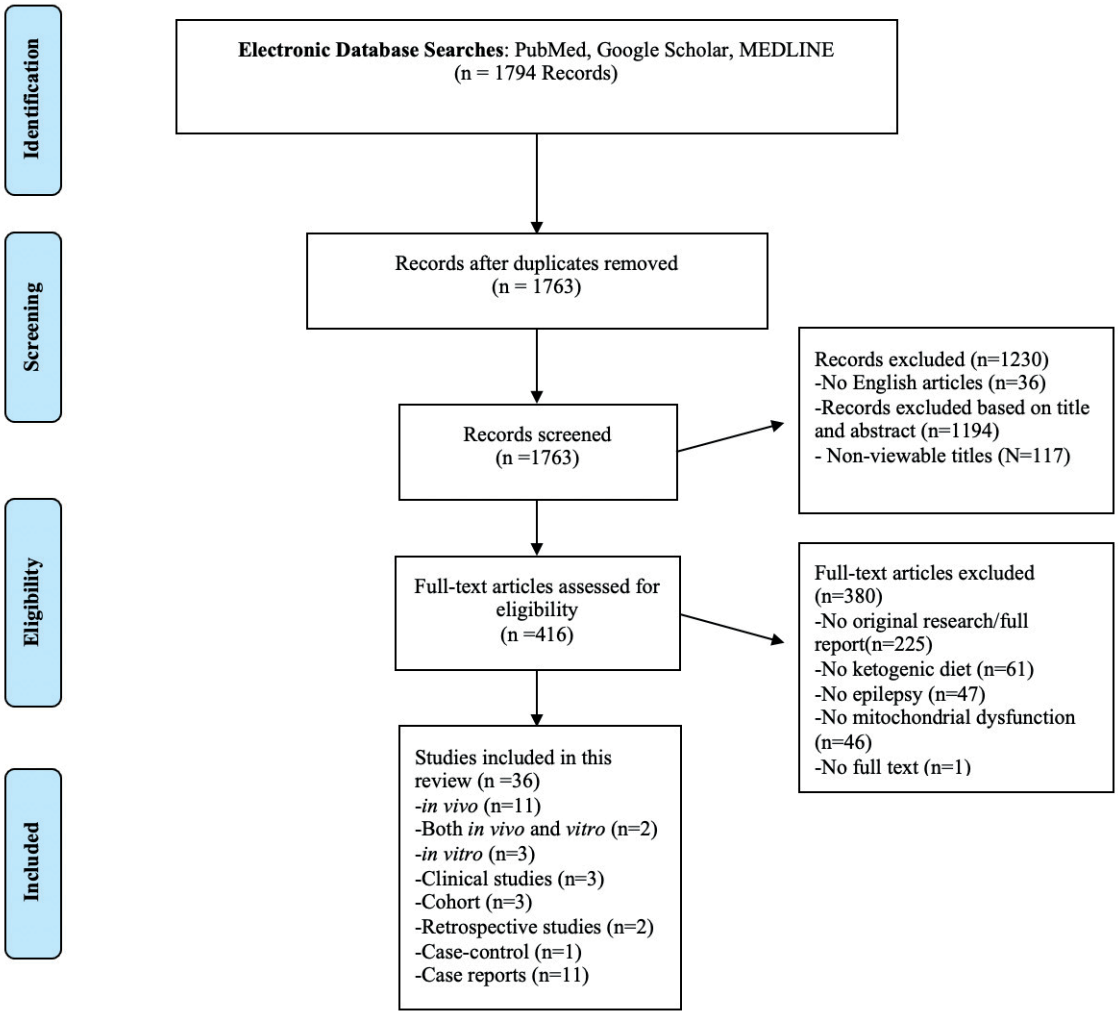

Fig. 1. **Summary of the process used to identify and select studies for the unanswered questions about the KD approach to mt epilepsy [38]**

and heteroplasmic mt mutations can cause mt dysfunction and the onset of various types of epilepsy [41]. Lee et al. had similar findings that 125 patients clinically suspected of LS and 25 patients were identified to have heteroplasmic mtDNA mutation associated to LS. Also, clinical features of this study can give some clues for mt dysfunction such as hyperlactatemia raised alanine, and muscle complex IV deficiency [42]. On the other hand, Gim nez-Cassina et al. reported that BCL-2-associated Cell Death Agonist (*BAD*) genetic variations that can be related to mt dysfunction because this genetic modification is very important to the prevention of apoptosis in mt and in the regulation of glucose and KB metabolism [43]. However, there was no other evidence, the effect of KD on AEDs response and seizures control in the studies regarding mt dysfunction in epilepsy caused by *BAD* mutation.

Twelve studies assessed the effect of KD on the mechanism of mt following the mutations or dysfunctions in epilepsy. Of the Twelve studies, only three were involved in the *in vitro* study. Geffroy et al. isolated *SH-SY5Y* human parental neuroblastoma cells from a postmortem patient with MELAS and containing 97.2% of the m.3243A> G. Then they treated cells for 3 weeks to explain the effect of KD for glucose restriction. As a result, they reported that OXPHOS protein and mtDNA copy number increased significantly and mt enzyme activity was improved in glucose restriction [44]. Frey et al. reported the same result by treated these cells (the same mutation) with KB for 4 weeks [45]. Hughes et al. also found the same results by applied the 250-μM C10 and C8 (on medium-chain triglyceride) diet to the *SH-SY5Y* neuronal cells separately [46].

