Cai *et al. Acta Epileptologica* (2022) 4:16
https://doi.org/10.1186/s42494-022-00082-4

Acta Epileptologica

REVIEW

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Ketogenic dietary therapy in adult status epilepticus: current progress and clinical application

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Abstract

Status epilepticus (SE) is a common fatal neurological disease with high morbidity and mortality. Even if a large proportion of patients might be relieved from anti-seizure medications, sedatives and anesthetics, some still remain out of control. The ketogenic dietary (KD) has been proven useful in patients refractory to medications and/or who have failed to respond to surgical intervention. Recently, KD has shown beneficial therapeutic effects in children with SE, but studies in adults have rarely been reported. In this paper, we review the efficacy and utility of KD in adult SE patients and highlight its application for clinical reference and management.

Keywords: Adults, Drug-resistant epilepsy, Ketogenic enteral nutrition, Ketogenic dietary, Ketogenic parenteral nutrition, Management, Status epilepticus

Background

Status epilepticus (SE) is a common medical and neurologic emergency with an overall incidence of ~ 7 to 41 per 100,000/year worldwide, and a mortality rate ranging from 20% to 57% [1, 2]. Historically, SE was defined as continuous seizures lasting for more than 5 min, or ≥ 2 discrete seizures with interictal incomplete recovery of consciousness [3]. As updated by the International League Against Epilepsy in 2015, the conceptual definition of SE was revised as a condition resulting from either the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alterations of neuronal networks, depending on the type and duration of seizures [4]. A subset of SE patients could benefit from initial treatments including anti-seizure medications (ASMs), sedatives and anesthetics, while the rest remained uncontrolled with increased mortality. Among those with SE, some (23% to 43%) might suffer persistent SE despite sufficient dose of benzodiazepines and at least 1 ASM irrespective of time; these cases are called refractory status epilepticus (RSE) [5, 6]. More seriously, in about 22% of SE cases, seizures might continue or relapse after treatment for 24 h or longer with highly sedating antiseizure medications, or when therapy is tapered after 24 h of use, causing super refractory status epilepticus (SRSE) [6, 7]. In view of those life-threatening medical emergency, safe and effective therapies are imperatively needed.

Ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate-protein diet that induces fat metabolism and production of ketone bodies for energy supply [8]. KD was first formulated in 1921 to mimic the biochemical changes associated with fasting and was recognized as a potent treatment for pediatric epilepsy in the mid-1990s [9–11]. Now, KD has been proved as an effective, safe, and feasible antiepileptic treatment by multiple lines of evidence, especially for some specific types of epilepsy

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and genetic epilepsy syndromes such as infantile spasms, Doose syndrome, Rett syndrome, tuberous sclerosis, glucose transporter 1 deficiency, Dravet syndrome, and pyruvate dehydrogenase deficiency [12, 13]. So far, KD has been recommended as an early-treatment-option for drug-resistant epilepsy (DRE), with a response rate (≥ 50% reduction from baseline) between 21% and 86% [14, 15]. However, there are only few recommendations and guides for KD use in adults, in contrast to the numerous pediatric consensus guidelines [15–19].

In this review, we provide a comprehensive overview of the values of KD in adult SE patients, combining evidence from the latest randomized clinical trials, recommendations in practice guidelines, findings from new research areas and partially from pediatric evidence. The aim of this review is to provide a detailed management guidance for clinicians, patients, and their caregivers.

Anticonvulsant mechanisms

The mechanisms of KD have not been completely understood yet. Hypotheses such as brain energy metabolism, oxidative stress, neurotransmitters, and ion channels have been proposed [20–22]. In the process of KD, the liver can use long-chain fatty acids to synthesise three ketone bodies, i.e., β-hydroxybutyrate (βHB), acetoacetate, and acetone [8]. These substances then enter the bloodstream and cross the blood–brain barrier to supply energy to the brain [20]. Previous studies suggested that long-term KD could increase energy reserves by up-regulating the expression of energy metabolism genes and improving mitochondrial function to improve neuronal activity. The following regulation of ion channel sensitivity could further increase the threshold of seizures [23].

