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Ketogenic Diet Interventions in Inborn Errors of Metabolism: A Review Article

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ABSTRACT

Objective: The ketogenic diet, which has been used in the treatment of epilepsy since the 1920s, is a diet containing high fat, sufficient protein, and low carbohydrate. The ketogenic diet mimics the metabolic effects of fasting by shifting metabolism towards fat utilization. The ketogenic diet, which has different variants, such as the classical ketogenic diet, modified Atkins diet, and medium-chain triglyceride diet, is used in inborn errors of metabolism to target the underlying metabolic state by bypassing the damaged metabolic pathway or to treat the clinical symptoms of inborn errors of metabolism, such as epileptic seizures. In this review, we assessed the evidence for ketogenic diet interventions in the treatment of inborn errors of metabolism.

Methods: The Google Scholar search engine, PubMed, Scopus, and Science Direct databases were used to find studies on the use of ketogenic diet interventions in the treatment of inborn errors of metabolism.

Results: The beneficial effects of different variants of the ketogenic diet on glucose transport type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency have long been recognized. There are also favorable data on its use in myopathic glycogen storage diseases, mitochondrial diseases, and nonketotic hyperglycinemia accompanied by epilepsy.

Conclusion: The evidence is mostly based on individual case reports, case series, and clinical trials with small sample sizes and is insufficient to make recommendations.

Keywords: Ketogenic diet, modified Atkins diet, glycogen storage disease, mitochondrial disease, GLUT1 deficiency.

1. INTRODUCTION

The ketogenic diet (KD), which has been used in the treatment of epilepsy since 1921, is a diet containing high fat, adequate protein, and low carbohydrate. KDs increase ketone (β-hydroxybutyrate, acetoacetate, and acetone) production in the liver by shifting metabolism towards the use of fats as the primary energy source, mimicking the metabolic effects of fasting (1). There are different types of KDs such as the classical ketogenic diet (CKD), modified Atkins diet (MAD), and medium-chain triglyceride (MCT) diet (2). In CKD, the fat-to-protein and carbohydrate ratio is 4-3:1 (4-3 g fat per 1 g protein + carbohydrate), thus reducing carbohydrate intake (3). Due to the restrictive properties of CKD, new variants have emerged, such as MAD with high-fat content, which allows higher protein intake and does not restrict calories and fluid (4). The MAD was first used in 2006 by Kossoff et al (5) in the treatment of intractable epilepsy. The fat/protein + carbohydrate ratio in MAD is 1:1, which offers a more palatable alternative. The MCT diet, is an alternative diet first developed by Huttenlocher et al (6) in 1971 to provide higher carbohydrate intake. The ketogenicity ratio is approximately 1.2:1, which is more palatable than that of CKD. However, it is less commonly used in clinical practice due to its potential gastrointestinal side effects (7).

KDs are used in inborn errors of metabolism (IEMs) to target the underlying metabolic state by circumventing the damaged metabolic pathway or to treat the clinical manifestations of IEMs, such as epileptic seizures (Figure 1). Ketosis must be attained and maintained without catabolism as symptoms may worsen (8). This review aims to examine the efficacy of KDs in the treatment of IEMs and to make recommendations based on current evidence.

2. GLYCOGEN STORAGE DISEASE TYPE III

Glycogen storage disease type III (GSD III, OMIM #232400), also known as Cori disease, is an autosomal recessive IEM

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caused by mutations in the ADL gene, resulting in a deficiency of glycogen debranching enzyme (amylo α-1,6-glucosidase) (9). The debranching enzyme is necessary for comprehensive glycogen breakdown. In GSD III, glycogenolysis and free glucose formation are limited, resulting in limit dextrin accumulation in the liver, muscle, and heart tissues, and hypoglycemia (10). In GSD III patients, glycogenolysis is impaired, whereas glycolysis and gluconeogenesis are preserved. Traditionally, nutritional therapy consists of adequate carbohydrate intake supplemented with raw cornstarch to maintain normoglycemia and adequate protein intake to provide gluconeogenic amino acids, which are substrates for gluconeogenesis (11). The GSD III consensus guideline published by the American College of Medical Genetics and Genomics recommends high protein (25% of total energy) and low complex carbohydrate (<50% of total calories) intake, as well as avoidance of simple sugars (10). Although these measures are effective in achieving metabolic control, they are ineffective in preventing long-term complications. There is no consensus on the optimal nutritional therapy to prevent long-term liver, cardiac, and muscle complications, even in well-metabolically controlled patients. However, eucaloric KD improves energy balance by increasing the blood levels of ketone bodies, which are alternative substrates for energy production in the brain, heart, and skeletal muscles (10). In addition to conventional treatment, novel nutritional therapies, including CKD, MAD, high-fat diet, and synthetic ketone bodies, applied to maintain normoglycemia and improve long-term complications such as cardiomyopathy (CMP) have been reported in recent studies (12-15).

The MAD was reported to lower creatine kinase (CK) levels and improve CMP in 8 pediatric GSD III patients (Olgac et al (12) (n=6), Mayorandan et al (13) (n=2)). Similar results were found in case reports evaluating the efficacy of MAD in three adult patients who reported improved heart and liver functions (Fischer et al (14) (n=2), Francini-Pesenti et al (15) (n=1)). In the evaluation of these 11 patients, asymptomatic hypoglycemia, increased low-density lipoprotein (LDL) cholesterol levels, and weight loss were reported as side effects of MAD. Case reports suggest that carbohydrate-restricted, high-fat, and high-protein diets may be effective in improving CMP in pediatric patients with GSD III (16, 17). A high-protein diet may reduce the accumulation of limit dextrin in myocardial cells and increase protein utilization through gluconeogenesis. A high protein intake can also increase the synthesis of muscle proteins. However, high-fat diets not only increase the activity of gluconeogenesis but also facilitate adenosine triphosphate (ATP) production from fatty acid oxidation and ketolysis as an alternative energy source (10). In a case report with the highest follow-up period, in which a 2:5:1 ratio of CKD was applied for 4 years, CMP and hepatopathy improved, but blood lipid levels were mildly to moderately elevated (n=1) (18). In a different case report, the combined use of a high protein 2:1 CKD and synthetic ketone bodies (3-hydroxybutyrate) for 24 months in a 2-month-old infant improved CMP and no side effects were observed (19). All case studies are reported in Table 1. In a recent systematic review by Rossi et al (20), a significant decline in CK concentration and cardiac hypertrophy was observed in 28 pediatric GSD III patients with cardiomyopathy/myopathy who were given a high-fat diet. Evidence supports the efficacy of a high-fat diet in pediatric GSD IIIa patients with cardiac hypertrophy; however, long-term monitoring is required to avoid potential complications (20). According to these findings, the necessity of raw corn starch in GSD III patients, in whom high protein and high fat diets are sufficient to maintain normoglycemia, is controversial because it causes hyperinsulinemia.