Seven of the Twelve studies were related to *in vivo* studies. Nylen et al. applied the KD on *ALDH5A1*$^{-/-}$ mice (Succinic semialdehyde dehydrogenase (SSADH) deficiency) from postnatal 12th day and found that KD had very significant role to improve hippocampal mt and ATP levels [47]. Bough et al. evaluated the effects of KD by observing a significant increase in metabolic gene transcription, mt protein translation and biogenesis after a three-week administration of KD which may have an anticonvulsant effect in an animal model of epilepsy (Sprague–Dawley rats) due to pentylenetetrazole (PTZ), not a mt disorder [36]. Jarret et al. also measured mt redox activity of 3-week KD treatment in Sprague-Dawley rats (P28) and KD significantly improved ($P < 0.05$) mt functions by preventing mt oxidative damage [24]. Hasan-Olive et al. reported that the effect of KD on the *mutUNG1* transgenic mice was significantly higher in the pericaria and axon terminals of the hippocampus CA1 pyramidal neurons than Standard Diet (SD) fed mice. Subsequently, the hippocampal neurons obtained from rats were treated with β-hydroxybutyrate (βHB) and the Oxygen Consumption Rate (OCR) and the NAD+/NADH ratio improved significantly [48]. Wang et al. applied Autophagy Inducer Rapamycin (RAP) and inhibitor 3-methyladenine (3-MA) by manipulating autophagy after applying KD therapy in an epilepsy-induced rat model induced by PTZ. As a result, KD improved mt damage and reduced mt cytochrome c release, RAP pretreatment increased the neuroprotective effect of KD, and 3-MA pretreatment abolished it. In addition, KD increased the level of autophagy, and regulated pretreatment with RAP or 3-MA autophagy as well [49]. Kumar et al. reported that KD with *Scn1Lab* mutant zebrafish decreased in baseline glycolytic rate and OCR compared to controls and showed a significantly slower and exaggerated increase of both glycolytic rates and OCR after 4-aminopyridine. The significant result from this study, *Scn1Lab* mutant zebrafish suggest that glucose and mt hypometabolism contribute to the pathophysiology of DS which can be related with mt epilepsy [50]. Pérez-Liébana et al. studied KD treatment in Aralar/AGC1/Slc25a12 deficiency characterized by hypotonia, hypomyelination, developmental arrest and epilepsy. Five days βHB administration on Aralar-KO mice improved bad mitochondrial respiration by bypassing the metabolic failure in neurons. βHB improved DA, DOPAC/DA ratio, VMAT2 protein (dopaminergic system) and MBP, MAG myelin proteins (myelinization). Cytosolic aspartate and NAA synthesis increased with βHB oxidation in mitochondria. Aralar deficiency are probably eliminated through citrate-malate shuttle by increased cytosolic aspartate and NAA [74].

One study was related to case-report. Nizon et al. reported 2 ½-year-old French girl, a case who had focal seizures with Iron-Sulfur Cluster Scaffold (*NFU1*) mutation and Leukoencephalopathy. 6-month oral lipoid acid (100 mg/kg/day) was administered but was stopped because no improvement was observed in the disease. Subsequently, KD (lipids 60% of calories) was applied, but acute dystonia and metabolic attack were observed

within 24 hours, and it was reported that the reason was partially blocked Krebs cycle in the α-setoglutarate dehydrogenase step [51]. One study was related to clinical research (case-control study). Miles et al. reported 65 epilepsy patients with suspected mt dysfunction. No significant clinical, pathological or biochemical differences were found between the epilepsy and control groups. Only three patients treated with KD, 2/3 patients had valproic acid (VPA) and one of the patients had AEDs as well. All three patients had low subsarcolemmal mt aggregates (SSMA) but no evidence of increased mt density or improved ETC function has been shown in humans [18].

These included studies give us a wide range of explanations of the KD mechanism on mt function, but KD might have also different mechanisms and those should be revealed by supporting with further research. Three of *in vitro* studies showed that KD was useful for increasing OXPHOS protein, mtDNA copy number, mt enzyme activity and glucose restriction. Molecular diagnoses related to mt have been made in clinical and case studies published in epilepsy due to mt dysfunction. Except for the clinical follow-up of the patients in the KD and AEDs applied, molecular level investigations have not been reported. Overall, behind the general scientific reality that KD was effective in epilepsy due to mt problems, there were positive effects such as improved mt function, mt mass, mt biogenesis leads to improved alternative energy stores, restoring complex I, II, III and IV stability and activity, reduced mt cytochrome c release, increasing ATP synthesis, and decreasing the NADH/NAD+ ratio.

2. Are there other specific treatments applied with/without KD for mt dysfunction in epilepsy?

Of the seven studies assessing other specific treatments with/without KD on mt dysfunction in epilepsy. Willis et al. developed a new anticonvulsant diet (triheptanoin diet which contains high fat) in two types of chronic mouse epilepsy models. Triheptanoin feeding (high fatty acid) increased intracellular acylcarnitines which is very important for mt biochemical activity, decreased seizures and propionyl-CoA levels and increased methylmalonil-CoA level [52]. Hughes et al. reported medium-chain triglycerides feeding [application of decanoic acid (C10)] increased mt biogenesis significantly in Pharmaco-resistant epilepsy animal model *in vivo* and *SH-SY5Y* neuronal cells *in vitro*. This mt biogenesis might be related with the activation of the Peroxisome Proliferator Activator Receptor γ (PPARγ) [46]. Willes et al. applied KD and mt cocktail therapy during 3 months to Ohtahara Syndrome and reported that this combined therapy was useful for controlling seizures [52]. Similarly, Lee et al. reported 36/48 patients receiving the mt cocktail treatment showed an improvement as measured by the caretaker's global assessment form. Eight of these (16.7%) showed marked improvement. None of the cases had side effects. The clinical outcome from the mt cocktail supplement was not dependent on the type of mt Chain Enzyme Complexes (MRC) defect [20]. Seo et al. was used SD, 20% triheptanoin diet and 35% triheptanoin diet (high fat diet) for up to 7.5 weeks on CF1 mice model and high fat diet had an anticonvulsant effect to seizure control [53]. Cheng et al. also reported propionate and KD regulated mt dysfunction, neuron necrosis and epileptic seizures, reduced mt disruption, hippocampal apoptosis, neurological deficiencies, and epileptic seizure intensity [54]. Coenzyme Q10 supplements were useful to control seizures in epilepsy with mt dysfunction [39]. As a result, combined specific methods such as coenzyme Q10 supplements, mt cocktail therapy, triheptanoin diet, medium-chain triglycerides feeding, and propionate have anticonvulsant effect to seizure control for the epilepsy with mt function.

3. Do KD and AEDs Treatments really help mt dysfunction in epilepsy together?

65 percent of patients with epileptic seizures can be controlled with AEDs. However, despite the treatment and medication, 35 percent of patients with seizures are not still under control and these patients are known to develop resistant epilepsy [55]. According to studies, some AEDs can cause mt dysfunction (toxic with side effects) and the treatment process should be followed carefully [8, 13, 17]. Haj-Mirzaian et al. showed that the effect of mt disorder due to lipopolysaccharide on minocycline application was investigated minocycline reduces the seizure threshold and may reduce the side effects of AEDs through regulating of mt function and decreasing of neuro-inflammation in PTZ-induced seizures animal model [56].

