



Advances in Ketogenic Diet Therapies in Pediatric Epilepsy

Battamir Enkhtuy, MD^{1,*}, Hye Eun Kwon, MD^{2,*}, Heung Dong Kim, MD³

¹Department of Neurology, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

²Department of Pediatrics, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Korea

³Division of Pediatric Neurology, Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author:

Heung Dong Kim, MD
Division of Pediatric Neurology,
Department of Pediatrics, Severance
Children's Hospital, Yonsei
University College of Medicine, 50
Yonsei-ro, Seodaemun-gu, Seoul
03722, Korea
Tel: +82-2-2228-2060
Fax: +82-2-392-9118
E-mail: hdkimmd@yuhs.ac

* These authors contributed equally
to the manuscript as first author.

Ketogenic diets are high in fat, low in carbohydrates, and contain an adequate amount of protein. In addition to the classic ketogenic diet, three alternative types of ketogenic diet therapies (KDTs) have emerged. In addition to clarifying the indications for early treatment using KDTs, ongoing research over the past decades has led to the recognition of their contraindications and adverse effects. Recent studies focusing on the targeted therapeutic range of KDTs are expected to elucidate the precise mechanisms by which they alleviate certain epilepsy syndromes and other disorders. In this review, we discuss recent advances in KDTs, focusing on six issues: the selection of a specific KDT; the use of KDTs for febrile infection-related epilepsy syndrome and super-refractory status epilepticus; the use of KDTs for infants with refractory epilepsy; links between the gut-brain axis and KDTs; triheptanoin; and the use of KDTs for disorders other than pediatric epilepsy.

Keywords: Diet, ketogenic; Drug resistant epilepsy; Child

Introduction

Ketogenic diet therapies (KDTs) are the first-line treatment for glucose transporter 1 deficiency syndrome (Glut1DS) and pyruvate dehydrogenase deficiency. KDTs are also an early course of treatment for several epilepsy syndromes, including Dravet syndrome, West syndrome (WS), and epilepsy with myoclonic atonic seizures, and should be offered to children who fail to benefit from two anti-epileptic drugs (AEDs) [1]. Based on clinical experience and research over the last decade, Kossoff et al. [1] updated recommendations for the use of dietary therapies for pediatric epilepsy in 2018 to include new indications, including febrile infection-related epilepsy syndrome (FIRES)/super-refractory status epilepticus (SRSE), Angelman syndrome, complex 1 mitochondrial disorders,

and Ohtahara syndrome. The updated recommendations also state that most centers prefer a non-fasting state at initiation of a KDT, making hospital admission optional; that although a diet can be selected from four major KDTs, the classic ketogenic diet (KD) is associated with a higher likelihood of a seizure-free outcome for children under 2 years of age, whereas alternatives to the classic KD are favored for adolescents and adults; and that additional lab tests (e.g., selenium, free and total carnitine) and electroencephalography (EEG) should be performed.

High-fat/low-carbohydrate diets induce production of ketone bodies (KBs), which become the primary source of energy for cell metabolism instead of glucose [2]. KDTs have a broad-spectrum therapeutic range than medications due to their multi-mechanism properties, with KBs directly inhibiting vesicular glutamate trans-

port, altering metabolism by inhibiting glycolysis and increasing mitochondrial adenosine triphosphate (ATP) production, activating ATP-sensitive potassium channels to prevent neuronal excitability, and increasing polyunsaturated fatty acid and decreasing reactive oxygen species by stimulating mitochondrial uncoupling proteins [3,4]. Thus, KDTs not only inhibit neuronal hyperexcitability but also have neuroprotective effects that correct cellular energy failure and guard against epileptic brain damage [3]. Some researchers anticipate that KDTs will be replaced by drugs that mimic the actions of KDTs or directly stimulate ketogenesis in the liver, making these dietary treatments more similar to pharmacological therapy [5-7]. At present, however, this possibility seems questionable because different KDTs involve different subsets of anti-seizure mechanisms that can be targeted to individual patients. In this review, we focus on recent advances in KDTs for pediatric epilepsy considering the following issues: selection of a specific KDT; use of KDTs for status epilepticus; use of KDTs for infants with refractory epilepsy (RE); links between the gut-brain axis and KDTs; triheptanoin; and use of KDTs for disorders other than pediatric epilepsy.

