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REVIEW

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Calculation and management of ketogenic diet parenteral nutrition in super-refractory status epilepticus

Ya Zeng[1], Jie Mu[2*] and Dong Zhou[2*]

Abstract

Super-refractory status epilepticus (SRSE) is an important neurological emergency associated with high mortality and morbidity and poses a heavy economic burden on patients. Ketogenic diet parenteral nutrition (KD-PN) is ketogenic diet therapy provided through parenteral administration and may be an adjuvant treatment for these who cannot accept enteral diet. However, the calculation and management of KD-PN presents a challenge for clinicians. This review focuses on the practical aspects of KD-PN therapy for treatment of SRSE, including the dietary composition, potential drug-diet interactions, and monitoring during KD-PN treatment. As with all SRSE treatments, KD-PN has many adverse effects, like hyperlipemia, hepatotoxicity, metabolic acidosis, insufficient ketosis or hyper-ketosis, and propofol infusion syndrome. We summarize monitoring and treatment methods in our review. This review provides some practical aspects for treatment of SRSE.

Keywords: Epilepsy, Super-refractory status epilepticus, Ketogenic diet parenteral nutrition

Background

Epilepsy is the most prevalent neurologic condition, affecting approximately 45.9 million people worldwide in 2016 [1]. Status epilepticus (SE) is an important neurological emergency [2]. In about 5%-10% of SE patients, SE will further develop into super-refractory status epilepticus (SRSE), in which treatment with anesthetics for > 24 h (with dosage reduction or withdrawal) will not terminate seizures or prevent relapse of seizures [3, 4]. The mortality of SRSE is about 30%-50% [5], and SRSE is posing a great burden on healthcare resources in the world.

Ketogenic diet (KD) is a high-fat, low-carbohydrate diet that mimics the metabolic changes occurring during starvation and has been used to treat epilepsy for 100 years. The classic KD was first used in 1921 by Wilder [6]. KD became popular in the early 1990s [7] and has been well-established, effective and affordable interventions for refractory epilepsy [8], such as some epilepsy syndromes, and RSE/SRSE. The application of oral or enteral KD is a challenge for patients who cannot be enterally fed, such as those with severe gastrointestinal affection. For these conditions, ketogenic-diet parenteral nutrition (KD-PN) may be required to maintain or achieve the level of ketosis and the anti-seizure effect.

We searched the Cochrane Library, PubMed, EMbase, Web of Science, and Google Scholar for literature published between January 1, 1990 and March 1, 2021 using the terms ketogenic, parenteral nutrition or intravenous KD, epilepsy or epilepticus under the medical subject headings (MeSH) terms. Both observational studies and case reports were included. Only studies published in English were included. KD-PN was first applied in 1990 to a 5-year-old girl with Lennox-Gastaut syndrome [9]. From 1990 to 2020, 6 retrospective studies [10–15] and 8 case reports [9, 16–22] have reported the use

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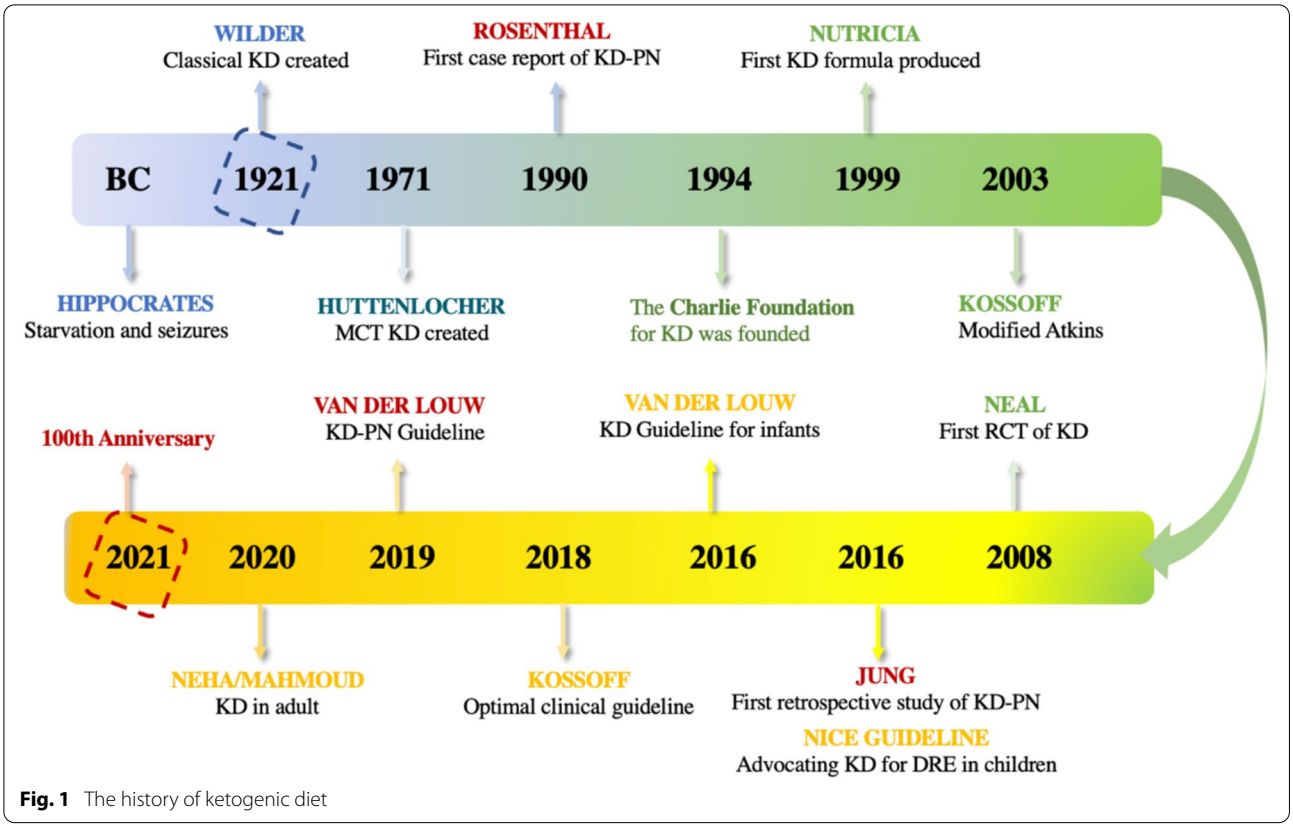