Nine studies assessed mt dysfunction in epilepsy following KD treatment and AEDs. Nine of the seven studies were case reports. Wesoł-Kucharska et al. reported an 8-month infant male with LS (m.12706T > C in MTND5),

Table 2. ***In vitro*** **evidence of KD for mt dysfunction in epilepsy**

Authors	Type of Epilepsy	Cell Line	Aim	Treatment	Time	Results
Hughes et al. 2014 [46]	Pharmacoresistant epilepsy.	SH-SY5Y neuronal cell line.	Medium-chain triglyceride diet and the observation level of the plasma C8 and C10 concentrations.	250-μM C10 and C8.	6-days	C10 made an increase on mt number, citrate synthase along with complex I activity and catalase activity. C8 use revealed no significant effect with regards to citrate synthase activity. This may occur via the activation of the PPARγ.
Geffroy et al. 2018 [44]	MELAS Syndrome	SH-SY5Y parental neuroblastoma cell line (postmortem MELAS woman) and neuronal-like cybrid cells 97.2% m.3243A>G.	To evaluate the metabolic part of carbohydrate reduction in KD.	Low glucose exposure.	3 weeks	Accumulation of complex I matrix intermediates in untreated mutant cells, led to a severe reduction in complex I-guided respiration (parallels the postmortem brain tissue of a MELAS patient). OXPHOS protein coding and mt DNA copy number were significantly increased in mutant cells compared to other control fibroblast and neuron cells by glucose restriction (KD).
Frey et al. 2017 [45]	MELAS Syndrome	m.3243A>G with 98.6% mutant SH-SY5Y parental cell line	To investigate metabolic mechanisms of KB in MELAS syndrome.	KB exposure.	4 weeks	KB treatment restored complex I stability and activity, increased ATP synthesis, the mtDNA copy number and lowered the NADH / NAD+ ratio.

Abbreviations: Decanoic Acid (C10), Ketogenic Diet (KD), Ketone Bodies (KB), Lactic Acidosis and Strokes Like Episodes (MELAS), mitochondrial DNA (mtDNA), Octanoic Acid (C8), Oxidative Phosphorylation System (OXPHOS), Peroxisome Proliferator Activator Receptor γ (PPARγ), Quantitative Polymerase Chain Reaction (Q-PCR).

seizures and bad echocardiography. After administration of KD diet for 10-month clinical condition and echocardiography improved, after age 12-month AEI administration was used and successful result was received [75]. However, Buda et al. reported a 13 years old case diagnosed homoplasmic 8344G>A mutation in the Mitochondrially Encoded TRNA-Lys (AAA/G) (*MTTK*) gene with LS, MERRF and chronic epilepsy which treated with KD and VPA administration or intensive rehabilitation. The result of the benefit of KD after AEDs application for mt tRNA-mutated patients could not be assessed but was associated with remission [57]. Samanta et al. reported an 18-year-old case report with heterozygous *POLG* mutation-p.W748S (c.2243 G > C) (diagnosed with Intractable left-sided EPC) and several AEDs and KD therapy applied together, but no regression was observed in her seizures [58]. In contrast, Cardenas and Amato reported a 14-month-old female presented with EPC with *POLG* heterozygous mutations. Her seizures were eliminated but remained severely encephalopathic [59]. Krysko and Sundaram et al. reported a 16-year-old female case with MELAS (the rare *ND3* mt mutation *T10191C)* and primidone, phenytoin, topiramate, phenobarbital, perampanel were applied with the KD treatment, but her seizure frequency increased [40]. Kwong et al. similarly reported a 13-year-old Chinese boy and his family had *ARX* genetic defect (ARX-associated (c.989G>A; p.Arg330His) encephalopathy). His epilepsy failed to respond to various anticonvulsants including phenobarbital, clobazam, lamotrigine, levetiracetam, nitrazepam and KD treatment [60]. Similarly, Lankford et al.

Table 3. ***In vivo*** **and** ***in vitro*** **evidence for KD for mt dysfunction in epilepsy**

Authors	Type of Epilepsy	Animal Model	Aim	Treatment	Time	Results
1	2	3	4	5	6	7
Hasan-Olive et al. 2019 [48]	Refractory Epilepsy	WT mice and *mutUNG1* transgenic mice, rat hippocampal neurons	To test the effects of a KD or the βHB on induced mt toxicity in hippocampal tissue in vivo. To explore mechanisms underlying ketone increased mt biogenesis and functions *in vitro*.	In vivo: high fat KD In vitro: βHB exposure	–	that KD and βHB treatments apparently changed the expression of mRNAs and proteins *(UCP2, PGC1α, Drp1 and Mfn1)* and help to increase mt mass and functional competence, apparently via the "PGC1α-SIRT3-UCP2 axis ($p < 0.05$). ***in vitro*** side: Especially, βHB treatments increased OCR and the NAD+/NADH ratio. *in vivo* side: The mt count of *UCP2* was significantly higher in the perikaria and axon terminals of hippocampus CA1 pyramidal neurons in KD treated *mutUNG1* mice compared with *mutUNG1* mice fed a SD.
Giménez-Cassina et al. 2012 [43]	Epilepsy	$BAD^{-/-}$ and BAD^{S155A} knocking mice neuronal cells	To examine the role of *BAD* modifications on seizures by regulating KB and glucose metabolism.	KB exposure	-	*BAD* modification found to act mainly in the liver, brain cells and preventing mt apoptosis, increasing mt functions, regulating glucose metabolism, increase the function of K_{ATP} channel. Reduced seizures in increasing the use of KB metabolism. *BAD* modification was related to enhancing the functions of mt, increasing KB and glucose in direct proportion.
Willis et al. 2010 [52]	Epilepsy	CF1 mice	Anticonvulsant effects of feeding triheptanoin diet (high fat diet) (the triglyceride of anaplerotic heptanoate).	2%0 triheotanoin diet and 35% triheptanoin diet	7.5 weeks	35% Triheptanoin feeding increased intracellular acylcarnitines, decreased seizures and caused a decrease in propionyl-CoA levels and increased methylmalonil-CoA levels in SE mice. Intracellular acylcarnitines was in balance with fatty acid acyl-Coenyme A intermediates in mt fatty acid beta oxidation.
Dolce et al. 2018 [73]	Epilepsy	Male NIH Swiss mice (aged 3–4 weeks)	To find that the KD and intermittent fasting, would differ in their acute seizure test profiles and mt respiration.	1:4 KD or CD-IF (24 h feed/ 24 h fast)	12–13 days	KD protected the mice against 6 Hz-induced seizures but had more severe seizure scores in the kainic acid test and it was opposite in CF-IF. KD and CD-IF did not share identical antiseizure mechanisms. These differences were not explained by differences in mt respiration (significance was $P \leq 0.05$).