Selection of a Specific KDT

As compliance with the strict regimen of the classic KD is difficult, more flexible alternative variants have been employed. In addition to the classic KD, three other major dietary treatments—the modified Atkins diet (MAD), low glycemic index treatment (LGIT), and medium chain triglyceride (MCT) diet—are now available for patients with epilepsy.

The MAD typically consists of a 1:1 to 1.5:1 ketogenic ratio, achieves more than 50% seizure reduction in two-thirds of children with RE [8-11], and is well tolerated by adolescents and adults [12] and those who do not adhere to the classic KD. Some studies report that the MAD is as effective as the classic KD; although, the classic KD is associated with a higher likelihood of seizure freedom in children under 2 years of age with RE [13,14] and epileptic individuals with myoclonic atonic seizures [13]. In addition to its advantages in regard to growth and physical abilities, the MAD can be a good option for long-term maintenance for Glut1DS patients [15]. Nevertheless, for infants with Glut1DS, the classic KD is still considered superior in the early course of treatment and is recommended for long-term maintenance if possible [1].

The LGIT involves swapping high glycemic index (GI) foods for low GI alternatives. The GI describes the tendency of foods to increase blood glucose, compared with an equivalent amount of reference carbohydrate, usually glucose. Thus, the LGIT uses a liberalized but still low carbohydrate intake, with carbohydrates sup-

plied only in the form of low GI foods and allows a more flexible lifestyle for patients by permitting increased intake of carbohydrates [16]. It achieves around 50% seizure reduction in half of pediatric patients with RE [17,18] and is useful for those who cannot tolerate the classic KD or MAD [17]. Considering its high efficacy, the LGIT is used as an alternative or supplementary treatment for Angelman syndrome [19,20].

The MCT diet, which produces MCT (C6-12) that are more ketogenic than long-chain triglycerides, was introduced by Huttenlocher in 1971 [21]. The efficacy of the MCT diet is comparable to that of the classic KD; over half of children achieve more than 50% seizure reduction with good tolerance and few side effects [22,23]. In animal models with MCT diet, KB concentrations in blood plasma are poorly correlated with seizure control [24,25], and there is a lack of evidence that KBs participate in stopping seizures [26]. This suggests that MCTs, rather than KBs, block seizure onset and raise the seizure threshold [27-29]. MCTs, which consist of approximately 60% octanoic acid (C8) and 40% decanoic acid (C10), exert anti-seizure effects via α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor inhibition [26] as well as peroxisome proliferator-activated receptor γ (PPAR γ) activation and mitochondrial biosynthesis [29] by using decanoic acid rather than octanoic acid [26,29,30]. In an animal model of acute seizures, decanoic acid increased seizure thresholds in both the 6 Hz stimulation test (a model of drug-resistant seizures) and maximal electroshock test (a model of tonic-clonic seizures), although it did not block pentetrazol-induced seizures (proposed to be a model of absence seizures) [30]. Decanoic acid is considered to be a PPAR γ agonist that increases brain mitochondrial function and ATP synthesis, thereby increasing seizure threshold [29,31], but it does not alter glycolytic enzymes [32]. MCTs have the direct and selective action of inhibiting AMPA receptors in an animal model, which has been considered to be the first targeted anti-seizure mechanism of the MCT diet [26]. This gives rise to the question of whether the MCT diet can be replaced by AMPA receptor-blocking agents such as perampanel [33]. However, a recent study showed a synergistic interaction between perampanel and decanoic acid, as perampanel binds at a different AMPA receptor site than decanoic acid [34].

Use of KDTs for Status Epilepticus

Although FIRES and SRSE are included in the updated recommendations, the efficacy of KDTs was first shown for refractory status epilepticus (RSE) as described by Kossoff and Nabbout [35] in 2013. At that time, 10 retrospective studies including 32 children and adults with RSE showed dramatic beneficial effects of

KDTs, with 78% of patients becoming seizure-free and most responding within 7 to 10 days. Patients with FIRES are also reported to be good responders to KDTs [36].