Fig. 1 The history of ketogenic diet

of KD-PN for epilepsy, involving a total of 47 patients (Fig. 1). KD-PN showed effectiveness in >80% of these patients. The most frequent adverse effect of KD-PN was transient hypertriglyceridemia, which occurred in about 60% of the patients.

Main text

Contraindications to the use of KD-PN

The contraindications are mainly based on the ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology and Nutrition)/ESPEN (The European Society for Parenteral and Enteral Nutrition)/ASPEN (The American Society for Parenteral and Enteral Nutrition)/GANM (The German Association for Nutritional Medicine) guidelines and the optimal clinical management of KD/KD-PN. The contraindications to KD-PN are listed in Table 1.

Dietary prescription

Ratio of KD-PN

Providing >60% of total energy as fat in PN increases the risk of ketosis [16], but high dosages of fat emulsions (FEs) may increase the risk of transient elevation of triglyceride (TG), liver enzymes, and pancreatic enzyme concentrations. [14]. Correlation analysis on the reported cases showed that the dietary ratio is not correlated with the anti-seizure effect of KD-PN (correlation coefficient, 0.036; $P=0.822$) but is significantly correlated with hypertriglyceridemia (correlation coefficient, 0.559; $P=0.031$). We recommend KD-PN start with a ratio <1:1 (fat: carbohydrate + protein) by weight at the first day with 50% of the estimated energy needs, and increase it every 2 days to the highest ratio within a week (usually less than 2:1-3:1) [31].

Energy

The total energy needs are the sum of 4 different components [32]. Basal metabolic rate (BMR) is the most important component and is usually replaced by the resting energy expenditure (REE) [32]. The indirect calorimetry is the most preferable method to estimate REE, and is generally calculated by the Weir formula: $BMR=3.941\times V_{O2}(l/min)+1.106\times V_{CO2}$ (l/min) [33]. The applicability of indirect calorimetry is limited in clinic by the poor availability and high cost. So far, there have been over 200 energy-prediction equations published [34, 35]. We recommend the following formula for calculating REE in mechanically ventilated patients (if the mechanism provided the option to measure V_{CO2}): REE (kcal/d) $=8.19\times V_{CO2}$ (ml/min) [36], and the

Table 1 Contraindications to the use of KD-PN

Absolute contraindications	
Disorders of fat metabolism [23]	Carnitine deficiency, carnitine palmitoyl transferase (CPT) I or II deficiency, carnitine translocase deficiency, β-oxidation defects, long /medium/short-chain acyl dehydrogenase deficiency, long/medium-chain 3-hydroxyacyl-CoA deficiency, pyruvate carboxylate deficiency, porphyria
Severe metabolic abnormalities or instabilities	Severe hyperlipidemia (serum TG > 500 mg/dl) [24]
	Metabolic acidosis (blood pH < 7.3 [25]; serum CO_2 < 12 mmol/l [14])
	Sodium < 130 mg/dl, > 150 mg/dL; albumin corrected calcium < 8 mg/dl [26]
	Severe hypoglycemia (glucose < 54 mg/dl) [27]
Disease state	Pregnancy [28, 29]
	Severe coagulopathy
	Severe liver failure; aspartate aminotransferase (AST), alanine aminotransferase (ALT), ammonia > 5*upper limit of normal; total bilirubin > 15 mg/dl, direct bilirubin> 5 mg/dl within 24 h) [26]
	Severe kidney failure [29]
	Pancreatitis
	Irreversibly decerebrate patients [30]
	Critical cardiovascular instability [30]
	Infants with less than 8 cm of the small bowel [30]
Drugs	Propofol concurrent use or on propofol within 24 h
Relative contraindications	
Disease state	Cardiovascular disease (hyperlipidemia, arrhythmia, cardiomyopathy); renal calculi; osteopenia; sepsis; decompensated diabetes mellitus
Metabolic abnormalities	Severe hyponatremia; hypoproteinemia; hyponatremia, hypernatremia, hypocalcemia, hyperketonemia [31]