Table 3 (continued)

1	2	3	4	5	6	7
Bough et al. 2006 [36]	Epilepsy	Sprague–Dawley rats	Anticonvulsant effect of KD on epilepsy	KD	3 weeks	KD upregulated 34 transcripts of energy metabolic enzymes and transcripts encoding mt proteins, by increasing number of mt profiles. KD induced mt biogenesis, increased neuronal functions, metabolic gene expression and energy reserves. KD's anticonvulsant mechanism includes mt biogenesis leading to improved energy stores.
Jarret et al. 2008 [24]	Epilepsy	Adolescent Sprague-Dawley rats (P28)	KD effect on mt redox status in the adolescent rat brain.	KD	3 weeks	KD regulated GSH biosynthesis upwards, increased the mt antioxidant status, and protected mtDNA from oxidant-induced damage ($P < 0.05$).
Wang et al. 2018 [49]	Epilepsy	PTZ kindled rats	Protective role of autophagy activated by KD in brain injury following seizure and regulation of mt functions, particularly cytochrome c release, by autophagy by KD.	KD	4 weeks	KD reduced the mt cytochrome c release and improved mt damage and showed neuroprotective effect ($P < 0.05$). KD and pretreatment with RAP or 3-MA regulated autophagy ($P < 0.05$).
Kumar et al. 2016 [50]	DS (Several types of epilepsy)	*Scn1Lab* mutant zebrafish	To develop novel techniques of glycolysis and mt respiration in a zebrafish model.	KD	–	A decrease in baseline glycolytic rate and OCR, a significantly slower and exaggerated increase of both glycolytic rates and OCR after 4-AP. Five glycolytic genes found downregulated identified PCR array. *Scn1Lab* mutant zebrafish suggest that glucose and mt hypometabolism contribute to the pathophysiology of DS.
Fogle et al. 2016 [71]	Epilepsy- ME	Drosophila human ME ($ATP6^1$)	Investigate caloric restriction and KD against the seizures of ME, the K_{ATP} channel and therapeutic potentials on behavioral and neuronal level.	KD	-	KD is found highly effective at reducing seizures in the $ATP6^1$ model, improving time to recovery by up to 90% even in late-stage disease. High fat/KD benefits were dependent upon a functional K_{ATP} channel which was protective for seizures.
Fogle et al. 2019 [72]	Epilepsy- ME	Drosophila human ME ($ATP6^1$ and $TPI^{sugarkill}$ genotypes	To reveal KD mechanisms in the ME model, ketone bodies, citric acid cycle and anaplerotic supplements.	KD	-	Six of these eight drugs (carbamazepine, gabapentin, phenytoin, lamotrigine, topiramate, ethosuximide) had no significant effect on seizure. Vigabatrin and VPA made seizure recovery significantly.

Table 3 (end)

1	2	3	4	5	6	7
						KD was beneficial to multiple *Drosophila* seizure models including those caused by global energetic deficit due to mt dysfunction. KD can be useful on human glycolytic enzymopathy.
Stewart et al. 2008 [70]	SSADH deficiency	Adult *ALDH5A1*$^{-/-}$ mice with *C57/129S* and *WT*	To determine seizure detection method (movement velocity) and conducted a behavioral study of KD to characterize daily patterns of spontaneous motor seizures.	KD	From weaning day onward	KD exhibited a seizure phenotype characterized by fits of wild running clonus accompanied by jumping and bouncing. The seizure rhythm showed a peak shortly after the onset of the dark phase with periodicity close to 24 hours. Older wild type pups showed no evidence of abnormal motor behavior. Generalized tonic-clonic seizures are more frequent at a certain time of day in *ALDH5A1* $^{-/-}$ mice treated with KD.
Pérez-Lie̬bana et al. 2020 [74]	Aralar/AGC1/Sl-c25a12 deficiency	*Aralar-KO*	Effect of βHB, in neuroprotective in Aralar-KO neurons and mice (AGC1-deficiency is characterized by hypotonia, hypomyelination, developmental arrest and epilepsy).	Injections of βHB	5 days	Dopaminergic system improved (DA, DOPAC/DA ratio and VMAT2 protein). MBP and MAG myelin proteins were markedly increased in the cortices. Increase in aspartate (3-fold) and NAA (4- fold) levels. It improved imperfect mitochondrial respiration by bypassing the metabolic failure in neurons. βHB oxidation in mitochondria increases the synthesis of cytosolic aspartate and NAA.

Abbreviations: 4-aminopyridine (4-AP), Aldehyde Dehydrogenase 5 Family Member A1 (ALDH5A1), Antiepileptic Drug (AED), BCL-2-associated Cell Death Agonist (BAD), Control Diet (CD), DNA Repair Enzyme UNG1 (mutUNG1), Dietary Modifications (DMs), Dopamine (DA), Dravet Syndrome (DS), Drosophila model of human ME (ATP61), Fission Protein Dynamin-related Protein-1 (Drp-1), Glutathione (GSH), Inhibitor 3-methyladenine (3-MA), Ketone Bodies (KB), Ketogenic Diet (KD), Micronutrients with Intermittent Fasting (CD-IF), Mitofusin-1 (Mfn-1), mt Uncoupling Protein-2 (UCP2), mt Encephalomyopathy (ME), Mitochondria (mt), models of human glycolytic enzymopathy (TPIsugarkill), Normal Diet (ND), Oxygen Consumption Rate (OCR), Oxidized Glutathione (GSSG), Oxygen Consumption Rate (OCR), Peroxisome Proliferator-activated Receptor-γ Coactivator-1α (PGC-1α),, Pentylenetetrazole (PTZ), Autophagy Inducer Rapamycin (RAP), Standard Diet (SD), Status Epilepticus (SE), Succinic Semialdehyde Dehydrogenase (SSADH), Succinic Semialdehyde Dehydrogenase Deficiency (SSADH-d), Mutations in a Voltage-activated Sodium Channel, Nav1.1 (Scn1Lab), Valproic acid (VPA), Wild Type (WT), β-hydroxybutyrate (βHB).

reported 6-year-old girl case with diagnosed with a complex I–deficient mt disorder and *SLCA2* gene mutation. She did not respond to drug treatment. KD was added to topiramate, levetiracetam and ethosuximide for two days but never continued as was seizures persisted [61]. Of the two study were clinical trials. Lee, Na and Lee examined that 25/125 patients were identified to have mtDNA mutation with LS and KD was given to 14 patients and 2 of them did not respond AEDs treatment [42]. Additionally, Saneto et al. reported 2/180 of children and adolescents with mt disease and they took KD and two traditional AEDs. However, the results of this combined treatment have not been reported [62].