Recent studies with 10 or more patients report good outcomes of KDTs regardless of etiology and a low rate of complications in critically ill patients with RSE/SRSE [37-40]. For instance, more than half of patients achieved more than 50% seizure reduction within a median of 7 days, desired ketosis was reached within a median of 4 days, and most patients successfully weaned off continuous infusion of anesthesia within 2 weeks after initiation of a KDT. Relatively low rates of adverse effects were noted, but these included gastrointestinal disturbances, electrolyte imbalance, and ketoacidosis, with the main causes of discontinuation being pancreatitis and hypertriglyceridemia [38,39]. These outcomes are consistent with those of other studies with fewer than 10 patients [41-49], and patients with FIRES have also been found to respond quickly after KDT initiation [40,46,47]. Most patients are good responders, weaning off infusion and successfully reaching ketosis, but the number of AEDs did not change significantly before and after undertaking a KDT [40,43]. The age of patients has varied across studies, but even 6 to 10-week-old neonates with RE are reported to tolerate KDTs well [42,50]. Intravenous (IV) KDT is recommended for patients with underlying concomitant ileus [41,44,48], and early administration of IV KDT should be considered before switching to an enteral route [44]. There are no significant differences in the time to reach ketosis between IV and enteral routes, although hypertriglyceridemia and pancreatitis are frequently associated with IV KDT. Considering that critically ill patients with FIRES/SRSE receive many concurrent medications and are prone to malabsorption, IV KDT could be temporarily substituted for an enteral route [41]. Nonetheless, before evaluating the efficiency and safety of KDTs among FIRES/SRSE patients, factors such as concomitant treatments, variations in timing before the initiation of KDTs, the specific outcomes assessed, and possible publication bias should be considered [38].

Use of KDTs for Infants with RE

Contrary to a conventional view, under 2 years of age may be the optimum time to initiate a KDT because of the metabolic advantages of infants [50-55]. Numerous studies provide evidence for the advantages of using KDTs in infants with RE. Infants under 1.5 years of age have a higher chance of achieving seizure freedom than children over 1.5 years of age, and, interestingly, infants under 9 months of age also have a higher likelihood of achieving seizure freedom, demonstrating the ease of KDT administration and good outcomes before solid feeding [51]. These outcomes remained

stable at long-term follow-up. Another study reports specific etiologic differences in long-term seizure-free outcomes among 115 patients who initiated KDTs before 1 year of age and shows that seizure freedom within the first 3 months could be a predictor of long-term seizure freedom [55]. A similar study including 109 patients with RE under 3 years of age with different etiologies reports that patients with a genetic etiology were particularly good responders to KDTs [54], with nearly half of patients with a confirmed genetic abnormality showing more than a 50% reduction in seizure frequency. Nevertheless, most studies report a high efficacy of KDTs for some specific epilepsy syndromes such as WS [53,56-59], epilepsy with myoclonic atonic seizures [14], and Dravet syndrome [60]. Around two-thirds of patients with WS experience a reduction in seizures with KDTs, and many show improvements in development, EEG activity, and number of concurrent AEDs [58]. Adrenocorticotropic hormone (ACTH) treatment is associated with a high responder rate and quick cessation of spasms, but it has higher rates of relapse and adverse effects than KDTs [53]. In a recent study comparing efficacy and safety between KDTs and standard high-dose ACTH treatment in WS infants [59], ACTH was associated with a higher rate of short-term remission among infants without prior treatment history of vigabatrin (VGB); however, it was also associated with a higher rate of relapse and similar rate of seizure-free outcome as KDTs at long-term follow-up. Also, KDTs had a higher rate of seizure freedom in long-term follow-up and a lower relapse rate in the short-term in infants with a prior treatment history of VGB. This study suggests that after VGB failure, a KDT could be a second-line treatment for WS.

The Gut-Brain Axis and KDTs

Several studies show that diversity in the diet significantly influences the composition of gut microbiota and the subsequent health of individuals [61]. Differences in the composition of gut microbiota between drug-sensitive/healthy control individuals and drug-resistant epilepsy patients indicates the possible involvement of dysbiosis in the development of drug-resistant epilepsy [62]. Dysbiosis may enhance susceptibility to seizures and accelerate illness resulting from chronic stress; thus, restoration and remodeling of a healthy gut microbial population could control seizures and boost quality of life [63,64]. In this regard, KDTs may positively impact seizures via alteration of the gut microbiota. In two mouse models, KDTs altered the composition of gut microbiota, including reducing bacterial alpha diversity and increasing certain bacteria [65]. Moreover, high-dose antibiotics, which deplete gut microbiota, increase seizure vulnerability in wild-type and *Kna1^{-/-}* mice receiving KDTs. In this study, gut microbiota and KDTs with antiseizure

properties were correlated with decreases in systemic gamma-glutamylated amino acid and enhanced γ -aminobutylic acid (GABA) levels in the hippocampus.