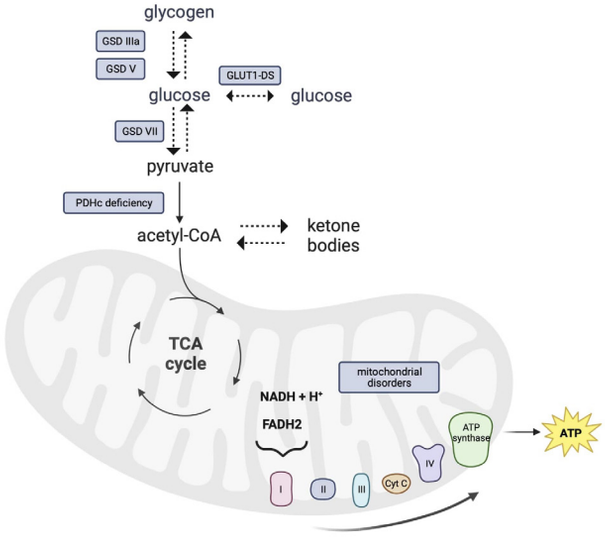

Figure 1. *Inborn errors of metabolism treated on a ketogenic diet (8) Abbreviations: ATP: Adenosine Triphosphate; Cyt C: Cytochrome C; GLUT1-DS: Glucose Transporter Type 1 Deficiency Syndrome; GSD: Glycogen Storage Disease; PDHc: Pyruvate Dehydrogenase Complex; TCA: Tricarboxylic Acid.*

3. GLYCOGEN STORAGE DISEASE TYPE V

Glycogen storage disease type V (GSD V, OMIM #232600), also known as McArdle disease, is an autosomal recessive IEM caused by myophosphorylase enzyme deficiency in the skeletal muscle due to mutations in the PYGM gene, which encodes the muscle isoform of the glycogen phosphorylase enzyme (21). Myophosphorylase, which catalyzes the first step in glycogenolysis by converting intracellular glycogen to glucose-1-phosphate, is responsible for energy production during anaerobic and high-intensity exercise. The absence of myophosphorylase activity in GSD V patients blocks glycogenolysis in the skeletal muscle, leading to exercise intolerance. All activities that require energy expenditure can result in muscle contracture, rhabdomyolysis, and renal failure in extreme cases (21, 22). To date, there is no effective and satisfactory treatment to improve exercise intolerance in patients with GSD V. Strategies to increase the utilization of alternative energy sources in the muscles during exercise are reasonable. Oral sucrose intake before exercise may alleviate muscle symptoms, but excessive consumption may lead to weight gain (23, 24). Interventions to increase fat oxidation are among other reasonable methods.

Table 1. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with glycogen storage disease*

Author, year	Type of GSD	Number of patients	Age at KD start	Duration on KD	Type of KD	Outcomes	Side effects
Olgac et al (12)	GSD III	6	6y (Range: 3y-31y)	6m (Range: 3m-7m)	MAD	• Transaminase levels dropped. CK levels dropped in 5 out of 6 patients.	Hypoglycemia was evident in 2 patients but was resolved by adding uncooked cornstarch to diet.
Mayorandan et al (13)	GSD III	2	9y-11y	Range: 32m-26m	MAD	• CK levels dropped. CMP improved.	Transient asymptomatic hypoglycemia.
Fischer et al (14)	GSD III	2	Unknown	Unknown	MAD	• Reduction of CK, stabilization of blood glucose.	Muscle weakness, tachycardia, stress dyspnea, tremor and a vertigo at the initiation in 1 patient. Weight loss in both.
Francini-Pesenti et al (15)	GSD III	1	34y	12m	MAD	• Heart and liver functions improved.	Increase of uric acid plasma level and C-LDL.
Marusic et al (18)	GSD III	1	11y	4y	2:5:1 CKD	• Improvement of CMP and hepatopathy.	Mildly-to-moderately elevated lipid levels.
Valayannopoulos et al (19)	GSD III	1	2m	24m	Combined use of ketone bodies (3-OH butyrate) and 2:1 KD and high protein diet	• Improvement of CMP.	None.
Løkken et al (29)	GSD V	8	Range: 18y-64y	3w	fat/pro/CHO; Diet 1: 65%/15%/20% Diet 2: 75%/15%/10% Diet 3: 80%/15%/5%	• Improvement of fatty acid oxidation rates and exercise capacity in all diet regimes. • Diet 2 had the highest acceptability score.	3 reported mild fatigue and headaches. 2 reported mild nausea in the beginning of the first week.
Løkken et al (30)	GSD V	8 patients, 4 healthy controls	42y (Range: 25y-70y	-	Administration of a drink containing 395 mgKE/kg D-β-hydroxybutyrate esters or placebo 25 min before a submaximal cycle exercise test.	• No improvement in exercise capacity.	None.
Busch et al (26)	GSD V	1	55y	1y	CKD (80% fat, 14% protein)	• Improvement of exercise tolerance. • Improvement of maximum strength and activity duration. • Reduction of CK. • No improvement in ^{31}P – MRS data during rest, work, and recovery.	Unknown.
Reason et al (28)	GSD V	3	Range: 12y-54y	Unknown	LCKD	• Improvement of activity and exercise tolerance. • Reduction of CK. • Improvement of quality of life.	Unknown.
Vorgerd and Zange (27)	GSD V	1	55y	1y	CKD + creatinine supplementation	• Reduction of CK. • Improvement of exercise tolerance. • No improvement in muscle energy metabolism.	Unknown.
Similä et al (33)	GSD VII	1	59y	5y	MAD	• Alleviation of muscle symptoms. • Improvement of exercise performance, and oxygen uptake.	Increase of cholesterol values.
Swoboda et al (32)	GSD VII	1	4m	1y8m	3:1 CKD	• Alleviation of clinical symptoms. • Improvement of motor skill development. • Improvement of muscle strength.	Unknown.

Abbreviations: CHO: Carbohydrate; CK: Creatine Kinase; CKD: Classical Ketogenic Diet; CMP: Cardiomyopathy; C-LDL: Low Density Lipoprotein Cholesterol; GSD: Glycogen Storage Disease; KD: Ketogenic Diet; LCKD: Low Carbohydrate Ketogenic Diet; MAD: Modified Atkins Diet; P-MRS: Phosphorous Magnetic Resonance Spectroscopy; m: months; y: years.

KD induces the production of ketone bodies by mimicking the metabolic effects of fasting. Ketone bodies are converted to acetyl-CoA, participate in the citric acid cycle (TCA cycle) and are thus used as an alternative energy source for muscle glycogenolysis during exercise (25). Busch et al (26) and Vorgerd and Zange (27) evaluated the effects of the KD in a 55-year-old male patient with GSD V. Administration of a KD containing 80% fat and 14% protein for 1-year increased exercise tolerance by 3-10 fold. Activity duration and maximal strength increased, whereas CK levels decreased. However, 31-phosphorus magnetic resonance spectroscopy data did not improve during rest, work, or recovery. In three adult GSD V patients, a low-carbohydrate KD was similarly reported to improve activity and exercise tolerance, lower CK levels, and improve quality of life (28). No side effects of KD were reported in these case reports. In a randomized pilot study of eight adult patients with GSD V, participants were assigned to one of three ketogenic dietary patterns (#1: 65%/15%/20%; #2: 75%/15%/10%; #3: 80%/15%/ 5%; fat, protein, and carbohydrate) for 3 weeks. Fatty acid oxidation rate and exercise capacity increased in all participants. The second dietary pattern containing 75% fat was found to have the highest acceptability score (29). In a randomized placebo-controlled, crossover study involving the same eight GSD V patients and four healthy controls, 395 mgKE/kg D-β-hydroxybutyrate-containing beverage consumption 25 minutes prior to a submaximal exercise test failed to enhance exercise capacity in both groups (30). Oral ketone ester supplementation probably leads to reduced availability of free fatty acids and glucose in the muscles. On the basis of the current investigation, oral ketone ester supplementation alone is not recommended for patients with GSD V.

4. GLYCOGEN STORAGE DISEASE TYPE VII

Glycogen storage disease type VII (GSD VII, OMIM #232800), also known as Tarui disease or muscle phosphofructokinase deficiency, is an autosomal recessive IEM characterized by muscle cramps, exercise intolerance, and mild myopathy caused by mutations in the PFKM gene. Phosphofructokinase enzyme deficiency in muscle tissue blocks the formation of pyruvate from glucose via glycolysis, preventing glucose from being used in energy metabolism in muscles. Therefore, energy sources other than glucose must be used in the muscle tissue in GSD VII (31).

To date, only two case reports have evaluated the effectiveness of KD in patients with GSD VII. In a child with phosphofructokinase deficiency who presented with severe myopathy, initiation of 3:1 CKD at 4 months of age relieved clinical symptoms, enhanced motor skills, and muscle strength (32). MAD administered to a 59-year-old patient with GSD VII for 5 years alleviated muscle symptoms, increased exercise performance and oxygen consumption. However, high total and LDL cholesterol levels have been reported as side effects of MAD (33).