Most of the studies included showed that KD and AEDs treatments did not respond well in epilepsy cases with mt disorders. KD is known to provide energy and reduces ROS and cure mt disorders [50] but according to included studies, KD did not have a positive effect on mt dysfunction in epilepsy. It may mean that the results of the combined administration of KD and AEDs therapy may vary with mt dysfunction with multiple mutations. In preclinical studies, KD were quite successful on mt functions. On the other hand, some cases can indicate that the use of KD with AEDs do not affect patient's clinical patterns. What may be the difference between the studies modeled in a laboratory environment from human studies? Are scientists failing to consider comorbid conditions that occur in patients with mt disorders? Consequently, the underlying failure of clinical trials and case-reports involving KD, and AEDs therapy can be supported by *in vitro* studies on samples as well to be collected from patients, supported by future research into mt function.

4. Can KD prevent drug resistance due to mt dysfunction in epilepsy?

According to included studies there were only two study related to KD prevention on AEDs resistance. Lee, Na and Lee reported 25/125 patients were identified to have mtDNA mutation with LS and AEDs response failure. KD was given to 14/25 patients and only 2 of them did not respond AEDs treatment [42]. Lee et al. reported 24 out of 48 epileptic children with medically intractable epilepsy were treated with a KD. However, there is no report regarding the drug response of KD. The important point here was that mt respiratory MRC defects progressed with the diagnosis of epilepsy due to many mt dysfunction clinically. In this study, depending on the MRC defects (in Table 4), there were also two cases (4.2%) of Ohtahara Syndrome, 10 cases (20.8%) of West syndrome, 12 cases (25.0%) of LGS, two cases (4.2%) of Landau-Kleffner syndrome, 14 cases (29.2%) of unclassified generalized epilepsy, and eight cases (16.7%) of partial epilepsy have been reported [53]. In conclusion, the treatment of KD needs further investigation in epilepsy models *(in vivo and vitro)* and clinics that have both mt dysfunction and drug resistance. There is no such evidence in the literature from a preclinical point of view and only one clinical study has been reported for this question.

5. What are the Possible Seizure Prevention Mechanisms of KD in Epilepsy due to mt Dysfunction?

There were twenty-one studies looked at prevention of KD treatment against of seizures in mt dysfunction in epilepsy. Six of twenty-one studies were clinical reports. Amin et al. indicated that forty-four patients with *CDKL5* mutation were taken AEDs, VNS and KD treatments. Twelve patients received VNS treatment, but six patients had epileptic seizure control. After one year of VNS treatment, this number increased to nine patients in seizure control. Subsequently, twenty-six patients received KD treatment, only twelve patients had a positive turn and sixteen patients had serious side effects. Epileptic seizures of 40/42 patients who only took AEDs could not be controlled at the end [63]. Na et al. reported a retrospective study about Lennox-Gastaut syndrome [(LGS) a typical intractable form of epilepsy] patients with mt dysfunction and they had diet therapies (DT) [(16/20 patients had KD therapy)] and KD therapy was found to be beneficial and significantly improve patient's prognosis in seizure control [64]. Lee et al. presented another retrospective study about 40/372 LGS patients with mt dysfunction and they were classified into two groups based on the history of West Syndrome (WS) (total 13 WS and 27 No WS patients). The initial symptoms of the patients were seizure (50%), delayed development (40%), ataxia, hemiparesis, perinatal asphyxia, and loss of consciousness. The results of KD treatment were shown in table 4. However, this study also did not report definitive results for the effects of KD, and it was reported that there was limited to not continuing to determine a prospective random model in selecting the subjects and determining other research items [65]. Lee et al. reported 48 epileptic patients (23 male, 25 female) with MRC defects (ratio of the MRCs defects were presented in table 4). 18 children (75.0%) with medically intractable epilepsy were treated with a KD, over 50% demonstrated a decrease in seizure frequency and 50.0% even became seizure-free [20]. Saneto et al. reported 174/180 children and adolescents with mt disease, 85 of them had seizures and 21 of them tried to take KD treatment. Seven of the 21 patients on the KD responded positively with over 75% seizure reduction. One patient was diagnosed with Pyruvate Dehydrogenase Complex Deficiency and was on the KD until death. This patient was not completely seizure-free, but breakthrough seizures were infrequent,

Table 4. **Clinical outcomes of KD for mt dysfunction in epilepsy**

Author	Type of Epilepsy	Type of Study	Aim	Patients	Treatment	Time	Results
Na, Kim and Lee 2020 [64]	LGS (a typical intractable form of epilepsy)	Retrospective	To investigate the clinical efficacy and safety of KD	20 LGS patients with mt dysfunction	DTs	2004–2014	16 patients received a KD with a lipid:nonlipid ratio of 4:1. 2 patients received a lipid:nonlipid ratio of 3:1. KD showed which efficacious and feasible for LGS patients with mt dysfunction and can significantly improve their prognosis. Improvement of seizures and cognitive function were not inferior to those in other patients treated with KD.
Lee, Baek and Lee 2019 [65]	LGS (a typical intractable form of epilepsy)	Retrospective	To investigate the clinical manifestations, diagnoses, treatments, and epilepsy in LGS	372 patients mt disease between	KD	2006–2016	*KD Retention with West Syndrome:* Nine out of 13 patients received KD, but 7 patients received more than 6 months and 2 patients less than 6 months. *KD Retention with no West Syndrome:* Of the 27 patients, 15 patients received KD, but 7 patients took longer than 6 months and 8 patients received less than 6 months.
Lee et al. 2008 [20]	Childhood epilepsy, intractable epilepsy	Clinical	To demonstrate that MRC defects in children with epilepsy	48 epileptic patients (23 male, 25 female) with MRC defects	KD, mt cocktail with coenzyme Q10 (5 mg/kg/day), vitamin B and C (25 mg/kg/day), vitamin E (200–400 mg) and L-carnitine (100 mg/kg/day)	–	MRC I deficient was 35 patients. MRC II deficient was 1 patient. No MRC III deficient reported. MRC IV deficient was 11 patients. MRC I+IV deficient together were 1 patient. *KD produced clinical improvements, including seizure reduction and global functional improvement in over 50% patients.*
Lee, Na and Lee 2019 [42]	Leigh Syndrome-Epilepsy	Clinical	To describe its dominant neurological clinical features and analyze data related to epilepsy in Leigh syndrome accompanied by a mtDNA mutation.	125 patients, 25 patients were identified to have mtDNA associated Leigh syndrome	KD	–	Patients with epilepsy in Leigh syndrome. There were 14/2 patients who was on KD and did not respond to anti-epileptic drugs.
Amin et al. 2017 [63]	Childhood epilepsy (drug-resistant epilepsy)	Cohort Study	To investigate the efficacy of different treatment modalities for epilepsy.	44 patients with *CDKL5* mutation (Thirty-nine female and Five male).	AED, VNS and KD		27 patients received a KD during two years for seizure control. 12 of them had positive results. Side effects: constipation, vomiting and feeling tired were observed in 18/26 patients. Half of the patients experienced improved quality of life with KD.