Similar to the results of animal studies, children with RE show alterations in the specific richness and diversity of gut microbiota, such as increased *Bacteroidetes* and decreased *Firmicutes* and *Actinobacteria*, after 6 months of KDT [66]. Moreover, the abundance of *Clostridiales*, *Clostridia*, *Ruminococcaceae*, *Lachnospiraceae*, *Alistipes*, and *Rikenellaceae* were significantly increased in those who failed to respond to KDT compared with good responders. The authors of this study speculated that specific microbiota might be therapeutic targets in the treatment of epilepsy and could serve as biomarkers indicating the efficacy of KDT.

Triheptanoin

Triheptanoin is a triglyceride composed of three heptanoate (C7 fatty acid) that is an artificial tasteless oil easily dissolved in food. Triheptanoin is used to treat many metabolic disorders because it has an anaplerotic role that replenishes substrates involved in the tricarboxylic acid (TCA) cycle and the ability to bypass metabolic blockade induced by enzyme deficiency [67]. Several studies using acute and chronic seizure mouse models demonstrate that triheptanoin exerts anti-seizure effects by increasing TCA intermediates and activating mitochondrial function, known as anaplerosis [68,69]. Calvert et al. [70] performed a study including 12 children with RE aged 3 to 18 years old and found that (1) children tolerated 30 to 100 mL triheptanoin per day (median, 55.5 mL); (2) the most frequent adverse effect was gastrointestinal disturbance; (3) eight children completed the trial, of whom four safely completed an extended treatment period up to 909 days; (4) five children showed > 50% reduction in seizure frequency, including one patient who was seizure-free for 6 months; (5) children who previously received KDT showed better tolerance and outcomes than those who initiated KDT for the first time, presumably as a result of good parental compliance; and (6) no drug interactions were observed. Therefore, triheptanoin could possibly be administered concurrently with AEDs. Another study in adults with RE reported that MCT or triheptanoin treatment was safe, feasible, and well tolerated as an add-on treatment [71]. In this double-blind study including 34 patients who took triheptanoin (n = 17) or MCT oil (n = 17) mixed into food, 11 and nine patients completed the study and showed good tolerance of the treatment at a median dose of 55 and 59 mL for 3 months, respectively, with reported side effects of diarrhea and abdominal pain. Although the aim of this study was not to investigate the efficacy of KDTs, it showed that MCT had good outcomes for focal un-

aware seizures. Recent studies examining the use of triheptanoin for treating Glut1DS [72-74] show that besides reducing glucose, its main benefit is a reduction in non-paroxysmal events.

KDTs for Other Neurologic Disorders

KDTs have been used for many neurologic disorders other than pediatric epilepsy, such as adult epilepsy, autism, Alzheimer's disease, and brain tumors [75]. The use of KDTs for treating autism is increasingly reported and, according to a systematic review in 2015, eight studies (five human and three animal) had tested the effect of KDTs in autism [76]. A prospective pilot study showed that 18 out of 30 children with autism showed better scores on an autism rating scale after KDT [77]. In addition, MCT was described as a potential supplement for mild Alzheimer's disease [78], and KDTs were proposed as a treatment for Down syndrome [79].

Another current interest is the potential anti-tumor effect of KDTs. Studies suggest that KDTs inhibit tumor cell growth by altering cell metabolism, which seems to enhance the response of other anti-tumor treatments [80,81]. A study with two glioma patients reported that KDTs as a monotherapy seemed ineffective in retarding tumor growth but had more promising effects when combined with standard treatments [82]. These patients received an energy-restricted KD that seemed effective in controlling the progression of primary brain tumors.

Conclusion

KDTs have diversified to alternative forms for different indications that can be selected based on the specific family and child situation. Recommendations for the use of KDTs have been strengthened by an increasing number of studies testing targeted therapeutic ranges.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Battamir Enkhtuy, <https://orcid.org/0000-0001-6616-9552>

Hye Eun Kwon, <https://orcid.org/0000-0001-5180-4218>

Heung Dong Kim, <https://orcid.org/0000-0002-8031-7336>

Author contributions

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