5. NONKETOTIC HYPERGLYCINEMIA

Nonketotic hyperglycinemia (NKH, OMIM #605899) is an autosomal recessive neurometabolic disorder resulting from mutations in the GLDC or AMT genes that reduce the activity of the glycine-cleavage enzyme complex. Glycine accumulates in body fluids and tissues, including the brain, because of insufficient activity of the glycine-cleaving enzyme complex (34). Currently, there are no effective treatments for severe NKH. Although there are some clinical reports on the use of drugs that lower glycine levels, such as high-dose sodium benzoate, or drugs that reduce the stimulatory effects of the N-methyl-D-aspartate receptors, such as ketamine and dextromethorphan, there has been no significant improvement in the relief of symptoms, such as epileptic seizures (35). It has been reported that combining low-dose sodium benzoate with 3:1 CKD lowers plasma glycine concentrations and offers more stable low glycine concentrations than high-dose benzoate therapy alone (36). Decreases in glycine levels in cerebrospinal fluid (CSF) have also been reported in other studies (37). The underlying mechanism involves a reduction in the glycine pool due to the utilization of glycine for gluconeogenesis. Therefore, ketosis is not the goal of KD in NKH but to support this mechanism with glucose restriction. However, ketosis may have additional benefits. Endogenous utilization of glycine by gluconeogenesis results in a significantly decreased glycine index and concomitant reduction in the required benzoate dose (36).

KD has been proven effective in treating refractory seizures in pediatric patients with different epileptic syndromes. KD mimics the biochemical response to fasting, meeting the brain's energy demand from ketone bodies instead of glucose (38). In recent years, the use of CKD in combination with pharmacological treatment in small groups of NKH patients has shown a reduction in the frequency and severity of seizures and an enhancement in quality of life (36, 37, 39, 40). Table 2 summarizes the study findings. The mechanism of action of KD in the treatment of epilepsy is not fully understood. The neuroprotective properties of KD are explained by increased energy production in the brain through upregulation of genes involved in energy metabolism, mitochondrial biogenesis, and increased energy reserves. KD-induced energy production modifies amino acid metabolism and stabilizes membrane potential in neurons, raising the seizure threshold and exerting anti-convulsant effects (41).

Table 2. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with nonketotic hyperglycinemia*

Author, year	Number of patients	Age at KD start	Duration on KD	Type of KD	Outcomes	Side effects
Kava et al (39)	1	7m	35m	3.5:1 CKD	Reduction in seizure severity and frequency. Normalisation of plasma glycine levels. Reduction in spasticity and hospital admissions. Improvement in quality of life.	Unknown.
Shelkowitz et al (36)	6	Range: 1m-26m	5/6 (Range: 6m->2yr) 1/6 discontinued after 1w.	3:1 CKD	Reduction in plasma glycine levels on average 28%. Reduction but not normalization in brain glycine levels. Reduction in seizure frequency in half of the patients.	Electrolyte perturbations, feeding intolerance.
Shbarou et al (40)	2	Range: 3d-1m	Range: 10m-2.5yr	4:1 CKD	Reduction in plasma glycine levels. Improvement of tonic spasms and tonic-clonic seizure control. Resolution of tonic-clonic seizures.	None.
Daida et al (37)	1	15m	9m	3:1 CKD	Reduction in CSF glycine levels. Reduction of focal seizures. Improvement in quality of life.	None.

Abbreviations: CKD: Classical Ketogenic Diet; CSF: Cerebrospinal Fluid; KD: Ketogenic Diet; d: days; m: months; y: years.

6. MITOCHONDRIAL DISEASES

Mitochondrial diseases are a diverse group of IEMs caused by mutations in genes encoding mitochondrial proteins required for substrate oxidation via the TCA cycle and oxidative phosphorylation (OXPHOS) for ATP production (42). Mitochondrial diseases, which are characterized by abnormal metabolic pathways, cause decreased ATP production and a range of clinical symptoms. Heterogeneous symptoms can occur at any age, particularly in tissues with high energy demands, such as the brain, skeletal, and cardiac muscles (43). The fact that no effective curative treatment has yet been developed makes supportive care for symptom relief a priority. KD stimulates mitochondrial biogenesis, enhances mitochondrial function, and decreases oxidative stress and glycolytic rate. Consequently, it has been suggested as a potential treatment option for mitochondrial diseases accompanied by epilepsy (44).

Current guidelines on the KD report a better response to the KD in respiratory chain complex I deficiency compared to epilepsy (45). Fatty acid beta-oxidation leads to a partial bypass of complex I by producing 5.7 times more $FADH_2$ that can enter complex II compared to carbohydrate oxidation. But since NADH is supplied from all substrates, complex I cannot be bypassed completely (46). Lee et al (47) evaluated the efficacy of 4:1 CKD in 24 patients with mitochondrial respiratory chain enzyme deficiency accompanied by epilepsy. It was reported that seizure frequency decreased by more than 50% in 75% of the patients and no seizures occurred in 50%. In a retrospective review of 20 patients with Lennox-Gastaut syndrome with mitochondrial dysfunction in whom MAD or 4:1/3:1 CKD was administered, it was found that seizure frequency decreased by 75% in 2 patients, 50% in 3 patients, 25% in 1 patient, and no seizures occurred in 2 patients (48). In a retrospective review of 14 patients with complex I, II, and IV defects, it was reported that seizure frequency decreased by more than 90% in one patient, 50-90% in two patients, and no seizure occurred in seven patients during 4:1 CKD intervention. However, four patients did not respond, and the intervention was discontinued due to complications (49). There is only one prospective controlled trial evaluating the effectiveness of KD in the treatment of mitochondrial diseases. In this study evaluating the 12-week intervention of 2:1 CKD, a total of 33 patients were randomized into intervention (n=22) and control (n=11) groups. The control group received a typical diet for one month, followed by three months of KD intervention. After 3 months of intervention, seizure frequency decreased by more than 50% in 40.9% (9/22) of the patients in the intervention group and 72.7% (8/11) of the patients in the control group. KD has been reported to be particularly effective and safe in mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS) syndrome, and pathologic variants of mitochondrial DNA (50). In a recent systematic review study, it was reported that seizure control was achieved in 7/8 patients with mitochondrial disease (no seizure in 5 patients, reduced seizure frequency in 1 patient, and stabilization in 1 patient) (51). There are also case reports regarding the effect of KD in mitochondrial diseases. Satisfactory therapeutic effects of KD have been observed in mitochondrial diseases such as mitochondrial respiratory chain complex I deficiency due to Landau-Kleffner and Ohtahara syndromes, MELAS syndrome, Alpers-Huttenlocher syndrome, POLG disease, MTO1 deficiency, AGC1 deficiency (52-55). The findings of these studies are presented in Table 3.

Table 3. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with mitochondrial diseases*

Author, year	Number of patients	Type of MD	Age at KD start	Duration on KD	Type of KD	Supplements	Outcomes	Side effects
Kang et al (49)	14	9 had Complex I defects 1 had a Complex II defect 3 had Complex IV defects 1 had combined Complex I and IV defects	45m	18m	4:1 CKD	CoQ, B2, L-carnitine	• 7 patients became seizure-free. • Reduction of seizure greater than 90% in 1 patient. • Reduction of seizure between 50% and 90% in 2 patients. • No improvement in 4 patients.	Symptomatic persistent hypoglycemia and persistent metabolic acidosis.
Lee et al (47)	24	Mitochondrial respiratory chain defects	Unknown	Unknown	4:1 CKD	CoQ, L-carnitine, B complex, C, E	• Decrease in seizure frequency over 50% in 18 patients (75%). • 12 (50%) patients became seizure-free.	Dehydration, gastrointestinal discomfort, infection, hyperlipidemia, hypo – glycemia, metabolic acidosis.
Na et al (48)	20	Lennox-Gastaut syndrome	4.6y	13.5m	MAD or 4:1/3:1 CKD	Mitochondrial cocktail treatment	Improvement of seizures and cognitive function.	Vomiting, diarrhea, metabolic acidosis.
Huang et al (50)	KD group: 22 Control group: 11	MELAS, suspected MELAS, MERRF, PDHD, Leigh, COQ10D7 with epilepsy, uncategorized	KD group: 79m Control group: 76m	12w	2:1 CKD	Unknown	• Reduction of seizures.	Vomiting, cold, bloating, gastrointestinal disturbance, hyperlipidemia.
Köse et al (52)	1	Mitochondrial DNA depletion syndrome 13	9m	5d	KD	B1, B2, B7, CoQ	• Non reported.	Metabolic acidosis, hyperlactatemia.
Pfeiffer et al (53)	1	Cerebral aspartate-glutamate carrier isoform 1 (AGC1) deficiency	21m	>4m	4:1 CKD	Unknown	• Reduction in seizures. • Improvement of head and neck control.	Unknown.
Koessler et al (54)	1	POLG disease	16y	3m	4:1 CKD	B1, B2, CoQ	• Improvement of seizures only short-term.	Unknown.
O'Byrne et al (55)	1	MTO1 deficiency	7y	10y	4.75:1/2:1 CKD	B1, B2, CoQ, E, D, L-carnitine	• Temporary seizure reduction.	Reduction in bilateral visual acuity, ptosis and generalized weakness.