The antiepileptogenic function of KD may be mediated by multiple neurotransmitters. The γ-aminobutyric acid (GABA) works essentially as an inhibitory neurotransmitter against initiation and spreading of seizure activity in the brain. Apart from promoting the synthesis and inhibiting the degradation of GABA, KD can also compensate for the metabolic deficits within epileptic foci and transient failure of GABAergic inhibition by increasing the energy metabolism. Similarly, the increased concentration of agmatine (an inhibitory neurotransmitter) can work together to enhance the anti-seizure performance, and meanwhile affect the function of monoamine neurotransmitters such as norepinephrine, dopamine, and serotonin [21]. Moreover, the polyunsaturated fatty acids produced by KD have a wide range of functions, including activating peroxisome proliferator-activated receptors, exerting anti-inflammatory and antioxidant effects, regulating mitochondrial genes, increasing energy reserves, stabilizing synaptic functions, and inhibiting excessive excitement [24].

Current applications and challenges of KD in adult SE patients

KD has been shown to be a safe and effective complementary therapy to current SE management in patients with DRE, based on evidence from several case reports and case series, yet without sufficient quality studies [2]. According to a latest systematic review, 31 of the total 38 patients (81.6%) in 4 observational studies, including 23 with SRSE and 8 with RSE, successfully achieved cessation of SE with KD. Meanwhile, among the 17 adults with RSE or SRSE in 13 case reports and series, 14 patients (82.3%) achieved SE resolution after 4 to 25 days of KD [2].

Notably, KD plays a significant and beneficial role in the management of those critical patients. Patients with SE have increased risks of infection and multiple organ failure due to their severe symptoms and complications, such as persistent seizure, long-term sedation, airway support, and the use of multiple ASMs. However, effective administration of KD could prevent the adverse effects of drugs and their impact on circulation. Meanwhile, it facilitates early withdrawal of sedatives and restoration of spontaneous breathing, further improving the prognosis in patients [25].

However, there are still challenges for clinical practice of KD. First, patients in the acute phase of SE are usually under intravenous anesthesia, which requires KD application in the enteral (such as nasal feeding) or parenteral form (such as deep vein catheterization). Accordingly, liquid or semifluid KD is needed with different compositions in different proportions, revealing the uncertainty of the therapeutic effect. Second, some hidden carbohydrates could hinder the achievement of ketosis. For instance, some sedatives and ASMs like benzodiazepines and barbiturates have high propylene glycol contents, and some antimicrobials (trimethoprim-sulfamethoxazole and vancomycin) require reconstitution with dextrose 5% in water. Meanwhile, other drugs like glucocorticoids could inhibit the production of ketone bodies. In addition, the impact of KD on the treatment of other primary diseases in patients needs to be further clarified.

Pre-treatment assessment

SE is a serious medical emergency that needs rapid evaluation and management. The respiratory and circulatory status should be taken into first consideration, followed by the identification and treatment of its idiopathic cause. An individualized treatment program of KD should be made after multidisciplinary assessments under the cooperation of neurology, critical care medicine, and

nutrition departments. Preparations including eliminating contraindications, assessment of relevant indicators, and determining the therapeutic times should be completed before formal implementation [17, 18, 26].

Contraindications

Patients with porphyria and inborn errors of metabolism that might affect the transport or oxidation of long-chain fatty acids are absolutely contraindicated for KD [18]. These devastating catabolic crises would break into conditions of primary carnitine deficiency, carnitine palmitoyltransferase I or II deficiency, carnitine translocator deficiency, fatty acid β-oxidation defects, long-chain/medium-chain/short-chain acyl dehydrogenase deficiency, long-chain/medium-chain 3-hydroxyacyl-CoA deficiency, pyruvate carboxylase deficiency, porphyria, and others [27]. Meanwhile, patients with severe electrolyte metabolism abnormalities, severe hemodynamic instability, acute respiratory infections, uncontrolled systemic infections, severe liver and kidney failure, cholesterolemia (> 300 mg/dL), abnormal blood coagulation, and acute pancreatitis are not suitable for KD [28]. Other conditions such as ingestion disturbances and food allergies, the compliance from patients or caregivers, and the increasing risk of adverse events, should also be seriously considered before initiation of KD.