Table 2 Energy requirements (kcal/kg per day) for parenteral nutrition in different phases of disease

	Recovery phase	Stable phase	Acute phase
Preterm	90-120		45-55
0-1	75-85	60-65	45-50
1-7	65-75	55-60	40-45
7-12	55-65	40-55	40-40
12-18	30-55	25-40	20-30
> 18	25-30		
> 65	20-25		

Table 3 Consensus recommendations for calculations of daily fluid requirement

Weight	Goal
0-10 kg	100 ml/kg per day
10-20 kg	1000 ml + 50 ml/kg*(x-10)
> 20 kg	< 50 years: 1500 ml + 20 ml/kg*(x-20)
	> 50 years: 1500 ml + 15 ml/kg*(x-20)

weight-based formula for others (Table 2) [32, 34]. The Schofield equation and the Penn State University equation have been recommended to calculate REE [32, 37].

Predictive equations should be corrected for overweight and obese patients [38]. The body mass index (BMI) ranges for overweight status (25.0–29.9), class 1 obesity (30–34.9; low risk), class 2 obesity (35.0–39.9; moderate risk), and class 3 obesity (≥40.0; high risk) are used to delineate the obesity grade [39]. We recommend adjusted body weight for obese patients as follows: adjusted body weight = ideal body weight + [0.4 × (actual body weight − ideal body weight)]. The ideal body weight can be calculated by the Devine formula: 50 + 2.3x[Height (cm)/2.54–60] for males, and Robinson formula: 48.67 + 1.65x[Height (cm)/2.54–60] for females [38].

Fluid

In 1957, Holliday Segar proposed a rehydration method based on calorie consumption, which is still on use today (Table 3) [38, 40, 41]. The permitted volume of PN is limited by the volume required to dilute the medications.

Protein

The amino acid (AA) intake of 1.0–2.0 g/kg per day may be considered for most patients (Table 4) [42]. An intake of 0.5 g/kg to 0.8 g/kg for short-term use might be acceptable [43, 44].

Table 4 Protein requirement in different patients

Patient	Protein requirements(g/kg per day)
Infants	1.5-3.0
Children/adolescents	1.0-2.0
Adult	
ICU	1.2-1.5
Liver disease	0.8-1.5
Kidney disease	0.6-1.5
Inflammatory bowel disease	1.0-1.5
Cancer	1.2-2.0
Surgery/ Perioperative	1.5-2.0
Elderly	1.2-2.0

Lipids

Lipids are important for seizure control and the achievement of ketosis [31]. ESPEN [45, 46] has recommended that the parenteral lipid intake not exceed 4 g/kg per day in infants, 3 g/kg per day in children and 1.5–2 g/kg per day in adults. We recommend that lipids in KD-PN start at 1-2 g/kg per day, and finally advance to 3-4 g/kg per day, during which lipids are increased every 1–2 days [31, 43].

Carbohydrates

In the first 2 days of KD-PN, additional glucose solution is usually not needed unless the serum glucose is < 50 mmol/l [16], because less carbohydrate can help a person achieve a state of ketosis faster. Carbohydrates from glycerol in the FEs provide sufficient substrate for the liver to continue gluconeogenesis and maintain serum glucose [16]. Intravenous (IV) medication products such as phenobarbital (PB), diazepam (DAP), lorazepam (LAP), and phenytoin (PHT) usually contain propylene glycol and alcohol, which would provide carbohydrate at about 30 kcal/d.

Electrolytes, vitamins, and minerals

The intake of electrolytes, vitamins and minerals is mainly affected by age and weight [38, 40, 47, 48] (Table 5). They are unlikely to be supplied separately, as most drugs are compound formulations. Electrolytes such as serum sodium, calcium, potassium, magnesium, chlorine, and phosphorus are the main components of body fluids. Vitamins are essential organic micronutrients and can be classified as lipid soluble (vitamins A, D, E, K) and water soluble (vitamins B and C). Vitamins and electrolytes should be administered daily, if possible.

Table 5 Recommended doses for KD-PN of electrolytes, vitamins, and minerals

Item	1-18y	>18y
Na	1–3 mmol/kg per day	80–100 mmol/day
K	1–3 mmol/kg per day	60–150 mmol/day
Cl	2–4 mmol/kg/d per day	
P		15–30 mmol/day
Vitamin D	400–600 IU/day	
Vitamin C	80 mg/day	
Vitamin E	11 mg/day or 11 IU/day	
Iron	50–100 μg/kg per day	5 mg/day
Zinc	50 μg/kg per day	5 mg/day
Copper	20 μg/kg per day	0.5 mg/day

Vitamin K can be given weekly. Supplementation of minerals is generally considered unnecessary for short-term KD-PN.