Abbreviations: B1: Thiamine; B2: Rivoflavin; B7: Biotin; C: Vitamin C; CKD: Classical Ketogenic Diet; CoQ: Coenzyme Q10; D: Vitamin D; E: Vitamin E; KD: Ketogenic Diet; MAD: Modified Atkins Diet; MD: Mitochondrial Disease; MELAS: Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes; d: days; m: months; y: years.

Considering the high rates of side effects, the KD should be considered as an individual treatment option in this patient group and requires an experienced team (56). Although studies have demonstrated the effectiveness and safety of KD in the treatment of mitochondrial diseases, most of these are case reports and case studies with small sample sizes. To fully comprehend the pathophysiology of mitochondrial diseases and to determine which individuals may benefit from therapeutic effects, further prospective clinical trials are required.

7. PYRUVATE DEHYDROGENASE COMPLEX DEFICIENCY

The pyruvate dehydrogenase complex (PDHc), which links glycolysis to the Krebs cycle, is central to energy metabolism. In PDHc deficiency, the glycolytic end product, pyruvate, cannot be metabolized by the TCA cycle, leading to increased lactate synthesis and impaired ATP synthesis through the mitochondrial respiratory chain. During a carbohydrate-restricted diet, cellular energy is derived from the breakdown of fatty acids instead of glycolysis. The brain uses ketone bodies generated via fatty acid oxidation as an alternative energy substrate to glucose (8).

Nutritional therapy is the CKD, which lowers intracellular pyruvate and lactate levels by providing energy from fat. However, even early initiation of KD is not sufficient to prevent neurologic and metabolic complications (57). Low long-term dietary adherence reduces the beneficial effects. A less restrictive, 10% carbohydrate KD provided clinical stability and improved compliance in neonatal-onset patients with low compliance to standard KD (58). A study evaluating CKD and MAD's long-term efficacy in 19 patients with PDHc deficiency reported that treatment mainly improved epilepsy, sleep disturbance, ataxia, speech and language development, and hospitalization frequency (59). Following the diagnosis of PDHc deficiency, it is recommended to start KD as soon as possible to prevent brain damage (59). The long-term efficacy of KD depends on regular monitoring of plasma ketone levels and adjustment of diet composition to maintain ketosis. In a case report in which intravenous KD was administered within the first 24 hours postpartum, lactic acidosis resolved immediately with no apparent adverse effects, developmental outcomes improved, and the cases did not show epilepsy (60). However, KD may cause some side effects, particularly energy and nutrient deficiencies, which can result in weight loss and growth retardation, and temporary elevation of plasma lipid levels (61). Therefore, triglyceride and cholesterol levels should be monitored periodically in patients with PDHc deficiency on KD, especially during acute illness, and adequate energy intake should be assessed to prevent growth retardation and the risk of energy deficiency (62). Data evaluating the efficacy of KD in PDHc deficiency are based on a few case reports (Table 4). Therefore, clinical studies evaluating adherence to KD variants and the long-term effects of less restrictive ketogenic dietary practices are needed.

Table 4. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with pyruvate dehydrogenase complex deficiency*

Author, year	Number of patients	Age at KD start	Duration on KD	Type of KD	Outcomes	Side effects
Inui et al (60)	2	1d	Range: 1y-2y	Intravenous KD	• Improvement of lactic acidosis. • Better developmental outcomes. • Epilepsy did not exhibit.	None.
El-Gharbawy et al (58)	1	15m	1y	#1 4:1 CKD and 3:1 CKD with MCT oil. #2 A less restrictive KD including ketocal formula, allowing 10% of CHO.	• Improvement of compliance. • Remaining clinically stable. • Showing developmental progress.	None.
Sofou et al (59)	19	2.5y (Range: 1w-15y3m)	2.9y (Range: 6m-6y11m)	7/19 received CKD 12/19 received MAD	• Improvement in epilepsy, ataxia, sleep disturbance, speech/language development, social functioning, and frequency of hospitalizations.	Acute pancreatitis in 1/19.
Pisa et al (62)	1	2.5y	6m	3:1 CKD	• Reduction of seizure frequency. • Improvement of psychomotor development.	Increase in cholesterol and TG.

Abbreviations: CHO: Carbohydrate; CKD: Classical Ketogenic Diet; KD: Ketogenic Diet; MAD: Modified Atkins Diet; MCT: Medium Chain Triglyceride; TG: Triglycerides; d: days; m: months; y: years.

Table 5. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with glucose transporter type 1 deficiency syndrome*

Author, year	Number of patients	Age at KD start	Duration on KD	Type of KD	Outcomes	Side effects
Ito et al (75)	6	Range: 7y-16y	Range: 1m-42m	MAD	• Reduction of epileptic seizures and other paroxysmal events. • Improvement in the background activity and disappearance of epileptic discharges. • Improvement of motivation and cognitive function. • Improvement of non-paroxysmal permanent ataxia, spasticity, dysarthria, and dystonia.	No serious side effects Nausea, vomiting, fatigue, headache, constipation, opsoclonus, hyperlipidemia, and hyperuricemia at the beginning.
Pong et al (72)	64	4y	>5y	4:1 CKD	• 67% (41/61) were seizure-free and 68% of seizure-free patients (28/41) resolved in <1 week and 76% (31/41) in <1 month.	None.
Bekker et al (79)	7	8y (Range: 4y-11y10m)	Range: 1w-3y8m	CKD, MAD, or MCT-KD	• Failure to reduce seizure frequency.	Nausea, belching, abdominal pain, diarrhea, constipation, vomiting.
Ramm-Pettersen et al (74)	10	15 y (Range: 3m-49y)	Unknown	2.5-4:1 CKD or MAD	• Disappearance of epileptic seizures. • Improvement of paroxysmal exercise-induced dyskinesias except 2 of the patients treated with MAD.	Hypoglycemia.
Sandu et al (73)	4	Range:7y-13y	Range: 6m-2y	MAD	• Improvement of movement disorder. • Improvement of seizures control.	Abdominal pain.
Fujii et al (76)	31	12y (Range: 3y–35y)	44m (Range: 1m–96m)	17/31: MAD 11/31: CKD 3/31: MCT-KD	• Improvement on seizures, transient aggravation after fasting and ataxia. • No improvement in intellectual development.	None.
Gumus et al (70)	6	2.5y-13y	Range: 6m-24m	4:1 CKD	• Disappearance of epileptic seizures in 5/6. • Less improvement in ataxia, spasticity, and dystonia. • No improvement in the intelligence quotient level or microcephaly. • Moderate improvement of alertness, concentration, motivation, and activity.	5 reported nausea, vomiting, constipation, and fatigue.
Amalou et al (77)	10	Range: 4m-16y	2.5y (Range: 6m-6y)	MAD	Improvement in epileptic seizures. Control of movement symptoms. Improvement in physical abilities and growth parameters.	Constipation, compliance.
Ruiz Herrero et al (78)	18	5y2m (Range: 3.5m-17y4m)	463d (Range: 170–1863d)	6/18 had 3:1 CKD 12/18 had MAD	Improvement in movement disorder. Reduction in seizures.	Constipation, hypercalciuria, hyperlipidemia.