Table 4 (end)

1	2	3	4	5	6	7	8
Saneto et al. 2017 [62]	Multi-regional epileptiform-status epilepticus	Cohort study	To describe the age of onset, EEG, seizure semiologist, response to medical management, and outcomes in a large cohort of infants, children, and adolescents with mt disease.	180 patients	AED and KD		7/21 patients on the KD had a positive response over 75% for the seizure reduction. 1 patient diagnosed with pyruvate dehydrogenase complex deficiency and was on the KD until death. This patient was not completely seizure-free, seizures were infrequent, 2 to 3 per month. 3 patients seizure-free, but had to be removed from the diet for compliance or quality of life issues. 2 patients who remained on the diet remained seizure-free to date, as stated above, the other 2 had seizures, but a certain decrease in seizure frequency was observed and a positive return was understood. 6 patients with epileptic spasms tried the KD and only 2 patients could go on the diet. 1 patient with complex III dysfunction became seizure-free for 5 years on the KD but had to be discontinued.
Vasta et al. 2012 [66]	Generalized epilepsy with febrile seizures plus type 2 DS	Cohort study	To analyze 26 patients with known or highly suspected mt disease of 908 nuclear genes and validate the methodology	18 patients	KD	–	Complex III deficiency in genetic tests: I / III = 31%, I = 59%, II / III = 47%, II = 89%, III = 16%, IV = 47%, CS = 107%. Also, the SCN1A mutation, C> T3733; Used for reference control found (SCN1A [NM_001165963], c.3733C> CT p.Arg1245Term, 604233/607208 / dominant). This mutation causes febrile seizures plus type 2/DS and generalized epilepsy. Seizures became overwhelming with multiple drugs, but the KD improved dramatically in motor skills and language development.
Miles et al. 2012 [18]	Epilepsy	Case-Control Study	To evaluate the effects of epilepsy-related factors associated with mt disorders.	65	VPA, KD, AED	2000–2008	No significant clinical, pathological, or biochemical differences were found between the epilepsy and control groups. 3 patients on the KD had low SSMA i.e., 0%, 0.5%, and 5%. The average SSMA for the epilepsy and control groups was 6.1% and 7.7%, respectively. The possibility of a KD to increase mt density or ETC complex activities could not be conclusively influenced in this study.

Abbreviations: Antiepileptic Drug (AED), Burrows-Wheeler Aligner (BWA), Cyclin-dependent Kinase-like 5 (CDKL5), Carnitine Palmitoyltransferase Type 2 Gene (CTP2), Dravet Syndrome (DS), Diet Therapies (DT), Electroencephalography (EEG), Electron Transport Chain (ETC), Ketogenic Diet (KD), Lennox-Gastaut Syndrome (LGS), Mitochondria (mt,) Mitochondrial Respiratory Chain Enzyme Complexes (MRCs), Diphosphate Synthase, Subunit 1 (PDSS1), Polymerase Gamma 1 (POLG1), Respiratory Chain Complex (RCC), Sodium Voltage-Gated Channel Alpha Subunit 1(SCAN1A), Subsarcolemmal Mitochondrial Aggregates (SSMA), Subunit D (SDHD), Ubiquitin-protein Ligase E3A (UBE3A), Vagal Nerve Stimulator (VNS), Valproic Acid (VPA).

2 to 3 per month. Three of the respondents were seizure-free but had to be removed from the KD for compliance or quality of life issues. While two of the patients who remained on the KD remained seizure-free to date, as stated above, the other 2 had seizures, but a certain decrease in seizure frequency was observed. Six patients with epileptic spasms tried the KD and only 2 patients could go on the diet. On the other hand, one patient with complex III dysfunction, became seizure-free for 5 years on the KD, but had to be discontinued due to family problems [37]. Vasta et al. performed genome analysis of 26 patients with mt disease and reported a young child who had hypotonia, language delay, delayed milestones, and ataxia with febrile seizures clinically. The patient had Complex III deficiency and multiple mutation which were characterized by seizures. Seizures became overwhelming with AEDs, but the KD treatment improved surprisingly her motor skills and language development [66].

Of eight studies were case reports. Ait- El-Mkadem et al. observed three case reports, it was conducted positive effects with KD which given to patients with mt Malate Dehydrogenase (MDH) 2 encodes mt MDH and refractory epilepsy showed reduction seizure frequency [67]. Seo et al. reported a case report with Ohtahara syndrome (intractable epileptic syndrome) with MRC I defect. KD and mt cocktail therapy showed completely controlled seizures and suppression burs patterns disappeared [23] also Cárdenas and Amato reported that a patient with Alpers-Huttenlocher Syndrome (diagnosed *POLG* heterozygous mutation), seizures were completely eliminated in the combined application of KD and AEDs therapies [59]. Similarly, Joshi et al. reported a case Alpers-Huttenlocher Syndrome (diagnosed two *POLG* heterozygous mutation). According to the result, the treatment with KD improved the patient's clinical prognosis and electroencephalogram (EEG) results [68]. Steriade et al. reported 22-year-old woman with multiple episodes of generalized and focal status epilepticus and migratory cortical stroke-like lesions (mtDNA disease-causing (m.3260A>G) transition mutation in the Mitochondrially Encoded tRNA leucine 1 (UUA/G) (*MT-TL1)* at 85% mutant heteroplasmy and after one-year KD treatment, she had continued to remain seizure free with no further stroke-like episodes [69]. In contrast, Krysko and Sundaram et al. reported patient with complex IV deficiency indicated that she had mt dysfunction and she treated with some multiple AEDs and KD, unfortunately, seizures have increased gradually [40]. Similarly, Samanta et al. reported a case who had heterozygote *POLG* mutation with mt dysfunction and treated with KD and some AEDs, likewise no improvement on his seizures [58]. The same seizure failure has been reported by Lankford et al. (see in Table 5) [61].