Infusion speed

In the reported studies, the KD-PN was infused continuously over 12 h [16], 16 h [10, 17, 18, 20], 20 h [11, 15] and 24 h [19, 21], and interrupted with 0.9% or 0.45% NaCl solution. For KD-PN, the infusion speed is mainly limited by the infusion of FEs. The maximal lipid oxidation rate is about 3 g/kg per day in young children and decreases with age to 1.7–2.5 g/kg per day in adults [46]. An overly high speed of FEs may cause the Fat Overload Syndrome. We recommend an infusion speed of < 0.15 g/kg per hour for FEs, < 0.1 g/kg per hour for AAs, and < 0.12 g/kg per hour for glucose [16]. FEs should be administered over at least 12 h/day [49]. Under a more critical metabolic situation, slower infusion rates such as continuous infusion over approximately 24 h is recommended [49].

Atwater factors and osmolality

Our algorithm incorporates detailed information of the dietary prescription (like calorie and osmolality) provided in the instruction leaflet. Some information not provided in the instructions was inferred from Atwater factors [32] and the general osmolality in guidelines [38]. The energy content of proteins, carbohydrates and lipids correspond to 4, 4 and 9 kcal/g, respectively [32]. The osmolarity of the PN solution is calculated as follows: osmolarity of the PN solution (mOsm/l) = [(glucose (g) × 5 mOsm/g + fat (g) × 1.3 ~ −1.5 mOsm/g + AA (g) × 10 mOsm/g + alanyl glutamine (g) × 5 mOsm/g + electrolytes (mEq) × 1 mOsm/mEq + elements × 19 mOsm/bottle]/total liquid volume (l) [38]. Generally, peripheral venous catheter is suitable for short-term infusion of nutrient solution with lower osmotic concentration (solution

osmolarity ≤900 mOsm/l for all patients) [50], and central venous catheter is required to maintain long-term venous access (> 2 weeks [38]).

Attention on KD-PN

Stability

PN can be prepared into "2-in-1" or "3-in-1" admixtures to improve the utilization of glucose and lipids and reduce the formation of thrombosis and phlebitis. However, there is also a potential for interactions between components. Some precautions should be paid to ensure the stability of the solution, as follows: (1) infusion route should be used exclusively for administration of PN but not for administering other fluids and drugs; (2) FEs should not be mixed with glucose directly; (3) calcium and phosphorus should be provided at different venous access sites [10], and phosphorus is preferred to be added in an organic-bound form; (4) vitamins should be added to the lipid emulsion or a mixture containing lipids to increase vitamin stability, and only vitamin C is recommended to be injected separately.

Influence of KD on the serum concentration of AEDs

Patients who have initiated KD-PN are usually under treatment with many AEDs. These AEDs include carbamazepine (CBZ), clobazam (CLB), clonazepam (CZP), lacosamide (LCM), levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), PB, pregabalin (PGB), PHT, topiramate (TPM), valproate (VPA), and zonisamide (ZNS). Anesthetics like midazolam and propofol are also commonly used. The potential interactions between AEDs and KD-PN must be considered.

The pharmacokinetic interactions between KD and AEDs remain unclear, and conclusions are controversial in different studies. KD may enhance the absorption of lipophilic drugs and alter the protein-binding capacity to change the serum concentrations. The serum concentrations of CBZ, LTG, LEV and TPM are decreased during KD [51]. It is unnecessary to adjust the AED doses when initiating KD-PN, but considering the possible reduction of serum AED concentrations that may counteract the seizure-reducing effect of the diet, we recommend monitoring of the serum concentrations of the concomitant AEDs in patients.

Adverse effects of and monitoring after KD-PN

Adverse effects

Hyperlipemia Mild and transient increase of TG can occur in most patients during KD-PN. Carnitine is an essential carrier for lipid metabolism, so it should be given at 50 mg/kg (< 1 g/d) when TG is > 200 mg/dl (2.3 mmol/Ll) [23]. The dosage of FEs should be reduced when serum TG is > 500 mg/dl (> 5.65 mmol/l) [24]. KD-PN should be stopped when TG is > 1000 mg/dl (> 11.3 mmol/l) [24, 49].

Hepatotoxicity PN is associated with complications affecting the hepatobiliary system, such as cholelithiasis, cholestasis and steatosis [52]. Too high dosage of FEs can increase the levels of liver enzyme, amylase, and lipase, sometimes even with progression to pancreatitis. Because KD-PN is always administered for a short term (< 1 week [10, 13, 18, 19]). In addition, both VPA and KD-PN can cause hepatotoxicity, although the combined use of VPA with KD may be safe. We therefore recommend a more frequent monitoring of serum concentrations of VPA and liver function.

Signals for a need of FE reduction include direct bilirubin level > 2 mg/dl, and transaminases or γ-glutamyl transpeptidase (GGT) level > 1.5 times the upper normal limit [28]. Restarting the enteral feeding as soon as possible is the best way to prevent adverse effects on the liver.