Abbreviations: CKD: Classical Ketogenic Diet; KD: Ketogenic Diet; MAD: Modified Atkins Diet; MCT-KD: Medium Chain Triglyceride-Ketogenic Diet; d: days; m: months; y: years.

8. GLUCOSE TRANSPORT TYPE 1 DEFICIENCY SYNDROME

Glucose transport type 1 deficiency syndrome (GLUT1-DS, OMIM #606777) is caused by mutations in the SLC2A1 gene, which encodes the GLUT1 protein involved in transporting glucose across the blood-brain barrier (63). Mutations in this gene block the transport of glucose into brain cells and cause low levels of glucose in the CSF, hypoglycorrhagia. GLUT1-DS is typically characterized by early onset epilepsy, growth retardation, complex movement disorders, and microcephaly (64). Since the identification of the disease in 1991, KD has been administered to an increasing number of GLUT1-DS patients (65). KD is considered the gold standard in the treatment of GLUT1-DS. In the brain, glycogen stores are quickly depleted during starvation. Since amino acids and lipids cannot be used for the generation of energy, ketones are used to maintain normal brain function. Ketones are produced by fatty acid oxidation in the liver and taken up into brain cells by facilitated diffusion regulated by the monocarboxylate transporter 1 (MCT1) transporter. When administered early, KD attenuates GLUT1-DS related

seizures. However, its effect on other symptoms is variable and moderate (66).

Treatment of GLUT1-DS with KD is not different from treatment of intractable epilepsy. Dietary carbohydrates should be restricted, individually calculated, and supplemented with multivitamins and minerals (67). A recent systematic review of 270 GLUT1-DS patients with a median follow-up of 53 months reported that epilepsy improved in 83% of 230 patients, movement disorders in 82% of 127 patients and cognitive function in 59% of 58 patients, and that the beneficial effects were more pronounced in patients who started treatment early (68). Epileptic seizure frequency was reported to be reduced by more than 50% in 95% of GLUT1-DS patients treated with KD and by more than 90% in 80% (69). The majority of GLUT1-DS patients have thus far been treated with 3:1/4:1 CKD (70). It has been reported that seizures did not occur in 60% of patients and movement disorders improved in 80% after CKD intervention (71). As a result of the intervention of 4:1 CKD for more than 5 years in 64 patients, 67% (41/61) were seizure-free and 76% (31/41) resolved in less than 1 month (72). In infants under 2 years of age, 4:1 CKD may be more effective in inducing ketosis, but it may cause growth retardation as it does not provide sufficient protein. Therefore, it has been suggested that 4:1 CKD may be effective in infants with severe phenotypes, whereas 3:1 CKD is recommended for infants with mild phenotypes and older patients (65).

Considering the long-term side effects of CKD, such as growth retardation and dyslipidemia due to high fat content, and the lack of compliance of patients with the diet, more palatable and easier-to-administer KD alternatives, such as MAD, have been tried, especially in school-age children and adolescents. For this reason, MAD has been used in GLUT1-DS patients in the last 10 years and its beneficial effects have been demonstrated (73, 74). Ito et al (75) reported the benefits of MAD used for 1-42 months in six patients aged 7-16 years. MAD resulted in a reduction of epileptic seizures and other paroxysmal events. Improvements in cognitive function, ataxia, spasticity, dysarthria, and dystonia have been reported with no serious adverse effects. In similar studies reported in the following years, it was reported that the frequency of epileptic seizures decreased, and movement disorders improved with MAD intervention (Fujii et al (76) (n=17), Amalou et al (77) (n=10), Ruiz Herrero et al (78) (n=12)). To date, the efficacy of the MCT diet has been evaluated in four patients. Fujii et al (76) (n=3) reported improvement in seizure frequency and ataxia, while Bekker et al (79) (n=1) reported no reduction in seizure frequency. All data from literature are reported in Table 5. Findings regarding the effects of KD on cognitive functions are contradictory. Some studies (80-83) reported improvement in cognitive function, while others (70,76,84) show no benefit of KD. Since the developing brain requires more energy in the first years of life, starting KD treatment as early as possible in the presence of suspected GLUT1-DS is essential for better cognitive outcomes (85).

The side effects of KD in GLUT1-DS patients are similar to those in children treated for refractory epilepsy. Growth retardation and dyslipidemia are among the long-term adverse effects and remain a cause for concern. Nonetheless, it should be continued until adolescence to satisfy the growing energy needs of the developing brain. The ketogenicity of MAD is similar to CKD and there are data reporting similar beneficial effects. Considering that MAD may be as effective as CKD in patients with GLUT1-DS, is less restrictive and has fewer side effects, it is recommended that the type of CKD to be applied should be decided individually.

9. CONCLUSION

Overall, KD has shown promising results in treating a range of IEMs and is becoming a more widely accepted treatment option. Numerous studies have demonstrated the efficacy of KD in treating GLUT1-DS and PDHc deficiency, and its positive effects are increasingly being reported for other IEMs. KD is used in IEMs to bypass the damaged metabolic pathway or to treat clinical symptoms such as epileptic seizures. The data regarding the improvement of the clinical outcome in GSDs with myopathy, NKH and mitochondrial diseases accompanied by epileptic seizures are promising, but the evidence is based on a few case reports and case series and is insufficient to make recommendations. Therefore, further research and clinical trials are needed to establish the efficacy and safety of these treatments in larger populations. It is important for healthcare professionals to continue monitoring and assessing the potential benefits and risks of these treatments for patients with these conditions.

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REFERENCES

[1] Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev. 2016;2:CD001903. DOI: 10.1002/14651858.CD001903.pub3.

[2] Verrotti A, Iapadre G, Pisano S, Coppola G. Ketogenic diet and childhood neurological disorders other than epilepsy: An overview. Expert Rev Neurother. 2017;17(5):461-473. DOI: 10.1080/14737.175.2017.1260004.

[3] Dhamija R, Eckert S, Wirrell E. Ketogenic diet. Can J Neurol Sci. 2013;40(2):158-167. DOI: 10.1017/S031.716.7100013676.

[4] Kossoff EH, Dorward JL, Molinero MR, Holden KR. The modified Atkins diet: A potential treatment for developing countries.

Epilepsia. 2008;49(9):1646-1647. DOI: 10.1111/j.1528-1167.2008.01580_6.x.

[5] Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia. 2006;47(2):421-424. DOI: 10.1111/j.1528-1167.2006.00438.x.

[6] Huttenlocher PR, Wilbourn AJ, Signore JM. Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology. 1971;21(11):1097-1103. DOI: 10.1212/wnl.21.11.1097.

[7] Liu YMC. Medium-chain triglyceride (MCT) ketogenic therapy. Epilepsia. 2008;49(Suppl. 8):33-36. DOI: 10.1111/j.1528-1167.2008.01830.x.

[8] Scholl-Bürgi S, Höller A, Pichler K, Michel M, Haberlandt E, Karall D. Ketogenic diets in patients with inherited metabolic disorders. J Inherit Metab Dis. 2015;38(4):765-773. DOI: 10.1007/s10545.015.9872-2.

[9] Sentner CP, Hoogeveen IJ, Weinstein DA, Santer R, Murphy E, McKiernan PJ, Steuerwald U, Beauchamp NJ, Taybert J, Laforet P, Petit FM, Hubert A, Labrune P, Smit GPA, Derks TGJ. Glycogen storage disease type III: Diagnosis, genotype, management, clinical course and outcome. J Inherit Metab Dis. 2016;39(5):697-704. DOI: 10.1007/s10545.016.9932-2.

[10] Kishnani PS, Austin SL, Arn P, Bali DS, Boney A, Case LE, Chung WK, Desai DM, El-Gharbawy A, Haller R, Smit GPA, Smith AD, Hobson-Webb LD, Wechsler SB, Weinstein DA, Watson MS. Glycogen storage disease type III diagnosis and management guidelines. Genet Med. 2010;12(7):446-463. DOI: 10.1097/GIM.0b013e3181e655b6.

