

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,500

Open access books available

118,000

International authors and editors

130M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Ketogenic Diet Therapies in Children and Adults with Epilepsy

Matthew Charles Lee Phillips

Abstract

Despite a wide array of anti-epileptic drugs and the option of surgery, one-third of children and adults with epilepsy continue to suffer from drug-resistant seizures. Many of these patients may benefit from a ketogenic diet, a non-pharmacologic therapy proven to improve seizure control in epilepsy. Ketogenic diets aim to mimic the metabolic profile of fasting, and probably improve seizure control through a variety of mechanisms that collectively stabilize synaptic function. Although many similarities exist with regards to patient selection, patient preparation, and diet implementation in children compared to adults, there are also important differences. The most conspicuous challenge to the more widespread use of ketogenic diets in children and adults with epilepsy is a lack of access to ketogenic services in many regions of the world. Moreover, the culinary and social restrictions associated with conventional ketogenic diets pose a significant barrier to their use in adults.

Keywords: ketogenic, diet, children, adults, epilepsy

1. Introduction

Epilepsy is defined by recurrent, spontaneous seizures arising from hyperexcitable neurons in the brain. Yet despite a wide array of anti-epileptic drugs and the option of surgery, approximately one-third of children and adults with epilepsy continue to experience drug-resistant seizures [1]. Many of these patients may be candidates for a ketogenic diet, a well-established, non-pharmacologic therapeutic option proven to improve seizure control in epilepsy [2, 3].

The origins of ketogenic diets derive from the ancient practice of fasting [4], widely acknowledged as effective in treating epilepsy since the 5th century BC; indeed, until the 19th century, epilepsy was believed to be a disease of “eating too much” [5]. Depending on a person’s body fat stores, fasting can be maintained for a considerable length of time (the record for a single continuous fast is 382 days) [6]. However, since everyone must eventually eat, fasting is not a feasible long-term solution for seizure control in epilepsy.

In 1921, Wilder addressed this problem by developing a high-fat, low-carbohydrate diet designed to mimic the metabolic profile of fasting [4]. The high-fat, low-carbohydrate nature of the diet elevated blood ketones and lowered blood glucose levels, producing a metabolic profile similar to that of a multi-day fast. Unlike fasting, Wilder’s diet provided adequate long-term nutrient intake, thus preventing malnutrition and promoting healthy long-term growth and development. Since the diet increased hepatic ketogenesis, it became known as a “ketogenic diet.”

2. Ketogenic diets

In essence, a ketogenic diet is any high-fat, adequate-protein, low-carbohydrate diet that forces the body to burn fats—not carbohydrates—as the primary energy source [7, 8]. During this process, the liver converts fats into ketone bodies, or “ketones” (organic molecules that readily serve as energy substrates for non-hepatic organs, particularly brain, heart, and skeletal muscle) [9]. The three endogenous ketones are acetone, acetoacetate, and beta-hydroxybutyrate (BHB) [7]; BHB is the primary blood ketone. During a sustained ketogenic diet, the blood BHB level is elevated, and lies within the range of 0.5–8 mmol/L, constituting a state of “physiological ketosis” (in contrast to pathological ketoacidosis, which is associated with a blood BHB level of 15–20 mmol/L or higher, and a concomitant lowering of blood pH) [10].

2.1 Mechanisms of ketogenic diets in epilepsy

Ketogenic diets appear to improve seizure control through a variety of mechanisms that collectively stabilize neuron synaptic function (**Table 1**) [7, 8]. It is not known whether the key mediators of improved seizure control are the ketones themselves, or additional metabolic changes induced by the diets [11].

2.1.1 Ketones as key mediators of seizure control

The most conspicuous metabolic change induced by a ketogenic diet is elevated blood ketone levels [7]. While it is well-documented that ketones enhance neuron energetics, accumulating evidence suggests they may also play direct and indirect roles in reducing neuron excitability, exerting direct antiseizure effects, and decreasing generation of reactive oxygen species and inflammatory mediators [7, 8, 11]. Thus, there are multiple avenues by which ketones may contribute to improved seizure control; they are not just “energy molecules” [11].

Ketones enhance intracellular adenosine triphosphate (ATP) levels and bioenergetic capacity by increasing mitochondrial oxidative phosphorylation [12]. The oxidation of acetoacetate and BHB feeds acetyl-CoA directly into the Krebs cycle

General mechanism	Specific mechanism
Enhanced neuron energetics	Enhanced neuron ATP production
	Stimulated mitochondrial biogenesis
	Hyperpolarized potassium channels
Reduced neuron excitability	Altered glutamate to GABA ratio
	Increased extracellular adenosine
	Ketone-mediated antiseizure effects
Direct antiseizure effects	Raised medium-chain fatty acids
	Reduced glucose metabolism
	Reduced oxidative stress
Other mechanisms	Reduced inflammation

ATP = adenosine triphosphate; GABA = γ -aminobutyric acid.

Table 1.
Mechanisms through which ketogenic diets may stabilize synaptic function.

through anaplerosis (the replenishing of depleted metabolic cycle intermediates) [7], which increases the turnover of the Krebs cycle, generating additional protons and electrons that are channeled to the electron transport chain where they may be used to enhance ATP production [12].

Ketones may also inhibit neuronal excitability. ATP-dependent potassium channels, which hyperpolarize the cell membrane, are activated by ketones, decreasing spontaneous cell firing rates [13]. Moreover, acetoacetate concentrations well within the range produced by a ketogenic diet inhibit vesicle loading of the excitatory neurotransmitter glutamate, resulting in reduced glutamate release into the synapse and enhanced synthesis of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) [14]. It is thought that the ensuing altered glutamate to GABA ratio reduces neuron excitability.

Studies dating back to the 1930s also support the direct antiseizure effects of ketones [15, 16]. In mice, acetone and acetoacetate raise seizure thresholds, resulting in fewer seizures [15, 16]. Although BHB did not appear to contribute to antiseizure effects in these earlier studies, more recent studies indicate that BHB probably does play a direct antiseizure role, and that its effects may have been previously missed for methodological reasons [11].

Lastly, ketones may influence seizure control by lowering cell oxidative stress and inflammation [11]. BHB inhibits histone deacetylases (enzymes that remove acetyl groups from lysine residues on histones, allowing DNA to wrap tightly and preventing gene expression), resulting in upregulated anti-oxidant genes and reduced oxidative stress in kidney cells [17]. Moreover, BHB inhibits the assembly of the immune sensor nucleotide oligomerization domain (NOD)-like receptor protein 3, a multi-protein complex that controls the release of various inflammatory mediators [18].

2.1.2 Additional metabolic changes that may mediate seizure control

Emerging evidence suggests that a number of additional metabolic changes induced by ketogenic diets may also contribute to enhanced neuron energetics, reduced neuron excitability, and direct antiseizure effects, improving seizure control [7, 8].

Ketogenic diets can improve seizure control in patients with mitochondrial disorders [19]. This observation may be partly explained by the action of the medium-chain fatty acid, decanoic acid, on peroxisomal proliferator-activated receptor γ , which stimulates neuronal mitochondrial biogenesis [19]. The increased mitochondrial biomass enhances neuron ATP production capacity and cell energy reserves.

Ketogenic diets may also alter brain levels of the neurotransmitter adenosine. The disruption of adenosine signaling induces seizures; this effect is reversible by a ketogenic diet [20]. This observation suggests that the diet increases extracellular adenosine levels, activating inhibitory adenosine A1 receptors and reducing neuron hyperexcitability [7].

Lastly, ketogenic diets may exert direct antiseizure effects by raising medium-chain fatty acid levels and decreasing glucose metabolism [7, 8]. The medium-chain fatty acid, decanoic acid, blocks seizure-like activity in animals [21]. Moreover, since the antiseizure effects of ketogenic diets can be rapidly reversed by glucose infusions, decreased glucose metabolism is thought to contribute to seizure control. The mechanism for this effect could be partially explained by the observation that ketogenic diets induce a reduction in glycolysis, subsequently repressing the expression of brain-derived neurotrophic factor, a known pro-convulsant [7].