Metabolic acidosis Application of KD-PN may make patients prone to metabolic acidosis because ketone body metabolism may produce protons and PH-lowering metabolic products [23, 29]. The carbonic anhydrase inhibitor type of AEDs (including TPM and ZNS) can lead to decreased levels of serum bicarbonate. So, the combination of KD-PN and carbonic anhydrase inhibitor could increase the risk of serum bicarbonate decrease, metabolic acidosis, and urolithiasis. For patients whose serum CO_2 is < 16 mmol/l, bicarbonate should be given [14, 18], at the dose of 1 mEq/kg per day when CO_2 = 16 mmol/l, 2 mEq/kg/d when CO_2 = 13-15 mmol/l, 3 mEq/kg/d when CO_2 < 12 mmol/l, split bid [13], or citric acid/sodium citrate (1-2 mg/kg per day, divided in 3-4 daily doses) is provided to keep serum bicarbonate level > 17 mmol/l [53].

Hypoglycemia Metabolic acidosis and hypoglycemia can occur commonly during KD-PN. Administer 12.5 g glucose if serum glucose < 54 mg/dl, then check q15 minutes until glucose > 70 mg/dl [27]. For patients whose serum CO_2 is < 16 mmol/L, bicarbonate should be given [14, 18], at the dose of 1 mEq/kg per day when CO_2 = 16 mmol/l, 2 mEq/kg/d when CO_2 = 13-15 mmol/l, 3 mEq/kg per day when CO_2 is < 12 mmol/l, split bid [13].

Insufficient ketosis or hyperketosis Ketonemia is indicated by a serum β-HBA level within the range of 2-5 mmol/l [14], or urine acetoacetate > 40 mg/dl [54].

Insufficient ketosis (< 1.5 mmol/l) is frequently observed [31]. Sometimes hyperketosis (> 6.5 mmol/l) can also occur [20, 31], which makes a person weak and lethargy. As benzodiazepines and PB also can cause lethargy, we recommend that their use be reduced gradually if the symptom of lethargy is getting worse.

Propofol infusion syndrome The combination of propofol and KD-PN has been banned in many studies because the combination may increase the risk of propofol infusion syndrome in patients [13, 17–19, 31]. Renal, liver, and cardiac functions should be strictly monitored if combination is considered necessary.

Sepsis and catheter thrombosis Through the authors' expert opinion, it is assumed that the use of KD-PN is associated with the same risk as regular parenteral nutrition such as sepsis [55] and catheter thrombosis [31].

Monitoring during KD-PN

We recommend monitoring of following items at the initiation of or during KD-PN (Table 6).

Discussion

Fasting

When starting KD-PN for the first time in RSE/SRSE patients [14, 17–19], to maximize its potential for ketosis achievement and seizure reduction, it is appropriate to add an additional fasting period of 24 h, and remove dextrose from IV fluids [31] and diluent from IV medications 12-24 h prior to diet initation [53].

Duration of KD-PN and switch from parenteral to enteral ketogenic diet

According to previous studies and cases, the duration of KD-PN ranges from 1 to 41 days (median 4.5; IQR 2-10), and the duration to achieve the goal level of ketosis ranges from 1 to 13 days (median 3.0; IQR 2-4). PN is a high-risk treatment, so limiting the period of PN application is important. The enteral route should be used immediately once enteral feeding (including nasogastric tube) is acceptable [31]. KD-PN should be stopped when patients are suffering severe adverse effects like pancreatitis or have no treatment response for > 15 days [31].

Detailed information on KD-PN switch to enteral KD is still controversial. Progressive KD-PN switch to the enteral KD nutrition has been reported in at least 8 patients [9, 14–16, 18, 20]. We recommend that weaning is performed on an individual basis. After enteral KD is initiated, calorie intake can be increased by 1/10–1/5 of the estimated daily intake, adjusted after each day to replace KD-PN [15].

Table 6 Items recommended to be monitored at baseline and/or during KD-PN

Item	Baseline	During KD-PN
Weight and height	Y	N
Vital signs	Y	Y (qd)
Intake/output	Y (dietary)	Y (qd)
Electroencephalogram (EEG)	Y	Y (qd)
Blood gas and osmolarity	N	Y (qd)
Comprehensive metabolic panel		
Serum glucose	Y	Goal range: 55-79 mg/dl
		< 50 mg/dl, repeat in 3 h
		< 45 mg/dl, repeat in 1 h
Serum β-HBA	Y	Y(qd)
AST, ALT, GGT,	Y	Y (biw-tiw)
Alkaline phosphatase (ALP)	Y	Y (biw-tiw)
Bilirubin	Y	Y (biw-tiw)
Amylase/lipase, pancreatic enzymes	Y	Y (qw)
Na, K, Cl, Mg, PO_4, Ca	Y	Y (qd)
Albumin	Y	Y (biw-tiw)
Lipid profile (TG, HDL-C)	Y	Y (qd)
Creatinine	Y	Y (biw-tiw)
Urea	Y	Y (biw-tiw)
Blood routine		
Complete blood count	Y	Y (biw)
Hemoglobin	Y	Y (biw)
Leukocyte	Y	Y (biw)
Urine analysis		
Urine ketones	Y	Y (qd)
Monitoring when possible		
Serum concentrations of AEDs	Y	Y (biw-qw)
Serum minerals (ferritin, copper, etc.)	Y	Y (monthy)
Vitamins D 25-OH	Y	Y (monthy)
Folic acid	Y	Y (monthy)
Urine calcium and creatinine	Y	Y (monthy)
Serum carnitine profiles (free and total)	Y	Y (monthy)