[11] Derks TGJ, Smit GPA. Dietary management in glycogen storage disease type III: What is the evidence? J Inherit Metab Dis. 2015;38(3):545-550. DOI: 10.1007/s10545.014.9756-x.

[12] Olgac A, İnci A, Okur İ, Biberoğlu G, Oğuz D, Ezgü FS, Kasapkara ÇS, Aktaş E, Tümer L. Beneficial effects of modified Atkins diet in glycogen storage disease type IIIa. Ann Nutr Metab. 2020;76(4):233-241. DOI: 10.1159/000509335.

[13] Mayorandan S, Meyer U, Hartmann H, Das AM. Glycogen storage disease type III: Modified Atkins diet improves myopathy. Orphanet J Rare Dis. 2014;9:196. DOI: 10.1186/s13023.014.0196-3.

[14] Fischer T, Njoroge H, Och U, Klawon I, Marquardt T. Ketogenic diet treatment in adults with glycogenosis type IIIa (Morbus Cori). Clin Nutr Exp. 2019;28:83-91. DOI: 10.1016/j.yclnex.2019.09.004.

[15] Francini-pesenti F, Tresso S, Vitturi N. Modified Atkins ketogenic diet improves heart and skeletal muscle function in glycogen storage disease type III. Acta Myol. 2019;38(1):17-20.

[16] Akin KB, Hismi BO, Daly A. Improvement in hypertrophic cardiomyopathy after using a high-fat, high-protein and low-carbohydrate diet in a non-adherent child with glycogen storage disease type IIIa. Mol Genet Metab Rep. 2022;32:100904. DOI: 10.1016/j.ymgmr.2022.100904.

[17] Brambilla A, Mannarino S, Pretese R, Gasperini S, Galimberti C, Parini R. Improvement of cardiomyopathy after high-fat diet in two siblings with glycogen storage disease type iii. JIMD Rep. 2014;17:91-95. DOI: 10.1007/8904_2014_343.

[18] Marusic T, Zerjav M, Sirca A, Mezek A, Berden P. Normalization of obstructive cardiomyopathy and improvement of hepatopathy on ketogenic diet in patient with glycogen storage disease (GSD) type IIIa. Mol Genet Metab Rep. 2020;24:100628. DOI: 10.1016/j.ymgmr.2020.100628.

[19] Valayannopoulos V, Bajolle F, Arnoux JB, Dubois S, Sannier N, Baussan C, Petit F, Labrune P, Rabier D, Ottolenghi C, Vassault A, Broissand C, Bonnet D, de Lonlay P. Successful treatment of severe cardiomyopathy in glycogen storage disease type III with d,l-3-hydroxybutyrate, ketogenic and high-protein diet. Pediatr Res. 2011;70:638-641. DOI: 10.1203/PDR.0b013e318232154f.

[20] Rossi A, Hoogeveen IJ, Bastek VB, de Boer F, Montanari C, Meyer U, Maiorana A, Bordugo A, Dianin A, Campana C, Rigoldi M, Kishnani PS, Pendyal S, Strisciuglio P, Gasperini S, Parenti G, Parini R, Paci S, Melis D, Derks TGJ. Dietary lipids in glycogen storage disease type III: A systematic literature study, case studies, and future recommendations. J Inherit Metab Dis. 2020;43(4):770-777. DOI: 10.1002/jimd.12224.

[21] Quinlivan R, Buckley J, Twist A, Ball S, Duno M, Vissing J, Bruno C, Cassandrini D, Roberts M, Winer J, Rose M, Sewry C. McArdle disease: A clinical review. J Neurol Neurosurg Psychiatry. 2010;81(11):1182-1188. DOI: 10.1136/jnnp.2009.195040.

[22] Quinlivan R, Martinuzzi A, Schoser B. Pharmacological and nutritional treatment for McArdle disease (Glycogen Storage Disease type V). Cochrane Database Syst Rev. 2014;11:CD003458. DOI: 10.1002/14651858.CD003458.pub5.

[23] Andersen S, Haller R, Vissing J. Effect of oral sucrose shortly before exercise on work capacity in McArdle disease. Arch Neurol. 2008;65(6):786-789. DOI: 10.1001/archneur.65.6.786.

[24] Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. N Engl J Med. 2003;349(26):2503-2509. DOI: 10.1056/NEJMoa031836.

[25] Mikkelsen K, Seifert T, Secher N, Grøndal T, van Hall G. Systemic, cerebral and skeletal muscle ketone body and energy metabolism during acute hyper-D-β-hydroxybutyratemia in post-absorptive healthy males. J Clin Endocrinol Metab. 2015;100(2):636-643. DOI: 10.1210/jc.2014-2608.

[26] Busch V, Gempel K, Hack A, Müller K, Vorgerd M, Lochmüller H, Baumeister FA. Treatment of glycogenosis type V with ketogenic diet. Ann Neurol. 2005;58(2):341. DOI: 10.1002/ana.20565.

[27] Vorgerd M, Zange J. Treatment of glycogenosys type V (McArdle disease) with creatine and ketogenic diet with clinical scores and with 31P-MRS on working leg muscle. Acta Myol. 2007;26(1):61-63.

[28] Reason SL, Westman EC, Godfrey R, Maguire E. Can a low-carbohydrate diet improve exercise tolerance in Mcardle disease? J Rare Disord Diagn Ther. 2017;3:1-5. DOI: 10.21767/2380-7245.100054.

[29] Løkken N, Hansen KK, Storgaard JH, Ørngreen MC, Quinlivan R, Vissing J. Titrating a modified ketogenic diet for patients with McArdle disease: A pilot study. J Inherit Metab Dis. 2020;43(4):778-786. DOI: 10.1002/jimd.12223.

[30] Løkken N, Storgaard JH, Revsbech KL, Voermans NC, Van Hall G, Vissing J, Ørngreen MC. No effect of oral ketone ester supplementation on exercise capacity in patients with McArdle disease and healthy controls: A randomized placebo-controlled cross-over study. J Inherit Metab Dis. 2022;45(3):502-516. DOI: 10.1002/jimd.12484.

[31] Reason SL, Godfrey RJ. The potential of a ketogenic diet to minimize effects of the metabolic fault in glycogen storage

disease V and VII. Curr Opin Endocrinol Diabetes Obes. 2020;27(5):283-290. DOI: 10.1097/MED.000.000.0000000567.

[32] Swoboda KJ, Specht L, Jones HR, Shapiro F, DiMauro S, Korson M. Infantile phosphofructokinase deficiency with arthrogryposis: Clinical benefit of a ketogenic diet. J Pediatr. 1997;131(6):932-934. DOI: 10.1016/S0022-3476(97)70048-9.

[33] Similä ME, Auranen M, Piirilä PL. Beneficial effects of ketogenic diet on phosphofructokinase deficiency (glycogen storage disease type VII). Front Neurol. 2020;11:57. DOI: 10.3389/fneur.2020.00057.

[34] Coughlin CR, Swanson MA, Kronquist K, Acquaviva C, Hutchin T, Rodríguez-Pombo P, Vaisanen ML, Spector E, Creadon-Swindell G, Bras-Goldberg AM, Rahikkala E, Moilanen JS, Mahieu V, Matthijs G, Bravo-Alonso I, Perez-Cerda C, Ugarte M, Vianey-Saban C, Scharer GH, Van Hove JLK. The genetic basis of classic nonketotic hyperglycinemia due to mutations in GLDC and AMT. Genet Med. 2017;19(1):104-111. DOI: 10.1038/gim.2016.74.

[35] Suzuki Y, Kure S, Oota M, Hino H, Fukuda M. Nonketotic hyperglycinemia: Proposal of a diagnostic and treatment strategy. Pediatr Neurol. 2010;43(3):221-224. DOI: 10.1016/j.pediatrneurol.2010.04.018.