In the preclinical side there were seven studies. Stewart et al. showed that KD treatment was effective to control tonic-clonic seizures on *Aldh5a1 null (Aldh5a1*$^{-/-}$*)* mice model [70]. *Similarly,* Fogle et al. found that KD was more beneficial to AEDs but depended on K_{ATP} channel function which should be supported by AEDs to reduce seizures on *Drosophila ATP6*^{1} model of mt encephalomyopathy previously [71]. After that, the same group showed two drugs (VPA and Vigabatrin) reduced seizures on the same model from eight AEDs and pharmacological therapy could be much more effective with KD for reducing seizures [72]. Giménez-Cassina et al. showed the *BAD* gene can also be effective in KB metabolism and associated with epileptic seizure *in vivo* and *vitro*. *BAD* modifications resulted in a significant increase in the activity of metabolically sensitive K_{ATP} channels in neurons, as well as in resistance to behavioral and electrographic seizures in *Bad*$^{-I-}$ and *Bad*^{S155A} knocking mice [43]. Additionally, Kumar et al. presented the effect of KD application on seizures in epilepsies due to mt damage in *Scn1Lab* mutant zebrafish. The neuroprotective effect of KD application against epileptic seizures was revealed by increasing mt cytochrome c release ($P < 0.05$) [19]. Willis et al. also found that 35% Triheptanoin feeding (high fatty acid) decreased seizures in CF1 mice model [52]. Dolce et al. reported KD treatment protected the Male NIH Swiss mice against to 6 Hz-induced seizures but had more severe seizure scores in the kainic acid test. This study also compared to micronutrients with intermittent fasting (CF-IF) and KD, as a result CD-IF did not share identical antiseizure mechanisms as a KD treatment [73].

Consequently, on average, more than 50% of the clinical trials with KD contributed to seizure control. While 5 cases out of 8 case studies showed positive effects in seizure control, only 3 cases did not show positive effects. Included preclinical studies also found that KD was effective on seizure control in epilepsy models with mt disorders.

Table 5. **Case report outcomes of KD for mt dysfunction in epilepsy**

Author	Type of Epilepsy	Type of Study	Aim	Patient	Treatment	Time	Results
Joshi et al 2009 [68]	Alpers-Huttenlocher Syndrome- Epilepsia partialia continua	Case report	To report a patient with Alpers-Huttenlocher Syndrome (mt depletion syndrome).	Infant female	KD	–	Sequencing of the mt *POLG* gene revealed two heterozygous mutations. First mutation, c.2243G>C, and the second was a novel splice donor-site mutation, c.2480+1g>a. *Improved clinically, and EEG improved after KD.*
Cardenas and amato 2010 [59]	Alpers-Huttenlocher Syndrome — Status epilepticus	Case report	To report a patient with Alpers-Huttenlocher Syndrome (mt depletion syndrome).	14-month-old female	AED and KD	–	c911T > G (p. L30 4R) mutation was accompanied by an unknown mutation c.1174C>G (PL39 2V) and a 3240-3242 duplication (pR1081dup). *Multiple AEDs with KD eliminated her seizures, but she remained severely encephalopathic.*
Seo et al. 2010 [53]	OS (intractable epileptic syndrome)	Case report	To report a patient with OS that is associated with MRC I defect.	3month age, OS patient	KD and mt cocktail therapy	–	With KD and mt cocktail therapy, seizures were completely controlled, and suppression-burst patterns disappeared 3 months after starting treatment.
Buda et al. 2013 [57]	MILS, MERRF Epilepsy	Case report	To report child with mt disorder (m.8344G>A mutation)	13 years old child	KD	–	VPA administration or intensive rehabilitation associated with worsening. The benefit of a KD for mt tRNA-mutated patients cannot be assessed until prospective blinded studies in larger groups of patients are performed. KD associated with remission.
Ait-El-Mkadem et al. 2017 [67]	Refractory epilepsy	Case report	To report clinical and genetic findings if 3 patients who have Biallelic *MDH2* Variants. Note: MDH2 encodes MDH.	P1: partial, afterward myoclonic P2: generalized tonic and spasms P3: myoclonic epilepsy and generalized tonic	P1: KD P2: KD P3: KD	P1: 3-year P2:18month P3: 2 years	P1: reduction epileptic seizure frequency alive in 5 years P2: reduction epileptic seizure frequency but died after 1.5 years (secondary to metabolic decompe Demonstration of all *in vitro* results related KD use in mt dysfunction in epilepsy nsation) P3: ? alive at 12 years.
Krysko and Sundaram 2018 [40]	Myoclonic epilepsy due to MELAS with the rare *ND3* mt mutation *T10191C*.	Case report	To report patient with myoclonic epilepsy	16-year-old female patient	KD	–	Seizure frequency increased despite the addition of primidone, phenytoin, topiramate, phenobarbital, perampanel, and the KD. Entered terminal refractory status epilepticus despite appropriate optimization of AEDs and mitochondrial supplementation.

Table 5 (continued)

1	2	3	4	5	6	7	8
Kwong et al.2019 [60]	Infantile epileptic-dyskinetic encephalopathy and clarified the unknown genetic etiology	Case report	To report and detect if *ARX* genetic defect is associated with a spectrum of neurodevelopmental disorders.	13-year-old male and his family	AEDs and KD	–	His epilepsy failed to respond to various anticonvulsants including phenobarbital, clobazam, lamotrigine, levetiracetam, nitrazepam and KD. ARX-associated (c.989G>A; p.Arg330His) encephalopathy showing mitochondrial dysfunction and transient responsiveness to pyridoxal phosphate treatment.
Steriade et al. 2014 [69]	MELAS	Case report	To report patient with multiple episodes of generalized and focal status epilepticus and migratory cortical stroke-like lesions.	22-year-old woman	KD	1 year	Muscle biopsy showed a mitochondrial DNA disease-causing (m.3260A>G) transition mutation in the *MT-TL1* gene at 85% mutant heteroplasmy. Skeletal muscle biopsy has 38% heteroplasmy for the same m.3260 A>G transition mutation. Her mother was asymptomatic and had almost 5% heteroplasmy for m.3260A>G in blood derived mitochondrial DNA. KD application for one year made her seizure free with no further stroke-like episodes.
Samanta et al 2019 [58]	Intractable left-sided EPC	Case report	To report patient with an EPC and mitochondrial dysfunction	18-year-old male *POLG* p.W748S, p.S305R with mutations			The patient was treated with several AEDs such as midazolam infusion, fosphenytoin, levetiracetam, lacosamide, pentobarbital infusion, clonazepam, topiramate, VPA and KD but *no definite improvement in his frequency of seizures*
Nizon et al. 2014 [51]	Secondary lesional epilepsy	Case report	To report patient with *NFU1, PDHA1* mutations and leukoencephalopathy with focal seizures.	2 ½ -year-old female	lipoic acid (100 mg/kg/day) then KD (lipids 60% of calories)	6 months	*NFU1* mutation and a generalized mt complex deficiency predominant on complex II were revealed. Lipoic acid did not prevent neurological regression without any effect and stopped after six months. However, trial of KD has worsened the patients status. She presented an acute episode of dystonia and metabolic attack within 24 hours following the test. *Possibly it happened because of the partial block of the Krebs cycle at the α-cetoglutarate dehydrogenase step.*
Lankford et al. 2011 [61]	Intractable epilepsy (multiple seizures per hour)	Case report	To report patient with multiple seizures.	6-year-old female	AEDs, DT	–	Spectrophotometric analysis demonstrated an absence of complex I activity. Diagnosed with complex I–deficient mt disorder and a mutation in *SLCA2* gene. *She failed therapy with topiramate, levetiracetam, and ethosuximide. KD was given for 2 days but never continued as was seizures persisted.*