2.2 Conventional ketogenic diets in epilepsy

To date, four major, “conventional” ketogenic diets are supported by published evidence in the treatment of children and adults with epilepsy (**Table 2**) [2, 3]. The primary difference between each diet lies in the ratio of fat to protein plus carbohydrate, described by weight or by calorie intake.

2.2.1 The classic ketogenic diet (CKD)

Created by Wilder in the 1920s [1], the CKD is the oldest of all ketogenic diet therapies and in its purest form consists of 80% fat by weight (roughly equivalent to 90% fat by caloric intake), translating to a 4:1 ratio of fat to protein plus carbohydrate, although a 3:1 ratio or lower can often be used [2]. In the CKD, the fat source consists predominantly of long-chain fatty acids, obtained from standard foods.

2.2.2 The medium-chain triglyceride (MCT) diet

In an effort to make the ketogenic diet more palatable, the MCT diet was introduced in the 1970s [22]. In its original form, the MCT diet is 60% fat by weight (roughly 75% fat by caloric intake), with fat sourced from MCT oils. Since medium-chain fatty acids yield more ketones per kilocalorie compared to long-chain fatty acids, the MCT diet allows for a lower overall fat intake, and a greater intake of protein and carbohydrate, compared to the CKD. A number of patients are prone to gastrointestinal side-effects on this diet, so a modified MCT diet was created in the 1980s, consisting of 30% medium-chain fatty acids plus 30% long-chain fatty acids by weight [23].

2.2.3 The modified Atkins diet (MAD)

In the early 2000s, the MAD was shown to be effective in treating epilepsy [24]. The MAD is approximately 50% fat by weight (65–70% fat by caloric intake),

Ketogenic diet	Macronutrient ratio (by weight)	Macronutrient ratio (by calorie intake)
CKD	Fat 80%	Fat 90%
	Protein 12%	Protein 6%
	Carbohydrate 8%	Carbohydrate 4%
MCT diet	Fat 60%	Fat 75%
	Protein 16%	Protein 10%
	Carbohydrate 24%	Carbohydrate 15%
MAD	Fat 50%	Fat 65–70%
	Protein 35%	Protein 25–30%
	Carbohydrate 15%	Carbohydrate 5%
LGIT diet	Fat 40%	Fat 60%
	Protein 45%	Protein 30%
	Carbohydrate 15%	Carbohydrate 10%

CKD = classic ketogenic diet; MCT = medium-chain triglyceride; MAD = modified Atkins diet; LGIT = low glycemic index treatment.

Table 2.

Conventional ketogenic diets supported by published evidence in treating epilepsy.

translating to a 1:1 ratio of fat to protein plus carbohydrate, although no set ratio is mandated; it may even approach a 4:1 ratio [2]. The MAD eases up on the protein and carbohydrate restrictions imposed by the CKD and MCT diet, and does not require food weighing.

2.2.4 The low glycemic index treatment (LGIT) diet

The LGIT, roughly 40% fat by weight (60% fat by caloric intake), was introduced in the early 2000s as a treatment for epilepsy [25]. The design of the LGIT was based on the hypothesis that stable glucose levels contribute to the seizure control conferred by ketogenic diets. The LGIT allows for relatively liberal levels of protein and carbohydrate intake, emphasizing carbohydrates with glycemic indices less than 50.

3. Ketogenic diet therapies in children with epilepsy

Unfortunately, many children throughout the world still lack access to a pediatric epilepsy center containing a specialized ketogenic service with both inpatient and outpatient management options [2]. Such a service should consist of a pediatric neurologist, nurse, dietitian, and ideally case managers, psychologists, social workers, and pharmacists [2, 26].

3.1 Selecting the right child for a ketogenic diet

Ketogenic diets in children are strongly indicated in drug-resistant epilepsy, two disorders of brain metabolism, and several other seizure disorders (**Table 3**) [2]. There is virtually no age restriction as to when the diet may be commenced; in fact, infants younger than 2 years may be an ideal age group [27].

3.1.1 Drug-resistant epilepsy in children

In 2010, the International League Against Epilepsy (ILAE) defined drug-resistant epilepsy as the failure of adequate trials of two appropriately chosen, tolerated, and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [28]. The drugs must have been appropriate for the seizure type, tolerated at therapeutic doses, and given a reasonable period of time to work (at least 6 months) [29] before declaring drug resistance.

When drug-resistant epilepsy is declared, further anti-epileptic drug trials or epilepsy surgery may be helpful [30]. However, even after carefully excluding confounding factors and optimizing the drug approach, subsequent trials have only a slight (about 5%) chance of inducing seizure remission [31]. Surgery should always be considered in children with drug-resistant epilepsy, especially when a lesion concordant to the epilepsy is detected on imaging [30], but many children are not surgical candidates due to a generalized or multifocal epilepsy syndrome, or nonresectable location of ictal onset.

When drug trials and surgery are no longer feasible, a ketogenic diet is indicated [2]. Numerous studies have demonstrated the efficacy and safety of using ketogenic diets to treat drug-resistant epilepsy in children, but until the previous decade there were no randomized controlled trials. Since 2008, four published randomized controlled trials have compared the efficacy of a ketogenic diet with continued medications or a placebo arm in children with drug-resistant epilepsy [32–35].

General disorder	Specific disorder
Drug-resistant epilepsy	2010 ILAE definition
Disorders of brain metabolism	GLUT1 DS
	PDHD
Specific seizure disorders	Angelman syndrome
	Complex I mitochondrial disorders
	Doose syndrome
	Dravet syndrome
	FIRES
	Formula-fed
	Infantile spasms
	Ohtahara syndrome
	Super-refractory status epilepticus
	Tuberous sclerosis complex

ILAE = International League Against Epilepsy; GLUT1 DS = glucose transporter type 1 deficiency syndrome; PDHD = pyruvate dehydrogenase complex deficiency; FIRES = febrile infection-related epilepsy syndrome.

Table 3.
Epilepsy disorders in children for which a ketogenic diet may be strongly indicated.

The first randomized controlled trial compared the efficacy of a CKD versus no diet intervention in 145 children with drug-resistant epilepsy [32]. After 3 months, 28 children (38%) in the CKD group had a greater than 50% seizure reduction compared to four children (6%) in the control group. One weakness of the study was its unblinded design, with both patients and assessors aware of the group allocations.

The following year, a randomized controlled trial was published in 20 children with drug-resistant Lennox-Gastaut syndrome [33]. All patients were fasted 36 hours and then randomized to receive either a CKD plus a daily solution containing 60 g glucose per day or a solution containing saccharin (an artificial sweetener); the aim of the design was to ensure that both patients and assessors remained blinded to treatment. To the surprise of the investigators, both groups had positive blood BHB levels after 6 days, indicating that the glucose solution did not suppress physiological ketosis. Perhaps as a result of this, the study demonstrated only a borderline, non-statistically significant reduction in seizures in the saccharin arm.

The next randomized controlled trial compared the efficacy of a MAD versus no diet intervention in 102 children with drug-resistant epilepsy [34]. Surgical candidates were not excluded. After 3 months, 52% of children in the MAD group had a greater than 50% seizure reduction compared to 11.5% of those in the control group. A weakness of the study was its unblinded design, with both patients and assessors aware of the group allocations.

The most recent randomized controlled trial compared the efficacy of a ketogenic diet (CKD or MCT diet) versus no diet intervention in 57 children and adolescents with drug-resistant epilepsy [35]. None of the patients were eligible for surgery. After 4 months, 13 children (50%) in the ketogenic diet group had a greater than 50% seizure reduction compared to 4 children (18.2%) in the control group.