N No, *Y* Yes

Correlations between the degree of ketosis achieved and the percentage of seizure reduction

Although the mechanism of KD is still unclear, KD is essentially a carbohydrate-limiting diet. As carbohydrate intake decreases, free fat acids (FAs) gradually replace glucose as a primary source of energy during KD intake. The ketone bodies produced from free FA oxidation can penetrate into the brain [25], and begin to be utilized as an energy source by the central nervous system when they achieve a concentration of about 4 mmol/l.

Therefore, theoretically there could be a significant correlation between the degree of ketosis and seizure reduction.

Studies on the relationship between ketosis and anti-seizure efficacy have come to conflicting results. We performed a correlation analysis based on the included patients and found no significant correlation between the level of ketosis and the anti-seizure effect in KD-PN (correlation coefficient = 0.138, $P = 0.384$). However, Dressler A et al. have found that there is a significant correlation between the degree of ketosis achieved and the percentage of seizure reduction ($P = 0.002$) [13]. We recommend that no further action is required once the patient shows clinical benefit such as seizure freedom [31].

Suitable FE product

Lipids are the most essential part of KD-PN for providing energy, and the choice of lipid may influence the clinical outcomes of critically ill patients. The FA chain length, and the presence, number and position of double bonds can affect the physical, physiological, and functional properties of the FAs [56]. Different FAs have different effects on physiological processes such as metabolism, inflammation, immune response, oxidative stress, blood coagulation, organ function and wound healing [56].

The most common commercially available types of FEs for PN are 50% medium chain triglycerides (MCT) + 50% soybean oil (SO), 80% olive oil (OO) and 20% SO, 100% SO, and 100% fish oil (FO). The pure SO may have some undesirable effects on physiological processes, such as promoting inflammation and suppressing immune function. So, it is no longer used as the main FEs in critically ill patients [34, 49]. The SO/MCT FEs are better than pure SO in critically ill patients [57], and have a stronger anti-seizure effect [38]. The FO has received most attention for research. It may decrease the length of stay in critically ill patients [46] and have liver-protective effects [58]. However, due to the low content of essential FAs content and the lack of experience in on application of FO alone, it is better not to use FO as the main FEs in KD-PN. We recommend the use of SO/MCT FEs as the main FEs if possible. The FEs of 80% OO and 20% SO can improve vitamin E status in patients, and could be a good choice.

Conclusions

Although KD-PN was first proposed in 1990, there have been only no more than 50 patients reported with KD-PN use. In addition, the prescription configuration, method of use, and contraindications of KD-PN have not been completely determined. However, existing studies have proved great potential of KD-PN in clinical use. More clinical studies are needed to verify the safety and efficacy of KD-PN.

Abbreviations

AAs: Amino acids; AEDs: Antiepileptic drugs; BMI: Body mass index; BMR: Basal metabolic rate; CBZ: Carbamazepine; CLB: Clobazam; CZP: Clonazepam; DAP: Diazepam; FAs: Fat acids; FEs: Fat emulsions; FO: Fish oil; IV: Intravenous; KD-PN: Ketogenic diet parenteral nutrition; LAP: Lorazepam; LCM: Lacosamide; LEV: Levetiracetam; LTG: Lamotrigine; MCT: Medium chain triglycerides; OO: Olive oil; OXC: Oxcarbazepine; PB: Phenobarbital; PGB: Pregabalin; PHT: Phenytoin; REE: Resting energy expenditure; SE: Status epilepticus; SO: Soybean oil; SRSE: Super refractory status epilepticus; TG: Triglyceride; TPM: Topiramate; VPA: Valproate; ZNS: Zonisamide.

Supplementary Information

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Additional file 1: Appendix S1. The algorithm of KD-PN.

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Authors' contributions

JM and DZ review conceptulization, YZ literature search and review, and design of computer-based algorithm (Additional file 1: Appendix S1). JM, DZ and YZ finished this study together. All authors read and approved the final manuscript.

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Consent for publication

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References

1. Cai M, Xu W, Zheng Y, Ding M. Ketogenic dietary therapy in adult status epilepticus: current progress and clinical application. Acta Epileptologica. 2022;4(1):16.
2. Lv RJ, Wang Q, Cui T, Zhu F, Shao XQ. Status epilepticus-related etiology, incidence and mortality: a meta-analysis. Epilepsy Res. 2017;136:12–7.
3. Ferlisi M, Shorvon S. The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. Brain. 2012;135(Pt 8):2314–28.
4. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus--Report of