It is worth noting that KD might increase the risk of propofol infusion syndrome (PIS) [29]. PIS is a rare fatal adverse effect with presentations of metabolic acidosis, hyperlipidemia, rhabdomyolysis, and heart failure. It might be related to the impairment of mitochondrial fatty acid metabolism. PIS generally occurs after intravenous propofol for more than 48 h at a dose of > 4 mg/kg per hour. Hence, KD should be avoided within 24 h of propofol treatment.

Assessment

First, a baseline nutritional and laboratory assessment should be performed prior to the commencement of KD. Certain medical conditions that might be aggravated by KD should be pre-treated, including kidney stones, hypercholesterolemia, liver disease, gastroesophageal reflux, constipation, cardiomyopathy, and chronic metabolic acidosis. The screenings could be divided to be mandatory and recommended according to the previous evidence and consensus of the international law enforcement academy [17, 27, 30], as shown in Table 1.

Initiation of KD

There is no clear evidence on the exact initiation time for KD. A multi-center prospective study of 15 adult SRSE patients suggested a time span from 2 to 39 days to start therapy and a median duration of 2 days to reach ketosis, with an remission rate of 73% [16, 28]. In another case report, the initial therapeutic time was 3 to 155 days and a time of 3.5 to 37 days was needed to reach ketosis. The remission rate was up to 82% after 4 to 25 days of KD [28].

Table 1 Recommendations of evaluation before KD

Evaluation	Baseline (pre-therapy)	Follow-up
Nutrition/monitoring		
Mandatory	Basic nutrition consultation, height, weight, BMI, food allergy/intolerance, food preference	Changes of BMI, seizure frequency
Recommended	Three-day food record/calorie count, seizure frequency before treatment, menstruation cycle monitoring	Food records/compliance, adverse effect, menstrual changes
Laboratory		
Mandatory	Basic metabolism examination, liver function (if on hepatically metabolized ASMs), human chorionic gonadotropin urine test (for premenopausal females)	Basic metabolic index, blood lipids, urinalysis, urine ketones (in the case of intolerance, consider stopping KD during treatment)
Recommended	Complete blood count, blood lipid, liver function, calcium, vitamin D, amylase, and lipase tests	Liver function, vitamin D, complete blood count, calcium, free/total carnitine, and urine ketone tests
	Serum-free carnitine, selenium, magnesium, phosphorus, ASM concentration, urinalysis, urine calcium, and creatinine ratio	Serum selenium, zinc, magnesium, phosphorus; urine calcium-to-creatinine ratio (especially when not taking citrate)
Diagnosis		
Mandatory	For patients with high suspicion of metabolic disease, diagnosis is required to determine the cause	-
Recommended	EEG/epilepsy center evaluation (when the diagnosis is unknown or if patients are suitable for surgery)	Bone density scan (at least once every 5 years), renal ultrasound (when suspected of kidney stones), carotid ultrasound (long-term fasting with elevated blood lipids)

ASM anti-seizure medication, *BMI* body-mass index, *EEG* electroencephalogram, *KD* ketogenic dietary

Treatment options

A large proportion of SE patients are sedated with additional enteral/parenteral supplements for basic nutrition maintenance and drug administration. The ketogenic ratio, i.e., the ratio of grams of fat to grams of carbohydrate plus protein, could greatly affect the therapeutic efficacy of KD.

Ketogenic enteral nutrition (KEN)

KEN refers to the administration of KD in a liquid form through a nasogastric tube, a nasointestinal tube, or a gastric/jejunal fistula tube. Many commercial formula products with abundant vitamins and minerals consistent with the requirements of dietary reference intakes (DRIs) are available for clinical administrations.

To date, the classic KEN formula is used most frequently with a 4:1 or 3:1 ratio of fat (long-chain saturated triglycerides, providing 90% of the energy) to protein and carbohydrates, and contains vitamin and mineral supplementation consistent with the requirement of daily DRIs [31]. A fasting (for 12 to 48 h) or non-fasting period could be applied before KD. The KEN is initiated at the time of negative urine ketone in order to accelerate the production of ketone bodies. Daily-needed energy is supplemented after reaching the target level of ketosis. The frequent adverse effects include weight loss, hypoglycemia, acidosis, etc. [32]. In another non-fasting method, KD is administered by gradually increasing the ketogenic ratio in KD (increase by 1:1, 2:1, 3:1, and 4:1) [33]. Yet there is no significant difference in the time to reach the target level of ketosis or the risk of hypoglycemia between the 2 methods [34].