Pooling the results from these randomized controlled trials suggests that 40–50% of children experience a greater than 50% seizure reduction after 3–4 months on a ketogenic diet, compared to 10–15% of children receiving no

dietary intervention. Given these encouraging results, many epilepsy specialists advocate that ketogenic diets be used earlier in the management of children with drug-resistant epilepsy [2].

3.1.2 Disorders of brain metabolism in children

Since ketogenic diets induce a shift away from glycolytic energy production towards mitochondrial oxidative phosphorylation, they are the treatment of choice in two childhood disorders of impaired brain glucose metabolism: glucose transporter type 1 deficiency syndrome (GLUT1 DS) and pyruvate dehydrogenase complex deficiency (PDHD) [2]. In both cases, the ketones produced by the diet bypass the metabolic defects, serving as an alternative energy source for the brain.

GLUT1 DS results from impaired glucose transport across the blood-brain barrier due to mutations in the SLC2A1 gene, which encodes the glucose transporter, GLUT1 [36]. Clinically, GLUT1 DS is characterized by cognitive impairment, mixed seizure types, and a complex movement disorder. The vast majority of children with GLUT1 DS achieve seizure freedom with a CKD, which should be introduced as early as possible and continued through to adulthood [36]. The CKD may be difficult to tolerate in older children and adolescents, in which case the MAD is also effective [2]. In GLUT1 DS, ketogenic diets may also enhance the child's alertness, and they frequently improve the movement disorder [36].

In PDHD, pyruvate is unable to be metabolized into acetyl-CoA, resulting in abnormal mitochondrial metabolism and lactic acidosis [37]. Clinically, PDHD is characterized by seizures, severe encephalopathy, and—usually—death during childhood. The CKD is effective and safe in PDHD, and appears to increase longevity and improve mental development [37]. However, severe forms of PDHD may not be appropriate for the diet if quality of life is not improved [2].

3.1.3 Specific seizure disorders in children

Ketogenic diets should be considered early in the management of children with seizure disorders that consistently demonstrate a 60–70% improvement in seizure control, well above the “usual” 40–50% improvement [2]. These disorders include Angelman syndrome, complex I mitochondrial disorders, Doose syndrome, Dravet syndrome, febrile infection-related epilepsy syndrome (FIRES), formula-fed infants or children, infantile spasms, Ohtahara syndrome, super-refractory status epilepticus, and tuberous sclerosis complex [2].

3.2 Preparing a child (and caregiver) for a ketogenic diet

Once the child is selected for a ketogenic diet, a medical and nutritional evaluation is both strongly advised (**Table 4**) [2, 26]. In addition to the caregiver (usually a parent), anyone else who will be helping institute the diet should attend.

3.2.1 Medical evaluation

A medical evaluation should be performed by a pediatric neurologist experienced in managing ketogenic diets in children, and include an assessment of the child's epilepsy, comorbidities, psychological and socioeconomic factors, medications, and investigations [2].

First, the pediatric neurologist must assess the child's baseline epilepsy state and any comorbidities that may complicate a ketogenic diet. Seizure symptomatology and frequency should be documented in sufficient detail so as to later gauge diet

Evaluation	Steps
Medical	Assess baseline epilepsy state and comorbidities
	Identify psycho-socioeconomic, cultural, and religious factors
	Review anti-epileptic drugs and medications
	Provide blood glucose and ketone monitor; show how to use
	Order investigations
Nutritional	Assess baseline physical parameters
	Select most appropriate conventional ketogenic diet
	Provide supplements
	Educate caregiver

Table 4.
Preparing a child (and caregiver) for a ketogenic diet.

efficacy on seizure control. Potential complicating comorbidities include gastrointestinal issues (such as gastroesophageal reflux and constipation), hypercholesterolemia, low weight gain, kidney stones, chronic metabolic acidosis, and cardiomyopathy [2]. Once identified, most comorbidities can be preventatively managed.

Second, it is critical to identify psychological, socioeconomic, cultural, and religious factors that may affect the child's diet [2]. Challenging behavior traits in the child or caregiver should be addressed early. Since many patients with epilepsy are of lower socioeconomic status, an appraisal of the family environment, including finances, is essential before deciding to proceed; even if deemed adequate, the caregiver must be made aware of the impact of a ketogenic diet on time and resources, including separate meal preparation from the rest of the family and increased costs [26]. It is also necessary to consider the family's cultural and religious background, which may result in some recipes being more suitable than others [2].

Third, the child's medications should be reviewed. Generally, blood levels of common anti-epileptic drugs are not significantly altered by a ketogenic diet, therefore dose adjustments are not required. However, it may be worth considering dose reductions in the case of valproate, zonisamide, and topiramate; although these drugs are generally safe alongside a ketogenic diet, there have been rare instances of hepatotoxicity and secondary carnitine deficiency with valproate, as well as chronic metabolic acidosis and a slight increase in kidney stones with zonisamide and topiramate [2]. All medications should be reviewed for carbohydrate content, which may necessitate a switch to lower carbohydrate preparations [26].

Fourth, the child and caregiver should be provided with a means of self-monitoring the diet, which critically provides feedback as to how effectively the child is achieving physiological ketosis [2]. Traditionally, this has been done using urine ketone dipstick testing, but it is now possible to prescribe a blood glucose and ketone monitor in many countries. The former is less expensive and avoids finger pricks, but the latter is easier, more specific, and more accurate [38]. Unless there is a compelling reason to measure urinary ketones, a blood glucose and ketone monitor should be prescribed and the caregiver instructed on its use.

Finally, investigations should be ordered before commencing a ketogenic diet in a child, primarily to rule out contraindications (a ketogenic diet is absolutely contraindicated in disorders of fat metabolism, including carnitine deficiency, carnitine palmitoyltransferase I and II deficiency, any of the short, medium, or long-chain acyl dehydrogenase deficiencies, and porphyria) [2]. Basic laboratory

investigations include complete blood count, electrolytes, liver and kidney function tests, fasting lipid profile, calcium, vitamin D, serum acylcarnitine profile, and a urinalysis [2]. Baseline anti-epileptic drug levels can be measured, although few concerns for drug-diet interactions exist. A recent EEG and MRI brain should be obtained to identify potential surgical candidates. Further tests, such as ECG and renal ultrasound, may be ordered as clinically indicated.

3.2.2 Nutritional evaluation

A nutritional evaluation should be performed by a dietitian experienced in managing ketogenic diets in children, and include an assessment of baseline physical parameters, selection of the most suitable ketogenic diet, and education of the caregiver on what to expect with the diet.

Baseline weight, body-mass index, and height are routinely measured (in infants, head circumference is also measured) [2]. The child's recommended calorie and fluid intake should be calculated, as well as the desired fat to protein to carbohydrate ratio. Food aversions and allergies must be clearly documented.

When selecting a conventional ketogenic diet for a child, the most important factor to consider is the family environment, rather than perceived diet efficacy [2]. The CKD is highly effective for seizure control, but restrictive and time-consuming; depending on the family environment, it may be more feasible to implement the MCT diet, MAD, or LGIT diet. Regarding diet efficacy, the CKD appears to be superior to the MAD in infants under 2 years of age, whereas both are equally effective in older children [27]. For the transition to adolescence, the MAD and LGIT diet are less restrictive and more appropriate; the LGIT diet may not provide an adequate level of ketosis to treat GLUT1 DS and PDHD, although it is highly effective in Angelman syndrome [2, 39]. For infants and children on enteral feeds, ketogenic diets can be administered in liquid form, which may be more convenient and efficacious [2].