[36] Shelkowitz E, Saneto RP, Al-Hertani W, Lubout CM, Stence NV, Brown MS, Long P, Walleigh D, Nelson JA, Perez FE, Shaw DWW, Michl EJ, Van Hove JLK. Ketogenic diet as a glycine lowering therapy in nonketotic hyperglycinemia and impact on brain glycine levels. Orphanet J Rare Dis. 2022;17(1):423. DOI: 10.1186/s13023.022.02581-6.

[37] Daida A, Hamano SI, Ikemoto S, Hirata Y, Matsuura R, Koichihara R, Oba D, Ohashi H. Use of Perampanel and a ketogenic diet in nonketotic hyperglycinemia: A case report. Neuropediatrics. 2020;51(6):417-420. DOI: 10.1055/s-0040.170.8536.

[38] Freeman J, Kossoff E. Ketosis and the ketogenic diet, 2010: Advances in treating epilepsy and other disorders. Adv Pediatr. 2010;57(1):315-329. DOI: 10.1016/j.yapd.2010.08.003.

[39] Kava MP, Robertson A, Greed L, Balasubramaniam S. Ketogenic diet, a potentially valuable therapeutic option for the management of refractory epilepsy in classical neonatal nonketotic hyperglycinemia: A case report. Eur J Clin Nutr. 2019;73(6):961-965. DOI: 10.1038/s41430.018.0286-8.

[40] Shbarou RM, Boustany RM, Daher RT, Pakdel P, Noureddine A, Karam PE. Outcome of nonketotic hyperglycinemia in Lebanon: 14-year retrospective review. Neuropediatrics. 2019;50(4):235-243. DOI: 10.1055/s-0039.169.2207.

[41] Bough K. Energy metabolism as part of the anticonvulsant mechanism of the ketogenic diet. Epilepsia. 2008;49(Suppl. 8):91-93. DOI: 10.1111/j.1528-1167.2008.01846.x.

[42] Thompson K, Collier JJ, Glasgow RIC, Robertson FM, Pyle A, Blakely EL, Alston CL, Olahova M, McFarland R, Taylor RW. Recent advances in understanding the molecular genetic basis of mitochondrial disease. J Inherit Metab Dis. 2020;43(1):36-50. DOI: 10.1002/jimd.12104.

[43] Kang HC, Lee YM, Kim HD. Mitochondrial disease and epilepsy. Brain Dev. 2013;35(8):757-761. DOI: 10.1016/j.braindev.2013.01.006.

[44] Bastin J. Regulation of mitochondrial fatty acid β-oxidation in human: What can we learn from inborn fatty acid β-oxidation deficiencies? Biochimie. 2014;96(1):113-120. DOI: 10.1016/j.biochi.2013.05.012.

[45] Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Bergqvist AGC, Blackford R, Buchhalter JR, Caraballo RH, Cross JH, Dahlin MG, Donner EJ, Guzel O, Jehle RS, Klepper J, Kang H, Lambrechts DA, Liu YMC, Nathan JK, Nordli DR, Pfeifer HH, Rho JM, Scheffer IE, Sharma S, Stafstrom CE, Thiele EA, Turner Z, Vaccarezza MM, van der Louw EJTM, Veggiotti P, Wheless JW, Wirrell EC. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3(2):175-192. DOI: 10.1002/epi4.12225.

[46] Rahman S. Mitochondrial disease and epilepsy. Dev Med Child Neurol. 2012;54(5):397-406. DOI: 10.1111/j.1469-8749.2011.04214.x.

[47] Lee YM, Kang HC, Lee JS, Kim SH, Kim EY, Lee SK, Slama A, Kim HD. Mitochondrial respiratory chain defects: Underlying etiology in various epileptic conditions. Epilepsia. 2008;49(4):685-690. DOI: 10.1111/j.1528-1167.2007.01522.x.

[48] Na JH, Kim HD, Lee YM. Effective and safe diet therapies for Lennox-Gastaut syndrome with mitochondrial dysfunction. Ther Adv Neurol Disord. 2020;13:1-12. DOI: 10.1177/175.628.6419897813.

[49] Kang HC, Lee YM, Kim HD, Lee JS, Slama A. Safe and effective use of the ketogenic diet in children with epilepsy and mitochondrial respiratory chain complex defects. Epilepsia. 2007;48(1):82-88. DOI: 10.1111/j.1528-1167.2006.00906.x.

[50] Huang L, Li H, Zhong J, Yang L, Chen G, Wang D, Zheng G, Han H, Han X, Long Y, Wang X, Liang J, Yu M, Shen X, Fan M, Fang G, Liao J, Sun D. Efficacy and safety of the ketogenic diet for mitochondrial disease with epilepsy: A prospective, open-labeled, controlled study. Front Neurol. 2022;13:880944. DOI: 10.3389/fneur.2022.880944.

[51] Zweers H, van Wegberg AMJ, Janssen MCH, Wortmann SB. Ketogenic diet for mitochondrial disease : A systematic review on efficacy and safety. Orphanet J Rare Dis. 2021;16:295. DOI: 10.1186/s13023.021.01927-w.

[52] Köse E, Köse M, Edizer S, Akisin Z, Yilmaz Z, Sahin A, Genel F. Different clinical presentation in a patient with two novel pathogenic variants of the FBXL4 gene. Turk J Pediatr. 2020;62(4):652-656. DOI: 10.24953/turkjped.2020.04.016.

[53] Pfeiffer B, Sen K, Kaur S, Pappas K. Expanding phenotypic spectrum of cerebral aspartate-glutamate carrier isoform 1 (AGC1) deficiency. Neuropediatrics. 2020;51(2):160-163. DOI: 10.1055/s-0039.340.0976.

[54] Koessler M, Haberlandt E, Karall D, Baumann M, Höller A, Scholl-Bürgi S. Ketogenic diet in a patient with refractory status epilepticus due to polg mutation. JIMD Rep. 2021;57(1):3-8. DOI: 10.1002/jmd2.12169.

[55] O'Byrne JJ, Tarailo-Graovac M, Ghani A, Champion M, Deshpande C, Dursun A, Ozgul RK, Freisinger P, Garber I, Haack TB, Horvath R, Baric I, Husain RA, Kluijtmans LAJ, Kotzaeridou U, Morris AA, Ross CJ, Santra S, Smeitink J, Tarnopolsky M, van Karnebeek CDM. The genotypic and phenotypic spectrum of MTO1 deficiency. Mol Genet Metab. 2018;123(1):28-42. DOI: 10.1016/j.ymgme.2017.11.003.

[56] Qu C, Keijer J, Adjobo-Hermans MJV, van de Wal M, Schirris T, van Karnebeek C, Pan Y, Koopman WJH. The ketogenic diet as a therapeutic intervention strategy in mitochondrial disease. Int J Biochem Cell Biol. 2021;138:106050. DOI: 10.1016/j.biocel.2021.106050.

[57] Prasad C, Rupar T, Prasad AN. Pyruvate dehydrogenase deficiency and epilepsy. Brain Dev. 2011;33(10):856-865. DOI: 10.1016/j.braindev.2011.08.003.

[58] El-gharbawy AH, Boney A, Young SP, Kishnani PS. Follow-up of a child with pyruvate dehydrogenase deficiency on a less restrictive ketogenic diet. Mol Genet Metab. 2011;102(2):214-215. DOI: 10.1016/j.ymgme.2010.11.001.

[59] Sofou K, Dahlin M, Hallböök T, Lindefeldt M, Viggedal G, Darin N. Ketogenic diet in pyruvate dehydrogenase complex deficiency: Short – and long-term outcomes. J Inherit Metab Dis. 2017;40(2):237-245. DOI: 10.1007/s10545.016.0011-5.

[60] Inui T, Wada Y, Shibuya M, Arai-ichinoi N. Intravenous ketogenic diet therapy for neonatal-onset pyruvate dehydrogenase complex deficiency. Brain Dev. 2022;44(3):244-248. DOI: 10.1016/j.braindev.2021.11.005.