Other KEN compositions include medium-chain triglyceride alternatives (providing 60% of energy and reducing gastrointestinal symptoms), modified Atkins diet (usually for children, ketogenic ratio of 1:1 or 1:2), low glycemic index treatment (carbohydrate decreased to 40 to 60 g/day with a glycemic index lower than 50, without limitation to fat or protein) [18]. A recent study indicated that the 4:1 KD ratio of fats to nonketogenic proteins and carbohydrates was used most frequently among adult SE patients with a remission rate of 73% to 82%. And the times from SE onset to KD initiation, to reach target ketosis levels and to achieve seizure control were 2 to 101 days, 0 to 23 days, and 4 to 25 days, respectively [2, 28].

Ketogenic parenteral/intravenous nutrition

Ketogenic parenteral nutrition (KPN, also named ketogenic intravenous nutrition) is applied through the intravenous approach for those with digestion and absorption dysfunctions that cannot further maintain the level of ketosis by KEN. KPN can also be used as an initial treatment for SE patients. Compared with KEN, KPN requires more strict monitoring of adverse effects, and the allergen information from each composition of substances should be confirmed explicitly. Considering that the carbohydrates in drugs are calculated into the carbohydrate ratio of KPN, non-carbohydrate forms of drugs are highly recommended. Additional attention should be paid to the carbohydrates potentially produced by intravenous vehicles and from interactions of drugs.

To date, few studies have focused on adult KPN. Current composition ratios of KPN preparations are mainly based on pediatric studies. The weight ratio of fat to carbohydrate plays an important role on the efficacy of treatment. With regard to carbohydrates, for patients who have been treated with KEN, the maximum daily maintenance intake of carbohydrate is determined based on their preceding intestinal intake. In clinical practice, the ultimate glucose support for ketosis depends on a diet ratio of the maximal possible fats and minimal safe protein intake to prevent malnutrition [35]. In addition, glycerol in lipid emulsion (2.2% to 2.5%), and glycerol and alcohol in some intravenous drugs (such as sedatives) could produce carbohydrates after metabolism, which hinders ketosis [35].

Lipids are predominant components in parenteral nutrition preparations and serve as an essential component of KPN to maintain the ketosis level and inhibit seizures. They provide essential fatty acids and contribute to supply calories with advantages of small volume and low osmotic pressure [36]. Yet, careful and regular monitoring is required to avoid adverse effects like hyperlipidemia. Meanwhile, allergies or hypersensitivity reactions should be concerned, in view that there are various ingredients in the intravenous fat emulsion, such as egg, soy, and peanut protein. The common fat components in KPN preparations including the medium-chain triglyceride emulsion (20% fat emulsion) and long-chain triglyceride emulsion (20% fat emulsion), are usually combined with amino-acid intravenous nutrient solution (6.7% or 10% concentration) in a ratio of 1:3. The latest pediatric practice guideline on KPN recommended a maximum of fat intake of 4 g/kg per day and a lower fat/non-fat ratio of merely 4:1, compared with KEN [35]. In case of lower ketosis in KPN, rapid introduction or reintroduction of enteral feeding is therefore recommended to increase the ketogenic ratio and the proportion of fat [37].

Furthermore, other essential compositions including fluid, calories, protein, and minerals also should be taken with caution in parenteral nutrition therapy. Even if there

is no exact requirement for fluid volume in KPN, adjustments to individual's general condition, weight, urine output, electrolytes, pH, hematocrit, urine specific gravity, and urine electrolytes are necessary to avoid circulatory failure. The requirement of calories in SE patients varies across different disease phases, with a relatively lower requirement in acute and stable phases. Calories usually start with 50% of goal and increase within a maximum of 1 week with increased intake of lipids. A reduction of resting energy expenditure to 50% to 75% is recommended, but this might be difficult to realize by adjusting the KPN formula [35, 38]. The supplement of protein is increased by 20% to 50% in severe conditions with the recommendation of 1.2 to 2.0 g/kg per day [39]. Moreover, the vitamins and minerals within DRI doses are beneficial for reducing mortality in severe illnesses [37]. Nevertheless, pharmacological issues during the actual application process should be attended, such as intravenous lumen adhesion, visible light decomposition, or mutual mixing that may affect stability. Hence, special attention should be paid to the selection and compatibility of drugs and solutions, as well as to the individual need.