Given the limited fruit, vegetable, and calcium content in conventional ketogenic diets, supplementation with a carbohydrate-free multivitamin containing minerals, as well as supplementation with calcium and vitamin D, is considered mandatory in children [26]. No particular recommendations exist for supplementing a ketogenic diet with magnesium, selenium, carnitine, laxatives, probiotics, or exogenous ketones [2, 26].

Caregiver education is essential; the caregiver needs to understand exactly what is required of them to implement the diet. A classroom-based format, with several different caregivers present, can be advantageous [26]. The dietitian should demonstrate how to identify sources of fat, protein, and carbohydrate, how to count net carbohydrate (total carbohydrate minus fiber) for those on a MAD, how to identify foods with a low glycemic index for those on an LGIT diet, and how to navigate potential pitfalls [26]. Helpful additional resources should be provided [40, 41] and any expectations addressed.

3.3 Implementing a ketogenic diet in a child

Once the child and caregiver have been prepared, it is time to implement the diet (Table 5) [2]. The pediatric ketogenic service should take on a strong supportive role, aiding the caregiver as much as possible in troubleshooting problems.

3.3.1 Diet initiation

Currently, it is recommended that the CKD be initiated with the child in hospital [2]. The advantages of an inpatient admission include the ability to closely observe

Stage	Steps
Initiation	Decide whether to initiate as inpatient or outpatient
	If inpatient, decide on induction fast and diet introduction
	If outpatient, provide clear instructions to caregiver
Maintenance	Caregiver monitors seizure control and ketone levels
	Review at 1, 3, 6, 9, 12 months, and 6-monthly after
	Monitor for adverse effects
Cessation	Identify when diet should be ceased (if ever)
	If to be ceased, consider switching to another ketogenic diet
	If to be ceased, decide on rate of diet cessation

Table 5.
Implementing a ketogenic diet in a child with epilepsy.

the child, medically intervene if necessary, and provide more time to educate the caregiver on how to maintain the diet upon returning home.

Traditionally, a 12–24 hours fast has been used to commence the diet in an inpatient setting [2]. Fasting may lead to a quicker onset of seizure reduction, which may be useful in refractory status epilepticus [2]. However, induction fasts do not improve ketosis or seizure control at 3 months, and fasted children experience weight loss, hypoglycemia, and acidosis more frequently, which may increase the length of hospital stay [42]. Thus, although an induction fast should be considered, most pediatric ketogenic services no longer routinely fast children, and none recommend fasting infants under 2 years of age [2].

Regardless of whether an induction fast is utilized, several approaches may be used to introduce the CKD in hospital [2]. One approach involves starting the diet at one-third or one-half of the final calorie level, increasing the calories by one-third or one-half over several days until full calorie intake is achieved, keeping the fat to protein to carbohydrate ratio constant. Another approach is to start with full calorie intake, but increase the ratio of fat to protein plus carbohydrate daily, from 1:1 to 2:1 to 3:1 to 4:1, allowing the child to gradually adapt to the increasing fat intake. Yet another approach is to simply commence the CKD at full calories and a 4:1 ratio on the first day, which does not appear to prolong hospital stay, increase adverse effects, or decrease diet efficacy at 3 months.

In older children, the CKD may be initiated as an outpatient, the advantages of which include reduced family stress and fewer hospital-associated costs [2]. Most pediatric ketogenic services also routinely initiate the less-restrictive MAD and LGIT diet in the outpatient setting. If a graded introduction is required at home, clear instructions must be given to the caregiver on how to do so.

3.3.2 Diet maintenance

Once initiated, ketogenic diets tend to work rapidly and effectively, with 75% of children responding within 14 days [43]. Complete seizure freedom often occurs within several months of initiation, although it may take up to 18 months [44]. The caregiver should monitor the child's ketone levels (ideally, the blood BHB level) daily for the first several weeks, then two or three times a week once readings consistently show the child to be in physiological ketosis. Most pediatric ketogenic services recommend a blood BHB level of 4–6 mmol/L, although this is not based on clinical evidence [3]. If seizure control or ketone levels are not responding as

expected, a 3-day food diary may be useful to discover potential oversights in diet implementation.

The pediatric neurologist and dietitian should be in frequent phone or email contact with the caregiver during the initial weeks of the diet, with additional follow-up visits occurring at 1, 3, 6, 9, and 12 months, and every 6 months thereafter [2]. The pediatric neurologist should document the child's seizure response, and regardless of any improvement, resist altering their anti-epileptic drugs unless necessary; alterations may make it difficult to gauge diet efficacy on seizure control. Recommended follow-up tests include complete blood count, electrolytes, liver and kidney function tests, fasting lipid profile, calcium, and vitamin D [2]. Since ketogenic diets and anti-epileptic drugs may predispose a child to osteopenia, some pediatric ketogenic services perform a bone density scan after 2 years on the diet [2]. The dietitian should monitor the child's physical parameters and nutritional intake at every visit. Ketogenic diets have a diuretic effect and fluid content in the food may be lessened, therefore fluid hydration must be monitored, and increased if necessary [26].

Both the caregiver and the pediatric ketogenic service must monitor the child for adverse effects. Gastrointestinal symptoms such as nausea, vomiting, abdominal pain, and constipation appear in up to 50% of children on the CKD, but are easily remedied by increasing fluid, salt, and fiber intake [2]. Hyperlipidemia is common, with raised triglyceride and low-density lipoprotein (LDL) levels seen in up to 60% of children on the CKD, but the increase is usually transient and normalizes within 1 year; if desired, the LDL can be lowered by altering the types of fats ingested (for example, by increasing olive oil and decreasing saturated fats) [2]. Moreover, ketogenic diets may slightly inhibit a child's growth; adjustments in calorie intake may compensate. Kidney stones may occur in 3–7% of children on the CKD, but can be prevented with oral citrates [2]. Ultimately, such common adverse effects are rarely sufficient reasons to discontinue the CKD, but rarer adverse effects such as cardiomyopathy, prolonged QT interval, and pancreatitis may provide sufficient reason to do so.

3.3.3 Diet cessation

Upon ceasing a ketogenic diet, the long-term benefits on seizure control often outlast the diet itself. In children who become seizure-free on a ketogenic diet, 80% will remain so after diet cessation [45], an effect that can persist for many years.

The child's ketogenic diet should be maintained for at least 3 months before passing judgment on its efficacy in seizure control [2]. The exception to this rule is if the seizures worsen for longer than 1–2 weeks after commencing the diet, or if a serious adverse effect occurs—in either case, it may be wise to discontinue the diet sooner.

If a child experiences the “usual” greater than 50% seizure reduction, the ketogenic diet is usually discontinued after 2 years [2]. In new-onset infantile spasms, the diet can be ceased at 6 months [46]. In drug-resistant epilepsy in which seizure control is virtually complete (over 90% seizure reduction) and GLUT1 DS, the diet can be carried into adulthood [2]. Older children may start to see their diet as overly restrictive; if it effectively controls the seizures, it may be switched over to another type of ketogenic diet (for example, from a CKD or MCT diet to a MAD or LGIT diet).

A child's ketogenic diet should be ceased gradually (over several months) [2]. In the case of the CKD, the ratio can be reduced by decreasing the ratio of fat to protein plus carbohydrate monthly, from 4:1 to 3:1 to 2:1 to 1:1, allowing the child to gradually adapt to the decreasing fat intake, followed by the reintroduction of regular foods. However, it is usually still possible to cease the diet more rapidly (over several weeks) without negative consequences, although some children may

experience a higher risk of increased seizures during the tapering-down period. If medically necessary, ketogenic diets can be stopped abruptly; this is best done in hospital.

4. Ketogenic diet therapies in adults with epilepsy

Few epilepsy centers in the world offer a dedicated adult ketogenic service [3]. Such a service should consist of a neurologist, nurse, dietitian, and ideally a psychologist and social worker [3, 47].