the ILAE Task Force on Classification of Status Epilepticus. Epilepsia. 2015;56(10):1515–23.
5. Kantanen AM, Reinikainen M, Parviainen I, Ruokonen E, Ala-Peijari M, Bäcklund T, et al. Incidence and mortality of super-refractory status epilepticus in adults. Epilepsy Behav. 2015;49:131–4.
6. Wilder RM. The effect of ketonemia on the course of epilepsy. Mayo Clin Bulletin. 1921;2(2):307–8.
7. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342(5):314–9.
8. Martin-McGill KJ, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020;6(6):Cd001903.
9. Rosenthal E, Weissman B, Kyllonen K. Use of parenteral medium-chain triglyceride emulsion for maintaining seizure control in a 5-year-old girl with intractable diarrhea. JPEN J Parenter Enteral Nutr. 1990;14(5):543–5.
10. Jung DE, Kang HC, Lee JS, Lee EJ, Kim HD. Safety and role of ketogenic parenteral nutrition for intractable childhood epilepsy. Brain and Development. 2012;34(8):620–4.
11. Appavu B, Vanatta L, Condie J, Kerrigan JF, Jarrar R. Ketogenic diet treatment for pediatric super-refractory status epilepticus. Seizure. 2016;41:62–5.
12. Arayakarnkul P, Chomtho K. Treatment options in pediatric super-refractory status epilepticus. Brain and Development. 2019;41(4):359–66.
13. Dressler A, Haiden N, Trimmel-Schwahofer P, Benninger F, Samueli S, Gröppel G, et al. Ketogenic parenteral nutrition in 17 pediatric patients with epilepsy. Epilepsia Open. 2018;3(1):30–9.
14. Farias-Moeller R, Bartolini L, Pasupuleti A, Brittany Cines RD, Kao A, Carpenter JL. A practical approach to ketogenic diet in the pediatric intensive care unit for super-refractory status epilepticus. Neurocrit Care. 2017;26(2):267–72.
15. Peng P, Peng J, Yin F, Deng X, Chen C, He F, et al. Ketogenic diet as a treatment for super-refractory status epilepticus in febrile infection-related epilepsy syndrome. Front Neurol. 2019;10:423.
16. Roan M. Management of Long-Term Ketogenic Parenteral Nutrition. ICAN: Infant, Child, & Adolescent Nutrition. 2011;3(5):282–7.
17. Strzelczyk A, Reif PS, Bauer S, Belke M, Oertel WH, Knake S, et al. Intravenous initiation and maintenance of ketogenic diet: proof of concept in super-refractory status epilepticus. Seizure. 2013;22(7):581–3.
18. Lin JJ, Lin KL, Chan OW, Hsia SH, Wang HS. Intravenous ketogenic diet therapy for treatment of the acute stage of super-refractory status epilepticus in a pediatric patient. Pediatr Neurol. 2015;52(4):442–5.
19. Chiusolo F, Diamanti A, Bianchi R, Fusco L, Elia M, Capriati T, et al. From intravenous to enteral ketogenic diet in PICU: a potential treatment strategy for refractory status epilepticus. Eur J Paediatr Neurol. 2016;20(6):843–7.
20. Armeno M, Verini A, Araujo MB, Reyes G, Caraballo RH. Ketogenic parenteral nutrition in three paediatric patients with epilepsy with migrating focal seizures. Epileptic Disord. 2019;21(5):443–8.
21. Lowe H, Segal S, Mouzaki M, Langos V, Dlamini N. Successful Management of Ketogenic Parenteral Nutrition: a pediatric case study. JPEN J Parenter Enteral Nutr. 2019;43(6):815–8.
22. Baba S, Okanishi T, Ohsugi K, Suzumura R, Niimi K, Shimizu S, Sakihama H, Itamura S, Hirano K, Nishimura M, et al. Possible Role of High-Dose Barbiturates and Early Administration of Parenteral Ketogenic Diet for Reducing Development of Chronic Epilepsy in Febrile Infection-Related Epilepsy Syndrome: A Case Report. Neuropediatrics. 2021;52(2):133–7.
23. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, 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):175–92.
24. Hong Xin WL, Zhengliang Z, Zhenghai B. Expert consensus on diagnosis and treatment of acute pancreatitis with hypertriglyceridemia. Chinese Gen Pract. 2021;24(30):3781–93.
25. Paoli A, Bosco G, Camporesi EM, Mangar D. Ketosis, ketogenic diet and food intake control: a complex relationship. Front Psychol. 2015;6:27.
26. Kaul N, Laing J, Nicolo J-P, Nation J, Kwan P, O'Brien TJ. Practical considerations for ketogenic diet in adults with super refractory status epilepticus. Neurol Clin Pract. 2021;11(5):438–44.
27. Association DBoCM. Guidelines for the prevention and treatment of type 2 diabetes in China (2020 edition). Chinese J Diab. 2021;13(04):315–409.
28. Francis BA, Fillenworth J, Gorelick P, Karanec K, Tanner A. The feasibility, safety and effectiveness of a ketogenic diet for refractory status epilepticus in adults in the intensive care unit. Neurocrit Care. 2019;30(3):652–7.
29. Mahmoud SH, Ho-Huang E, Buhler J. Systematic review of ketogenic diet use in adult patients with status epilepticus. Epilepsia Open. 2020;5(1):10–21.
30. Hamdan M, Puckett Y. Total Parenteral Nutrition. In: StatPearls. Treasure Island: StatPearls Publishing. Copyright © 2020, StatPearls Publishing LLC.; 2020.
31. van der Louw E, Aldaz V, Harvey J, Roan M, van den Hurk D, Cross JH, et al. Optimal clinical management of children receiving ketogenic parenteral nutrition: a clinical practice guide. Dev Med Child Neurol. 2020;62(1):48–56.
32. Joosten K, Embleton N, Yan W, Senterre T. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: energy. Clin Nutr. 2018;37(6 Pt B):2309–14.
33. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109(1-2):1–9.
34. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40(2):159–211.
35. Schlein KM, Coulter SP. Best practices for determining resting energy expenditure in critically ill adults. Nutr Clin Pract. 2014;29(1):44–55.
36. Stapel SN, de Grooth HJ, Alimohamad H, Elbers PW, Girbes AR, Weijs PJ, et al. Ventilator-derived carbon dioxide production to assess energy expenditure in critically ill patients: proof of concept. Crit Care. 2015;19:370.
37. Frankenfield D. Validation of an equation for resting metabolic rate in older obese, critically ill patients. JPEN J Parenter Enteral Nutr. 2011;35(2):264–9.
38. Guangdong Pharmaceutical Association. Clinical Pharmacy Consensus on Parenteral Nutrition (Second Edition). Pharmacy Today. 2017;27(05):289–303.
39. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309(1):71–82.
40. Jochum F, Moltu SJ, Senterre T, Nomayo A, Goulet O, Iacobelli S. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: fluid and electrolytes. Clin Nutr. 2018;37(6 Pt B):2344–53.
41. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics. 1957;19(5):823–32.
42. Gao Chun LM, Junmin W, Yuzhen L, Weijun T. Expert consensus on clinical application of compound amino acid injection. Electron J Tumor Metab Nutr. 2019;6(2):183–9.
43. Zupec-Kania B PA, Aldaz V, et al: White Paper. Proceedings of Ketogenic Diet Therapies Symposium,March 2015. The Charlie Foundation for Ketogenic Therapies 2016 (Manhattan Beach, CA).
44. Stein J, Boehles HJ, Blumenstein I, Goeters C, Schulz R. Amino acids - Guidelines on Parenteral Nutrition, Chapter 4. Ger Med Sci. 2009;7:Doc24.
45. Lapillonne A, Fidler Mis N, Goulet O, van den Akker CHP, Wu J, Koletzko B. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Lipids. Clin Nutr. 2018;37(6 Pt B):2324–36.
46. Calder PC, Adolph M, Deutz NE, Grau T, Innes JK, Klek S, et al. Lipids in the intensive care unit: recommendations from the ESPEN expert group. Clin Nutr. 2018;37(1):1–18.
47. Bronsky J, Campoy C, Braegger C. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: vitamins. Clin Nutr. 2018;37(6 Pt B):2366–78.
48. Domellöf M, Szitanyi P, Simchowitz V, Franz A, Mimouni F. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals. Clin Nutr. 2018;37(6 Pt B):2354–9.
49. Adolph M, Heller AR, Koch T, Koletzko B, Kreymann KG, Krohn K, et al. Lipid emulsions - Guidelines on Parenteral Nutrition, Chapter 6. Ger Med Sci. 2009;7:Doc22.
50. Kolaček S, Puntis JWL, Hojsak I. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: venous access. Clin Nutr. 2018;37(6 Pt B):2379–91.
51. Kverneland M, Taubøll E, Molteberg E, Veierød MB, Selmer KK, Nakken KO, et al. Pharmacokinetic interaction between modified Atkins diet