[61] Kwiterovich PO, Vining EPG, Pyzik P, Skolasky R, Freeman JM. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. JAMA. 2003;290(7):912-920. DOI: 10.1001/jama.290.7.912.

[62] Pisa VD, Cecconi I, Gentile V, Pietro ED, Marchiani V, Verrotti A, Franzoni E. Case report of pyruvate dehydrogenase deficiency with unusual increase of fats during ketogenic diet treatment. J Child Neurol. 2012;27(12):1593-1596. DOI: 10.1177/088.307.3812436424.

[63] Klepper J. Absence of SLC2A1 mutations does not exclude glut1 deficiency syndrome. Neuropediatrics. 2013;44(4):235-236. DOI: 10.1055/s-0033.133.6015.

[64] De Giorgis V, Veggiotti P. GLUT1 deficiency syndrome 2013: Current state of the art. Seizure. 2013;22(10):803-811. DOI: 10.1016/j.seizure.2013.07.003.

[65] Klepper J, Leiendecker B. Glut1 deficiency syndrome and novel ketogenic diets. J Child Neurol. 2013;28(8):1045-1048. DOI: 10.1177/088.307.3813487600.

[66] Pascual JM, Ronen GM. Glucose transporter type I deficiency (G1D) at 25 (1990-2015): Presumptions, facts, and the lives of persons with this rare disease. Pediatr Neurol. 2015;53(5):379-393. DOI: 10.1016/j.pediatrneurol.2015.08.001.

[67] Klepper J. Glucose transporter deficiency syndrome (GLUT1DS) and the ketogenic diet. Epilepsia. 2008;49:46-49. DOI: 10.1111/j.1528-1167.2008.01833.x.

[68] Schwantje M, Verhagen LM, van Hasselt PM, Fuchs SA. Glucose transporter type 1 deficiency syndrome and the ketogenic diet. J Inherit Metab Dis. 2020;43(2):216-222. DOI: 10.1002/jimd.12175.

[69] Kass HR, Winesett SP, Bessone SK, Turner Z, Kossoff EH. Use of dietary therapies amongst patients with GLUT1 deficiency syndrome. Seizure. 2016;35:83-87. DOI: 10.1016/j.seizure.2016.01.011.

[70] Gumus H, Bayram AK, Kardas F, Canpolat M, Çağlayan AO, Kumandas S, Kendirci M, Per H. The effects of ketogenic diet on seizures, cognitive functions, and other neurological disorders in classical phenotype of glucose transporter 1 deficiency syndrome. Neuropediatrics. 2015;46(5):313-320. DOI: 10.1055/s-0035.155.8435.

[71] Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T, van Engelen BG, Wevers RA, Arthur T, Bahi-Buisson N, Ballhausen D, Bekhof J, van Bogaert P, Carrilho I, Chabrol B, Champion MP, Coldwell J, Clayton P, Donner E, Evangeliou A, Ebinger F, Farrell K, Forsyth RJ, de Goede CGEL, Gross S, Grunewald S, Holthausen H, Jayawant S, Lachlan K, Laugel V, Leppig K, Lim MJ, Mancini G, Marina AD, Martorell L, McMenamin J, Meuwissen MEC, Mundy H, Nilsson NO, Panzer A, Poll-The BT, Rauscher C, Rouselle CMR, Sandvig I, Scheffner T, Sheridan E, Simpson N, Sykora P, Tomlinson R, Trounce J, Webb D, Weschke B, Scheffer H, Willemsen MA. Glucose transporter-1 deficiency syndrome: The expanding clinical and genetic spectrum of a treatable disorder. Brain. 2010;133(3):655-670. DOI: 10.1093/brain/awp336.

[72] Pong AW, Geary BR, Engelstad KM, Natarajan A, Yang H, De Vivo DC. Glucose transporter type i deficiency syndrome: Epilepsy phenotypes and outcomes. Epilepsia. 2012;53(9):1503-1510. DOI: 10.1111/j.1528-1167.2012.03592.x.

[73] Sandu C, Burloiu CM, Barca DG, Magureanu SA, Craiu DC. Ketogenic diet in patients with GLUT1 deficiency syndrome. Maedica. 2019;14(2):93-97. DOI: 10.26574/maedica.2019.14.2.93.

[74] Ramm-Pettersen A, Nakken KO, Skogseid IM, Randby H, Skei EB, Bindoff LA, Selmer KK. Good outcome in patients with early dietary treatment of GLUT-1 deficiency syndrome: Results from a retrospective Norwegian study. Dev Med Child Neurol. 2013;55(5):440-447. DOI: 10.1111/dmcn.12096.

[75] Ito Y, Oguni H, Ito S, Oguni M, Osawa M. A modified Atkins diet is promising as a treatment for glucose transporter type 1 deficiency syndrome. Dev Med Child Neurol. 2011;53(7):658-663. DOI: 10.1111/j.1469-8749.2011.03961.x.

[76] Fujii T, Ito Y, Takahashi S, Shimono K, Natsume J, Yanagihara K, Oguni H. Outcome of ketogenic diets in GLUT1 deficiency syndrome in Japan: A nationwide survey. Brain Dev. 2016;38(7):628-637. DOI: 10.1016/j.braindev.2016.01.002.

[77] Amalou S, Gras D, Ilea A, Greneche MO, Francois L, Bellavoine V, Delanoe C, Auvin S. Use of modified Atkins diet in glucose transporter type 1 deficiency syndrome. Dev Med Child Neurol. 2016;58(11):1193-1199. DOI: 10.1111/dmcn.13167.

[78] Herrero JR, Villarroya EC, Gutiérrez-Solana LG, Alcolea BG, Fernández BG, Macfarland LP, Pedrón-Giner C. Classic ketogenic diet and modified atkins diet in SLC2A1 positive and negative patients with suspected GLUT1 deficiency syndrome: a single center analysis of 18 cases. Nutrients. 2021;13(3):840. DOI: 10.3390/nu13030840.

[79] Bekker YAC, Lambrechts DA, Verhoeven JS, van Boxtel J, Troost C, Kamsteeg EJ, Willemsen MA, Braakman HMH. Failure of ketogenic diet therapy in GLUT1 deficiency syndrome. Eur J Paediatr Neurol. 2019;23(3):404-409. DOI: 10.1016/j.ejpn.2019.02.012.

[80] Leen WG, Mewasingh L, Verbeek MM, Kamsteeg EJ, van de Warrenburg BP, Willemsen MA. Movement disorders in GLUT1 deficiency syndrome respond to the modified Atkins diet. Mov Disord. 2013;28(10):1439-1442. DOI: 10.1002/mds.25515.

[81] Slaughter L, Vartzelis G, Arthur T. New GLUT-1 mutation in a child with treatmentresistant epilepsy. Epilepsy Res. 2009;84(2-3):254-256. DOI: 10.1016/j.eplepsyres.2009.01.004.

[82] Ohshiro-Sasaki A, Shimbo H, Takano K, Wada T, Osaka H. A three-year-old boy with glucose transporter type 1 deficiency syndrome presenting with episodic ataxia. Pediatr Neurol. 2014;50(1):99-100. DOI: 10.1016/j.pediatrneurol.2013.09.002.

[83] Haberlandt E, Karall D, Jud V, Baumgartner SS, Zotter S, Rostasy K, Baumann M, Scholl-Buergi S. Glucose transporter type 1 deficiency syndrome effectively treated with modified Atkins diet. Neuropediatrics. 2014;45(2):117-119. DOI: 10.1055/s-0033.134.9225.

[84] Veggiotti P, Teutonico F, Alfei E, Nardocci N, Zorzi G, Tagliabue A, De Giorgis V, Balottin U. Glucose transporter type 1 deficiency: Ketogenic diet in three patients with atypical

phenotype. Brain Dev. 2010;32(5):404-408. DOI: 10.1016/j.braindev.2009.04.013.

[85] Veggiotti P, De Giorgis V. Dietary treatments and new therapeutic perspective in GLUT1 deficiency syndrome. Curr Treat Options Neurol. 2014;16(5):291. DOI: 10.1007/s11940.014.0291-8.

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