4.1 Selecting the right adult for a ketogenic diet

Ketogenic diets in adults are indicated in drug-resistant epilepsy and certain seizure disorders (**Table 6**); they may be used in adults of all ages [47].

4.1.1 Drug-resistant epilepsy in adults

In 2010, the ILAE defined drug-resistant epilepsy as the failure of adequate trials of two appropriately chosen, tolerated, and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [28]. Since adults may suffer from drug-resistant epilepsy for decades, many adult patients have already failed multiple trials of anti-epileptic drugs over their lifetime.

Further anti-epileptic drug trials and epilepsy surgery may be feasible options in adults with drug-resistant epilepsy [30]. However, subsequent drug trials confer only a slight (about 5%) chance of inducing seizure remission [31]. Surgery should always be considered, but some eligible adults may not be ready to pursue surgery [48], and many others will not be eligible due to a generalized or multifocal epilepsy syndrome, or nonresectable lesion of ictal onset.

When drug trials and surgery are not feasible, a ketogenic diet may be indicated [48]. Many single-arm studies have demonstrated the efficacy and safety of ketogenic diets in treating drug-resistant epilepsy in adults, but to date there are no randomized controlled trials of a ketogenic diet in adults with drug-resistant epilepsy.

Surprisingly, a 1930 study remains the largest retrospective case series to examine a ketogenic diet in adults with epilepsy [49]. In this study, 100 adolescents and adults with epilepsy were treated with a CKD. After 1–46 months, 56% of patients had a greater than 50% seizure reduction.

General disorder	Specific disorder
Drug-resistant epilepsy	2010 ILAE definition
Disorders of brain metabolism	GLUT1 DS
	PDHD
Specific seizure disorders	JME
	Lennox-Gastaut syndrome
	Rett syndrome

ILAE = International League Against Epilepsy; GLUT1 DS = GLUT1 deficiency syndrome; PDHD = pyruvate dehydrogenase complex deficiency; JME = juvenile myoclonic epilepsy.

Table 6.

Epilepsy disorders in adults for which a ketogenic diet may be indicated; this list is not comprehensive.

In 2014, a review of all subsequently published ketogenic diet studies in adults with drug-resistant epilepsy was published [50]. Five studies examined the use of a CKD to treat a combined total of 47 adults with drug-resistant epilepsy. After 3–26 months, 15 patients (32%) had a greater than 50% seizure reduction, with 24 patients (51%) stopping the diet before study completion. Another five studies examined the use of a MAD to treat a combined total of 85 adults with drug-resistant epilepsy. After 3–12 months, 24 patients (28%) had a greater than 50% seizure reduction, with 36 patients (42%) stopping the diet before completion. For both diets, most patients withdrew due to culinary and social restrictions.

In 2016, the largest observational study of a ketogenic diet in adults with drug-resistant epilepsy was published, in which 106 patients were treated with a MAD [48]. After 3 months, 38 patients (36%) had a greater than 50% seizure reduction, with 47 patients (44%) not completing the study, largely due to diet restrictiveness.

Pooling the results from these single-arm studies suggests that 30–40% of adults with drug-resistant epilepsy experience a greater than 50% seizure reduction after 3 or more months on a ketogenic diet. While these results are encouraging, they emanate from single-arm studies; moreover, 40–50% of adults stopped their diet before study completion. Clearly, randomized controlled trials involving less restrictive ketogenic diets are needed in adults with drug-resistant epilepsy.

4.1.2 Specific seizure disorders in adults

Ketogenic diets remain standard treatments for disorders of impaired brain glucose metabolism in adults [47]. In GLUT1 DS, ketogenic diets have been shown to confer seizure freedom in up to 90% of patients, including adults [47]. The prognosis in more severe forms of PDHD may be poor, but less severely affected individuals may benefit from a ketogenic diet as they transition to adulthood.

In addition to GLUT1 DS and PDHD, ketogenic diet therapy may be warranted in several seizure disorders often seen in adults, including juvenile myoclonic epilepsy (JME), Lennox-Gastaut syndrome, and Rett syndrome [48]. JME is particularly common, representing 5–10% of all epilepsy cases, and typically manifests in adolescence or early adulthood with a combination of myoclonic jerks or seizures, absence seizures, and generalized tonic-clonic seizures. In two separate case series, 60–70% of adolescents and adults with JME experienced a 50% seizure reduction after 3 months of MAD therapy [51, 52].

4.2 Preparing an adult (and partner) for a ketogenic diet

Once the adult has been selected for the diet, a medical and nutritional evaluation is advised (**Table 7**) [3, 47]. If possible, a cohabiting partner (spouse or family member) should accompany the adult to the evaluations, and ideally participate in the diet alongside them.

4.2.1 Medical evaluation

A brief medical evaluation should be performed by a neurologist with experience managing ketogenic diets in adults, and should include a history of the epilepsy, comorbidities, psychological and socioeconomic factors, level of commitment to the diet, medications, and investigations [47].

First, the neurologist must ascertain the adult's baseline epilepsy state and any comorbidities that may complicate their ketogenic diet. The symptomatology and frequency of the various types of seizures should be documented in sufficient detail so as to later gauge diet efficacy on seizure control. Potentially complicating

Evaluation	Steps
Medical	Assess baseline epilepsy state and comorbidities
	Identify psycho-socioeconomic, cultural, and religious factors
	Elucidate level of commitment
	Review anti-epileptic drugs and medications
	Provide blood glucose and ketone monitor; show how to use
	Order investigations
Nutritional	Assess baseline physical parameters
	Select most appropriate conventional ketogenic diet
	If none appropriate, offer a non-conventional ketogenic diet
	Provide list of foods for social settings
	Provide supplements
	Educate patient

Table 7.
Preparing an adult (and partner) for a ketogenic diet.

comorbidities include hypercholesterolemia, underweight body-mass index, kidney stones, osteopenia or osteoporosis, gastrointestinal issues (such as gastroesophageal reflux and constipation), cardiomyopathy, and diabetes [3]. Adults with type 1 diabetes can safely pursue a ketogenic diet, but must be closely monitored as their insulin requirements often decline, putting them at risk of hypoglycemia if they do not adjust their insulin doses accordingly [53]. Adults with type 2 diabetes may also start a ketogenic diet [3]; in fact, such adults may be ideal candidates.

Second, it is critical to identify psychological, socioeconomic, cultural, and religious factors with the potential to disrupt the adult’s ketogenic diet [3]. Diet adherence in adults may be endangered by any number of factors, including personality traits, alcohol habits, income, cultural influences, and religious preferences; each must be realistically appraised before the adult and ketogenic service commit to the diet.

Third, the adult’s level of commitment to ketogenic diet therapy must be elucidated. Diet modification often involves a major change in lifestyle, therefore anything less than a full commitment is likely to fail. If the adult holds any reservations about commencing the diet, these should be explored; if unsolvable, the adult may not yet be ready for the diet. The neurologist should counsel the adult on how to deal with inevitable “mixed messages” regarding the purported negative aspects of high-fat diets from friends, family, and even other medical professionals. Lastly, it can be helpful to emphasize the additional positive aspects of a ketogenic diet, such as beneficial effects on cognition, energy, and mood [47].

Fourth, the adult’s medications should be reviewed. In general, anti-epileptic drug blood levels are not altered by a ketogenic diet, therefore dose adjustments are not usually required. However, for the same reasons as in children, exceptions might be made in the case of valproate, zonisamide, or topiramate [2]. All medications should be reviewed for carbohydrate content, which may necessitate a switch to lower carbohydrate preparations [47].

Fifth, the adult should be provided with a means of self-monitoring their diet, which critically provides feedback as to how effectively they are achieving physiological ketosis. In adults, it is best to prescribe a blood glucose and ketone monitor given that this method is easier, more specific, and more accurate than urine dipstick testing [38]. The adult should be shown how to use the monitor.