Table 5 (end)

1	2	3	4	5	6	7	8
Wesoł-Kucharska et al. 2021 [75]	LS (m.12706T>C in MTND5), seizure	Case report	To report a LS patient	Male 8-month infant	KD	10 months	After 10-month echocardiography and general condition improved. Although after age of 12-month patient required implementation of treatment with AEDs.

Abbreviations: Anti-epileptic Drugs (AEDs), Aristaless-related Homeobox (ARX), Diet Therapies (DT), electroencephalography (EEG), Epilepsia Partialis Continua (EPC), Ketogenic Diet (KD), Leigh Syndrome (LS), Magnetic Resonance Imaging (MRI), Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like Episodes (MELAS), Mitochondria (mt), Mitochondrial Respiratory Chain Enzyme Complexes (MRCs), Myoclonic Epilepsy with Ragged Red Fibres (MERRF), Mitochondrially Encoded tRNA Leucine 1 (UUA/G) (MT-TL), Mitochondrially Inherited Leigh Syndrome (MILS), Mitochondrial Malate Dehydrogenase (MDH), Mitochondrial Malate Dehydrogenase 2 (MDH 2), Mitochondrially Encoded TRNA-Lys (AAA/G) (MTTK), Mitochondrially Encoded tRNA leucine 1 (UUA/G) (MT-L1) Iron-Sulfur Cluster Scaffold (NFU1), Ohtahara syndrome (OS), Pyruvate Dehydrogenase E1 alpha 1 subunit (PDHA1), Polymerase Gamma 1 (POLG), Solute Carrier Family 2 (SLCA2), Facilitated Glucose Transporter Member 1 Gene (SLCA2), Valproic Acid (VPA).

To the best of our knowledge this is the first report systematically appraising KD treatment for the mt dysfunction in epilepsy. The systematic review process identified 36 articles which met the inclusion and exclusion criteria. This review discusses the topic starting from the basics with five questions with the included preclinical, clinical, retrospective and case studies. This umbrella review makes a number of recommendations for KD applications to preclinical and clinical practice in mt epilepsies for the future research. Healthcare institutions, researchers, neurologist, health promotion organizations and dietitians should consider these in order to improve the effectiveness of KD interventions for patients with multiple mt dysfunctions in epilepsy. Healthcare settings, researchers, neurologist, health promotion organizations, dietitians and neuropsychiatry should consider these in order to improve the effectiveness of KD interventions for patients with multiple mt dysfunctions in epilepsy.

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ВИКОРИСТАННЯ КЕТОГЕННОЇ ДІЄТЕРАПІЇ В ЕПІЛЕПСІЇ З МІТОХОНДРІЙНОЮ ДИСФУНКЦІЄЮ: СИСТЕМАТИЧНИЙ ТА КРИТИЧНИЙ ОГЛЯД

R. R. Kocatürk[1, 2], *A. Temizyürek*[3], *E. Reis*[1], *S. Tur*[1], *S. Yilmaz*[1], *Ha. Demirkaya*[1], *Ö. Ö. Özcan*[4], *M. Karahan*[1, 5]

[1]Nutrition and Dietetics, Faculty of Health Sciences, Üsküdar University, Istanbul, Turkey
[2]Molecular Biology, Institute of Science, Üsküdar University, Istanbul, Turkey
[3]Physiology, Faculty of Medicine, Altinbas University, Istanbul, Turkey,
[4]Molecular Neuroscience, Health Sciences Institute, Üsküdar University, Istanbul, Turkey
[5]Biomedical Device Technology, Vocational School of Health Sciences, Istanbul, Turkey, Üsküdar University

E-mail: mesut.karahan@uskudar.edu.tr

З розвитком молекулярних методів з часом більше 60% епілепсії асоціювалося з мітохондріальною (мт) дисфункцією. Кетогенна дієта (КД) використовується для лікування епілепсії з 1920-х років.

Мета. Оцінити докази, що лежать в основі дисфункції МТ при епілепсії.

Методи. У базах даних PubMed, Google Scholar та MEDLINE було здійснено загальний підхід до 12 березня 2021 року англійською мовою. Для визначення відповідних досліджень були розроблені конкретні стратегії пошуку за такими темами: (1) мітохондріальна дисфункція, (2) епілепсія, (3) лікування КБ.

Результати. З 1794 статей до аналізу було включено 36 статей: 16 (44,44%) доклінічних досліджень, 11 (30,55%) повідомлень про ипадки, 9 (25%) клінічних досліджень. У всіх доклінічних дослідженнях KD регулював кількість профілів mt, транскриптів метаболічних ферментів та кодувальних протеїнів mt, захищав мишей від судом і мав протисудомний механізм. Звіти про випадки та клінічні випробування повідомляли про пацієнтів з хорошими результатами в контролі судом та функціях МТ, хоча не всі вони дають хороші результати, а також доклінічні.

Висновок. Закладам охорони здоров'я, дослідникам, невропатологам, організаціям зі зміцнення здоров'я та дієтологам слід урахувати ці результати, щоби покращити програми КД та результати захворювання при дисфункції МТ при епілепсії.

Ключові слова: епілепсія; кетогенна дієта; дисфункція мітохондрій; лікування.