Management

Treatment and monitoring

The successful implementation of KD needs multidisciplinary cooperation, which is associated with the therapeutic response, development of complications and need for optimization of nutritional status. In general, the sedating drugs should be maintained and titrated until seizure suppression for 72 h after initiation of KD in the acute phase of SE [28]. Yet, the response to KD remains unclear. In some cases, allowing for anesthetic wean or antiseizure regimen simplification is considered effective. In contrast, KD might be useless if no improvement is observed within 2 weeks of treatment. In the following time, KD termination and maintenance of sedative anesthetics is recommended [17, 40].

The maintenance of KD is affected by many factors, such as the degree of seizure control and the tolerance of patients. After initiation of KD, ketone monitoring (blood βHB or urine acetoacetate) is recommended to reflect the biochemical response. Yet, symptom management, rather than the level of ketosis, is the primary goal of KD [18]. Moreover, regular tests of glucose should be done every 4 h to maintain a serum glucose level of > 50 mg/dL, and the urine ketones and serum βHB should be tested every 12 h. A comprehensive test of metabolism should be done every 48 h to ensure serum bicarbonate > 18 mRq/L. Routine monitoring during follow-up should be conducted to identify and manage possible KD complications (Table 1).

The duration of adult KD depends on the underlying conditions being treated and the therapeutic response. A minimum of 3 months of KD is recommended before any judgement of response [18]. Previous evidence suggested that persistent ketosis could be achieved after KD for a duration of 37 days, and patients with a 2-year maintenance of KD obtained a seizure freedom rate of 80% [41]. It is recommended to discontinue KD gradually, with reduction of ketogenic ratio (i.e., 4:1 to 3:1 to 2:1) [17, 27]. Notably, abrupt withdrawal of KD is only recommended for emergencies, due to the potential risk of recurrence of seizures or SE [27].

Adverse reactions

The adverse reactions of KD play an important role in determining the treatment process and compliance of patients. Previous studies have indicated a good tolerance to KD in SE patients. The reported adverse reactions include metabolic acidosis, hyperlipidemia, hypoglycemia, gastrointestinal symptoms, kidney stones, and induction of infection, with the former 3 occurring most frequently [2]. Other potential side effects include cardiovascular effects, and osteoporosis caused by vitamin and mineral deficiency [28]. In general, KD should be ceased in the case of persistent adverse reactions and failure of symptomatic treatment.

Conclusions

KD has a favorable efficacy and good tolerance in adult SE patients. Compared with traditional ASMs and anesthetic sedative drugs, KD has higher safety with fewer adverse drug reactions. However, the potential effects of KD on metabolism, digestion, and the urinary system should be monitored closely. In the future, multicenter, randomized, controlled studies with large sample sizes are needed to verify the therapeutic effect of KD in adult SE patients.

Abbreviations

ASM: Anti-seizure medication; DRE: Drug-resistant epilepsy; DRI: Dietary reference intake; GABA: γ-Aminobutyric acid; KEN: Ketogenic enteral nutrition; KD: Ketogenic dietary ; KPN: Ketogenic parenteral nutrition; PIS: Propofol infusion syndrome; RSE: Refractory status epilepticus; SE: Status epilepticus; SRSE: Super refractory status epilepticus; βHB: β-Hydroxybutyrate.

Acknowledgements

Not applicable.

Authors' contributions

MTC searched and summarized the reviews and was a major contributor to writing the manuscript. WYX contributed to conception of the work and revised the manuscript. YZ helped with the writing and revision of the manuscript. MPD revised the manuscript for intellectual content. All authors read and approved the final manuscript.

Funding
This study was supported by the National Natural Science Foundation of China (82071443).

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interest.

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Received: 13 December 2021 Accepted: 28 February 2022
Published online: 15 April 2022

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