Finally, investigations should be ordered to rule out contraindications to a ketogenic diet (as a rule, it is not necessary to screen for disorders of fat metabolism in adults, unless the history suggests otherwise) [47]. Laboratory investigations include complete blood count, electrolytes, liver and kidney function tests, fasting lipid profile, calcium, vitamin D, and a urinalysis [3]. Given that the effects of a ketogenic diet on pregnancy are not known [3], pregnancy testing may be indicated in women of childbearing age. Baseline anti-epileptic drug levels can be measured, although few concerns for drug-diet interactions exist. A recent EEG and MRI brain should be obtained to identify potential surgical candidates. Given that ketogenic diets and anti-epileptic drugs may predispose adults to osteopenia, a baseline bone density scan may be wise. Further tests, such as ECG and renal ultrasound, are ordered as clinically indicated.

4.2.2 Nutritional evaluation

A nutritional evaluation should be performed by a dietitian experienced in managing ketogenic diets in adults, and ought to include an assessment of baseline physical status, a decision as to which is the most appropriate ketogenic diet option for that adult, and education about their chosen ketogenic diet.

Baseline weight and body-mass index should be measured and recommended calorie and fluid intake calculated, including the desired ratio of fat to protein to carbohydrate [48]. Food aversions and allergies must be clearly documented.

When selecting which conventional ketogenic diet to use, the most important factors to consider in adults are culinary and social restrictions [48, 50]. Since the CKD is the most restrictive of the four, it is rarely a viable long-term option in adults (unless given as a formula). The MCT diet is slightly less restrictive, but still not viable in most adults due to the copious quantities of MCT oil and resulting gastrointestinal side-effects. The MAD and LGIT are less restrictive conventional options in adults, but both are still associated with considerable dropout rates [54]. Thus, although conventional ketogenic diets should be offered, the adult may not be motivated to pursue any of them; this will negatively impact diet implementation.

If conventional ketogenic diets do not appeal to the adult, a fifth option, that of a non-conventional ketogenic diet, can be considered. Such a diet might consist of dietitian-verified recipes obtained from trusted ketogenic diet books and websites, a major advantage of which is that it can be specifically tailored towards the adult's food preferences, reducing the perception that their diet is restrictive. It is now possible to prepare a variety of ketogenic diets, including vegetarian and culturally-tailored ketogenic diets (theoretically, as long as a ketogenic diet sustains physiological ketosis, it is "ketogenic"). Given that each conventional ketogenic diet is decades old (nearly a century old in the case of the CKD), a newer, less restrictive, patient-tailored ketogenic diet is appealing to many adults, although it must be emphasized that evidence for such a diet in epilepsy may be lacking.

Since many adults with epilepsy are of lower socioeconomic status, the dietitian must strive to minimize any socioeconomic impediments that may disrupt their ketogenic diet. Social activities are to be encouraged, but they can also jeopardize the diet; it is extremely helpful if the dietitian provides a list of appropriate food options relevant to most restaurants and social gatherings that will inform the adult as to what they can and cannot eat, so as not to disrupt the diet. For meals made at home, the dietitian should recommend foods that are both within the adult's budget range as well as readily available at their local food markets.

Given the limited fruit, vegetable, and calcium content in many ketogenic diets, adults should be commenced on a carbohydrate-free multivitamin [3, 47]. Some

ketogenic services also supplement adults with calcium, vitamin D, and magnesium [3, 47].

Lastly, education is essential; the adult needs to understand exactly what is required of them to implement their diet. A classroom-based format, with multiple adult patients present, can be advantageous [26]. The dietitian should demonstrate how to identify sources of fat, protein, and carbohydrate, how to count net carbohydrate (total carbohydrate minus fiber) for those on a MAD or non-conventional ketogenic diet, how to identify foods with a low glycemic index for those on an LGIT diet, and how to navigate potential pitfalls [26]. Helpful additional resources should be provided [55] and any expectations addressed.

4.3 Implementing a ketogenic diet in an adult

Once the adult has been prepared, their chosen diet can be implemented (Table 8) [47]. The ketogenic service should provide as much support as the adult needs, but also encourage them to develop a sense of “ownership” over their diet, thus conferring a feeling of empowerment over their epilepsy.

4.3.1 Diet initiation

In younger and disabled adults, it may be more appropriate to initiate a ketogenic diet as an inpatient [48]. The advantages of an admission include the ability to observe the patient and medically intervene if needed, and provide more time to educate the caregiver on how to maintain the diet upon returning home. In general, fasting is not employed in adults, although an induction fast might be useful if a quicker response is required (for example, if the adult is having multiple daily seizures, an induction fast might lessen the interference of the epilepsy on the initiation of the diet) [48]. The same graded approach used to introduce the diet in children may also be used in adults [48].

In most cases, adults with epilepsy can initiate their ketogenic diet as an outpatient, especially if they have selected the MAD, LGIT diet, or a non-conventional ketogenic diet. In most adults, it is not necessary to employ a graded approach when initiating a ketogenic diet at home, but if required then clear instructions should be provided on how to do so.

Stage	Steps
Initiation	Decide whether to initiate as inpatient or outpatient
	If inpatient, decide on induction fast and diet introduction
	If outpatient, provide clear instructions to caregiver
Maintenance	Adult self-monitors seizure control and ketone levels
	Review at 3 and 6 months, and 6-monthly after
	Monitor for adverse effects
	Document beneficial effects
Cessation	Identify when diet should be ceased (if ever)
	If to be ceased, consider switching to another ketogenic diet
	If to be ceased, decide on rate of diet cessation
	If relevant, consider diet cessation and driving

Table 8.
Implementing a ketogenic diet in an adult with epilepsy.

4.3.2 Diet maintenance

Ketogenic diets often work rapidly, within days [43]. The adult should regularly monitor their blood BHB level daily for the first several weeks, then two or three times a week once readings indicate that constant physiological ketosis has been achieved. There are no firm recommendations regarding optimal blood BHB levels in adults [3], although aiming for at least 2 mmol/L at all times seems reasonable. If seizure control or ketone levels are not responding as expected, a 3-day food diary may be useful to discover potential oversights in diet implementation.

The neurologist or dietitian should be in regular phone or email contact during the initial weeks of the diet, with multidisciplinary follow-up visits at 3 and 6 months, and every 6 months thereafter [3]. The neurologist should document the adult's seizure response to the diet; regardless of any improvement, anti-epileptic drugs should not be altered unless necessary, as alterations may make it difficult to gauge diet efficacy on seizure control. Recommended follow-up tests include complete blood count, electrolytes, liver and kidney function tests, fasting lipid profile, calcium, and vitamin D [47]. If osteopenia is a concern, a bone density scan may be warranted every 5 years or less [47], and bone protection therapy prescribed as needed. The dietitian should monitor weight, nutritional intake, and fluid hydration at every visit, and alter each as required.

Adverse effects may occur in adults on a ketogenic diet, but are generally transient, and rarely serious enough to necessitate stopping the diet [47]. The two most common adverse effects in adults are hyperlipidemia and weight loss [48]. Raised LDL levels are seen in least one-quarter of adults with epilepsy [48]. However, triglyceride levels often decline, and HDL levels usually increase [47]. Moreover, among healthy adults following a low-carbohydrate diet, the LDL increase is due to increased LDL particle size rather than particle number, which may be associated with a lower risk of atherosclerosis [56]. Furthermore, LDL and total cholesterol levels typically normalize within a year of commencing the diet [57], and return to baseline within 3 months of stopping it [50]. Weight loss is also common on a ketogenic diet, seen in at least one-fifth of adult with epilepsy [48], but since many such adults are overweight or obese, this adverse effect is often desired and beneficial [47]. Other adverse effects, such as kidney stones and osteopenia or osteoporosis, are rare in adults [47].