and antiepileptic drugs in adults with drug-resistant epilepsy. Epilepsia. 2019;60(11):2235–44.
52. Madan PL, Madan DK, Palumbo JF. Total parenteral nutrition. Drug Intell Clin Pharm. 1976;10(12):684–96.
53. Cobo NH, Sankar R, Murata KK, Sewak SL, Kezele MA, Matsumoto JH. The ketogenic diet as broad-spectrum treatment for super-refractory pediatric status epilepticus: challenges in implementation in the pediatric and neonatal intensive care units. J Child Neurol. 2015;30(2):259–66.
54. Cervenka MC, Hocker S, Koenig M, Bar B, Henry-Barron B, Kossoff EH, et al. Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. Neurology. 2017;88(10):938–43.
55. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247.
56. Calder PC. Functional roles of fatty acids and their effects on human health. JPEN J Parenter Enteral Nutr. 2015;39(1 Suppl):18s–32s.
57. Iovinelli G, Marinangeli F, Ciccone A, Ciccozzi A, Leonardis M, Paladini A, et al. Parenteral nutrition in ventilated patients with chronic obstructive pulmonary disease: long chain vs medium chain triglycerides. Minerva Anestesiol. 2007;73(1-2):65–76.
58. Wang J, Yu JC, Kang WM, Ma ZQ. Superiority of a fish oil-enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: a randomized clinical trial. Nutrition. 2012;28(6):623–9.