Benefits other than seizure control may also occur with a ketogenic diet, including improved arousal, alertness, concentration, energy, and mood [3, 47]. Moreover, adults on a ketogenic diet often report increased quality of life scores [58]. Given that many adults with epilepsy suffer from impaired quality of life, these additional benefits may be significant and should be documented.

4.3.3 Diet cessation

Unlike children, the long-term benefits on seizure control in adults with epilepsy may not outlast dietary therapy [59]. Further studies are needed to determine if this is the case for all adults.

It is customary to maintain a ketogenic diet for at least 3 months before passing judgment on its efficacy in seizure control [3]. The exception to this rule is if the seizures worsen for longer than 1–2 weeks after commencing the diet, or if a serious adverse effect occurs—in either case, it may be wise to discontinue the diet sooner.

If the adult experiences a greater than 50% seizure reduction and no serious adverse effects, their ketogenic diet can be maintained indefinitely [3]. If the adult starts to perceive their diet as overly restrictive, yet it remains effective at controlling seizures, it can be switched over to another type of ketogenic diet.

Most ketogenic diets in adults are ceased slowly, over weeks or months on an individual basis [3], although many can be ceased abruptly without negative consequences. The sole exception may be the CKD, which can be ceased gradually by decreasing the ratio of fat to protein plus carbohydrate weekly or monthly, from 4:1 to 3:1 to 2:1 to 1:1, followed by the reintroduction of regular foods.

An important consideration during diet cessation is the effect on driving restrictions. If a ketogenic diet has conferred complete seizure freedom for a long enough period of time such that the adult has returned to driving, stopping the diet applies the same driving restrictions as when anti-epileptic drugs are altered or modified [3].

5. Conclusions

Historically, ketogenic diets have been utilized as “end of the line” therapeutic options in children and adults with epilepsy. However, given recent advances in the possible mechanisms through which these diets improve seizure control and the growing evidence base supporting their use in epilepsy, this is changing. Significant challenges to the more widespread use of ketogenic diets in children and adults with epilepsy remain, most conspicuously a lack of access to ketogenic services in many regions of the world. Moreover, the culinary and social restrictions associated with conventional ketogenic diets are barriers to their use in adults. If these issues can be addressed, there may come a day when ketogenic diet therapies are utilized more widely, as first-line options alongside drugs and surgery, in the management of children and adults with epilepsy.

Acknowledgements

The author is grateful for the support of Waikato Hospital, Hamilton, New Zealand.

Conflict of interest

The author declares no conflict of interest.

Author details

Matthew Charles Lee Phillips
Waikato Hospital, Hamilton, New Zealand

*Address all correspondence to: matthew.phillips@waikatodhb.health.nz

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Granata T, Marchi N, Carlton E, et al. Management of the patient with medically refractory epilepsy. *Expert Review of Neurotherapeutics*. 2009; **9**(12):1791-1802. DOI: 10.1586/ern.09.114
- [2] Kossoff EH, Zupec-Kania BA, Auvin S, et al. 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
- [3] Schoeler NE, Cross JH. Ketogenic dietary therapies in adults with epilepsy: A practical guide. *Practical Neurology*. 2016; **16**:208-214. DOI: 10.1136/practneurol-2015-001288
- [4] Wilder RM. The effect on ketonemia on the course of epilepsy. *Mayo Clinic Bulletin*. 1921; **2**:307-318. DOI: 10.1001/jama.1927.02680470024012
- [5] Kim JM. Ketogenic diet: Old treatment, new beginning. *Clinical Neurophysiology Practice*. 2017; **2**: 161-162. DOI: 10.1016/j.cnp.2017.07.001
- [6] Stewart WK, Fleming LW. Features of a successful therapeutic fast of 382 days' duration. *Postgraduate Medical Journal*. 1973; **49**(569):203-209
- [7] Rho J. How does the ketogenic diet induce anti-seizure effects? *Neuroscience Letters*. 2017; **637**:4-10. DOI: 10.1016/j.neulet.2015.07.034
- [8] Lutas A, Yellen G. The ketogenic diet: Metabolic influences on brain excitability and epilepsy. *Trends in Neurosciences*. 2013; **36**(1):32-40. DOI: 10.1016/j.tins.2012.11.005
- [9] Puchalska P, Crawford PA. Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics. *Cell Metabolism*. 2017; **25**(2):262-284. DOI: 10.1016/j.cmet.2016.12.022
- [10] Paoli A. Ketogenic diet for obesity: Friend or foe? *International Journal of Environmental Research and Public Health*. 2014; **11**(2):2092-2107. DOI: 10.3390/ijerph110202092
- [11] Simeone TA, Simeone KA, Stafstrom CE, et al. Do ketone bodies mediate the anti-seizure effects of the ketogenic diet? *Neuropharmacology*. 2018; **133**:233-241. DOI: 10.1016/j.neuropharm.2018.01.011
- [12] Politi K, Shemer-Meir L, Shuper A, et al. The Ketogenic diet 2011: How it works. *Epilepsy Research and Treatment*. 2011; **2011**:1-4. DOI: 10.1155/2011/963637
- [13] Ma W, Berg J, Yellen G. Ketogenic diet metabolites reduce firing in central neurons by opening K(ATP) channels. *The Journal of Neuroscience*. 2007; **27**: 3618-3625. DOI: 10.1523/JNEUROSCI.0132-07.2007
- [14] Juge N, Gray JA, Omote H, et al. Metabolic control of vesicular glutamate transport and release. 2010; **68**(1): 99-112. DOI: 10.1016/j.neuron.2010.09.002
- [15] Keith HM. Factors influencing experimentally produced convulsions. *Archives of Neurology & Psychiatry*. 1933; **29**(1):148-154. DOI: 10.1001/archneurpsyc.1933.02240070154009
- [16] Keith HM, Stavrakys GW. Experimental convulsions induced by administration of thujone. *Archives of Neurology and Psychiatry*. 1935; **34**(5): 1022-1040. DOI: 10.1001/archneurpsyc.1935.02250230094008
- [17] Shimazu T, Hirschey MD, Newman J, et al. Suppression of oxidative stress

by β -hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science*. 2013;**339**(6116):211-214. DOI: 10.1126/science.1227166

[18] Youm YH, Nguyen KY, Grant RW, et al. The ketone metabolite β -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nature Medicine*. 2015;**21**:263-269. DOI: 10.1038/nm.3804

[19] Augustin K, Khabbush A, Williams S, et al. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. *Lancet Neurology*. 2018;**17**: 84-93. DOI: 10.1016/S1474-4422(17)30408-8.

[20] Masino SA, Li T, Theofilas P, Sandau US, et al. A ketogenic diet suppresses seizures in mice through adenosine A(1) receptors. *The Journal of Clinical Investigation*. 2011;**121**(7): 2679-2683. DOI: 10.1172/JCI57813.

[21] Chang P, Augustin K, Boddum K, et al. Seizure control by decanoic acid through direct AMPA receptor inhibition. *Brain*. 2016;**139**(2):431-443. DOI: 10.1093/brain/awv325

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

[23] Schwartz RH, Eaton J, Bower BD, et al. Ketogenic diets in the treatment of epilepsy: Short-term clinical effects. *Developmental Medicine and Child Neurology*. 1989;**1**:145-151. DOI: 10.1111/j.1469-8749.1989.tb03972.x

[24] Kossoff EH, McGrogan JR, Bluml RM, et al. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia*. 2006;**47**: 421-424. DOI: 10.1111/j.1528-1167.2006.00438.x

[25] Pfeifer HH, Thiele EA. Low-glycemic-index treatment: A liberalized ketogenic diet for treatment of intractable epilepsy. *Neurology*. 2005; **65**:1810-1812. DOI: 10.1212/01.wnl.0000187071.24292.9e

[26] Roehl K, Sewak SL. Practice paper of the academy of nutrition and dietetics: Classic and modified ketogenic diets for treatment of epilepsy. *Journal of the Academy of Nutrition and Dietetics*. 2017;**117**:1279-1292. DOI: 10.1016/j.jand.2017.06.006

[27] Kim JA, Yoon JR, Lee EJ, et al. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. *Epilepsia*. 2016;**57**: 51-58. DOI: 10.1111/epi.13256

[28] Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. *Epilepsia*. 2010;**51**(6):1069-1077. DOI: 10.1111/j.1528-1167.2009.02397.x

[29] Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *The New England Journal of Medicine*. 2011; **365**(10):919-926. DOI: 10.1056/NEJMra1004418

[30] Dalic L, Cook MJ. Managing drug-resistant epilepsy: Challenges and solutions. *Neuropsychiatric Disease and Treatment*. 2016;**2016**:2605-2616. DOI: 10.2147/NDT.S84852

[31] Callaghan B, Schlesinger M, Rodemer W, et al. Remission and relapse in a drug-resistant epilepsy population followed prospectively. *Epilepsia*. 2011;**52**(3): 619-626. DOI: 10.1111/j.1528-1167.2010.02929.x

[32] Neal EG, Chaffe HM, Schwartz RH, et al. The ketogenic diet in the treatment of epilepsy in children: A randomised, controlled trial. *Lancet Neurology*.

2008;7:500-506. DOI: 10.1016/S1474-4422(08)70092-9

[33] Freeman JM, Vining EP, Kossoff EH, et al. A blinded, crossover study of the efficacy of the ketogenic diet. *Epilepsia*. 2009;50:322-325. DOI: 10.1111/j.1528-1167.2008.01740.x

[34] Sharma S, Sankhyan N, Gulati S, et al. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: A randomized controlled trial. *Epilepsia*. 2013;54:481-486. DOI: 10.1111/epi.12069

[35] Lambrechts DA, de Kinderen RJ, Vles JS, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. *Acta Neurologica Scandinavica*. 2017;135:231-239. DOI: 10.1111/ane.12592

[36] 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

[37] Sofou K, Dahlin M, Hallböök T, et al. Ketogenic diet in pyruvate dehydrogenase complex deficiency: Short- and long-term outcomes. *Journal of Inherited Metabolic Disease*. 2017;40:237-245. DOI: 10.1007/s10545-016-0011-5

[38] Arora S, Henderson SO, Long T, et al. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: {Beta}-hydroxybutyrate versus the urine dipstick. *Diabetes Care*. 2011;34:852-854. DOI: 10.2337/dc10-1844

[39] Grocott OR, Herrington KS, Pfeifer HH, et al. Low glycemic index treatment for seizure control in Angelman syndrome: A case series from the Center for Dietary Therapy of Epilepsy at the Massachusetts General Hospital. *Epilepsy & Behavior*. 2017;68:45-50. DOI: 10.1016/j.yebeh.2016.12.018

[40] Whitmer E, Riether JL. *Fighting Back with Fat: A parent's Guide to Battling Epilepsy through the Ketogenic Diet and Modified Atkins Diet*. New York: Demos Health; 2013. 136 p

[41] Martenz DM, Cramp L. *The Keto Cookbook: Innovative Delicious Meals for Staying on the Ketogenic Diet*. New York: Demos Health; 2012. 160 p

[42] Bergqvist AG, Schall JI, Gallagher PR, et al. Fasting versus gradual initiation of the ketogenic diet: A prospective, randomized clinical trial of efficacy. *Epilepsia*. 2005;46:1810-1819. DOI: 10.1111/j.1528-1167.2005.00282.x

[43] Kossoff EH, Laux LC, Blackford R, et al. When do seizures improve with the ketogenic diet? *Epilepsia*. 2008;49:329-333. DOI: 10.1111/j.1528-1167.2007.01417.x

[44] Taub KS, Kessler SK, Bergqvist AG. Risk of seizure recurrence after achieving initial seizure freedom on the ketogenic diet. *Epilepsia*. 2014;55:579-583. DOI: 10.1111/epi.12583

[45] Martinez CC, Pyzik PL, Kossoff EH. Discontinuing the ketogenic diet in seizure-free children: Recurrence and risk factors. *Epilepsia*. 2007;48:187-190. DOI: 10.1111/j.1528-1167.2006.00911.x

[46] Hong AM, Turner Z, Hamdy RF, et al. Infantile spasms treated with the ketogenic diet: Prospective single-center experience in 104 consecutive infants. *Epilepsia*. 2010;51:1403-1407. DOI: 10.1111/j.1528-1167.2010.02586.x

[47] Williams TJ, Cervenka MC. The role for ketogenic diets in epilepsy and status epilepticus in adults. *Clinical Neurophysiology Practice*. 2017;2:154-160. DOI: 10.1016/j.cnp.2017.06.001

[48] Cervenka MC, Henry BJ, Felton EA, et al. Establishing an adult epilepsy diet center: Experience, efficacy and

challenges. *Epilepsy & Behavior*. 2016; **58**:61-68. DOI: 10.1016/j.yebeh.2016.02.038

[49] Barborka CJ. Epilepsy in adults: Results of treatment by ketogenic diet in one hundred cases. *Archives of Neurology and Psychiatry*. 1930;**23**: 904-914. DOI: 10.1001/archneurpsyc.1930.02220110066004

[50] Klein P, Tyrlikova I, Mathews GC. Dietary treatment in adults with refractory epilepsy: A review. *Neurology*. 2014;**83**(21):1978-1985. DOI: 10.1212/WNL.0000000000001004

[51] Kossoff EH, Henry BJ, Cervenka MC. Efficacy of dietary therapy for juvenile myoclonic epilepsy. *Epilepsy & Behavior*. 2013;**26**:162-164. DOI: 10.1016/j.yebeh.2012.11.007

[52] Kverneland M, Selmer KK, Nakken KO, et al. A prospective study of the modified Atkins diet for adults with idiopathic generalized epilepsy. *Epilepsy & Behavior*. 2015;**53**:197-201. DOI: 10.1016/j.yebeh.2015.10.021

[53] Phillips MCL, Murtagh DKJ, Gilbertson LJ, et al. Low-fat versus Ketogenic diet in Parkinson's disease: A pilot randomized controlled trial. *Movement Disorders*. 2018;**33**(8): 1306-1314. DOI: 10.1002/mds.27390

[54] Payne NE, Cross JH, Sander JW, et al. The ketogenic and related diets in adolescents and adults—A review. *Epilepsia*. 2011;**52**(11):1941-1948. DOI: 10.1111/j.1528-1167.2011.03287.x

[55] Diet Doctor [Internet]. 2018. Available from: <http://www.dietdoctor.com> [Accessed: Dec 11, 2018]

[56] Song TJ, Cho HJ, Chang Y, et al. Low-density lipoprotein particle size predicts a poor outcome in patients with atherothrombotic stroke. *Journal of Clinical Neurology*. 2015;**11**(1):80-96. DOI: 10.3988/jcn.2015.11.1.80

[57] Cervenka MC, Patton K, Eloyan A, et al. The impact of the modified Atkins diet on lipid profiles in adults with epilepsy. *Nutritional Neuroscience*. 2014;**19**(3):131-137. DOI: 10.1179/1476830514Y.00000000162

[58] Lambrechts DAJE, Wienders LHP, Aldenkamp AP, et al. The ketogenic diet as a treatment option in adults with chronic refractory epilepsy: Efficacy and tolerability in clinical practice. *Epilepsy & Behavior*. 2012;**23**:310-314. DOI: 10.1016/j.yebeh.2012.01.002

[59] Klein P, Janousek J, Barber A, et al. Ketogenic diet treatment in adults with refractory epilepsy. *Epilepsy & Behavior*. 2010;**19**:575-579. DOI: 10.1016/j.yebeh.2010.09.016