A computer based algorithm for calculating ketogenic parenteral nutrition in refractory epilepsy

Ya Zeng[1], Hanrui Zheng[2],Ting Xu*, Jie Mu*

Author affiliations:

*Ting Xu: the corresponding author

postal address: No. 37, Guoxue Alley, Wuhou District, Chengdu City, Sichuan Province, China

e-mail: tingx2009@163.com

institutions: Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, China

*Jie Mu: the corresponding author

postal address:No. 37, Guoxue Alley, Wuhou District, Chengdu City, Sichuan Province, China

e-mail: somebody19951@hotmail.com

institutions: Department of Neurology, West China Hospital, Sichuan University, Chengdu, China

[1]Ya Zeng: First author

postal address: No. 37, Guoxue Alley, Wuhou District, Chengdu City, Sichuan Province, China

e-mail: 294507731@qq.com

telephone: 15682380735

institutions: Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, China

[2]Hanrui Zheng: Second author

postal address: No. 37, Guoxue Alley, Wuhou District, Chengdu City, Sichuan Province, China

institutions: Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, China

Word count: 3176(exclude author affiliations and references)

Abbreviation:

ESPGHAN: the 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

Abstract

Objective Ketogenic diet parenteral nutrition (KD-PN) has shown considerable effect in refractory epilepsy for the patients who can't enteral feeding. Objective was to evaluate the efficacy and safety of KD-PN in refractory epilepsy on the evidence-based perspective, clarify the detailed calculation method of KD-PN prescriptions, and create a new computer based algorithm for accurate component calculating, with promotion value to use in clinical.

Method RevMan5.4 was used to perform a systematic review and a meta-analysis of the efficacy and safety of KD-PN in refractory epilepsy. the primary outcome of the study is maintaining or achieving a reduction in seizures frequency ≥50%. Summarize parenteral nutrition(PN) guidelines (including ESPGHAN/ESPEN/ASPEN/GANM and the Chinese Parenteral Nutrition Clinical Pharmacy Consensus), Optimal clinical management of children receiving KD for epilepsy, and the instructions for each PN. To get the calculation formulas of daily requirements such as energy, fluid, amino acids, fat emulsion(FE), glucose, and trace elements; parameters (including height, weight, age, gender, etc.); and the relevant data such as the concentration and osmotic pressure of each PN in instructions. Enter all these contents into an Excel table to form a computer algorithm.

Result A total of 42 patients were included, with a mean(±SE) age 5.23±4.91years (range from 0.03 to 22 years).29 patients (69.05%) who have an ongoing enteral KD before can maintain the efficacy (P=0.30); 13 patients (30.95%) who initiated KD for the first time can achieve the efficacy of controlling seizures (P=0.005). There was no significant correlation between the degree of ketosis and the reduction of seizures (correlation coefficient=0.138, p=0.384). 21 patients (50%) developed transient hyperlipidemia without treatment, 4 patients stopped treatment for high triglycerides (TG,>1000mg/dl) or pancreatitis, and 1 patient (2.5%) died of sepsis.

Resting energy expenditure(REE) (kcal/d)=8.19×V_{CO2} (ml/min) was recommended for mechanically ventilated patients; and weight-based formula REE(kcal/d)=20~65×weight (kg) was recommended for the others, obese patients should be corrected with ideal body weight(IBW). The Holliday Segar formula is recommended for liquid calculation. the amino acid dosage (0.6-2.0g/kg/d) was influenced of different ages and diseases. Lipids start from 1-2g/kg/d and gradually increase to the maximum 4g/kg/d. The glycerol in FE, the ethanol and propylene glycol contained in some intravenous drugs (like phenobarbital, diazepam, etc.) should all be considered as carbohydrates. In the initial phase of KD-PN, it is not recommended to add additional glucose in order to achieve ketosis as soon as possible. In principle, vitamins and electrolytes should be given every day. Monitor blood sugar, blood lipids, electrolytes, etc. daily to adjust the specific dosage of each nutrient.

Conclusion Our study proved efficacy and safety of KD-PN in refractory epilepsy from an evidence-based perspective. In addition, a computer algorithm of KD-PN has been built to assist clinicians in formulating an individualized plan for intravenous ketosis treatment in a concise manner.

Keywords: computer based algorithm ;epilepsy; parenteral nutrition ketogenic diet

1. Introduction

1.1 Ketogenic diet in epilepsy

Epilepsy is the most prevalent neurologic condition, affecting approximately 45.9 million people worldwide in 2016[1]. Approximately 30% of people with epilepsy will continue to have seizures even when taking multiple antiepileptic drugs (AEDs)—referred to as drug-resistant epilepsy(DRE)[2]. In addition, uncontrolled refractory status epilepticus(RSE) or super-refractory status epilepticus(SRSE) with mortality rate of RSE and SRSE is about 17%-23%[3,4] and 30%-50%[5-7] are likely to be a strong risk factors of death in epilepsy. There are four treatment options available for DRE, namely medication, KD, neurostimulation devices and epilepsy surgery.

Ketogenic diet (KD) is a high-fat, low-carbohydrate diet that mimics the metabolic changes occurring during starvation[8] and has 4 main forms currently[9]. It's an available way for DRE, and it increased in popularity in the early 90s[10] and is well-established, effective and affordable alternative interventions for DRE patients. KD has been shown particular effect in certain epilepsy syndromes, such as Lennox-Gastaut syndrome(LGS), Dravet syndrome, febrile infection-related epilepsy syndrome (FIRES)[9,11] and RSE/SRSE [2,7,12-16].

1.2 Ketogenic diet parenteral nutrition in epilepsy

To maintain or achieve the level of ketosis and anti-seizure effect, patients who cannot be enterally fed (such as severe illness with gastrointestinal affection, food refusal, transient intestinal failure and requiring complete bowel rest for surgery)[11], may require intravenous (IV) KD administration. Ketogenic diet parenteral nutrition (KD-PN) was first applied in 1990. And since Tarrant, S. L et al[17] reported a case about a girl who had successful maintenance of ketosis using parenteral nutrition(PN) therapy in 64th Annual Meeting of the American Epilepsy Society in 2010, there were reports of successful use of KD-PN almost every year.

1.3 Indication and contraindications of KD-PN

In general, indications and contraindications for KD-PN and enteral KD are similar[15].

For most patients, the aim of KD-PN is to maintain the level of ketosis and anti-seizure effect when enteral KD is not possible. it also be applied for the initiation of the KD in patients who continue to have seizures after multiple AEDs and anaesthetics[18-21], especially in RSE/SRSE. It also can be a bridge to the enteral KD in the immediate postoperative period in patients who underwent surgery and in whom the enteral route is temporally contraindicated[11].

The absolute contraindications of KD-PN including: disorders of fat metabolism[9]; severe metabolic abnormalities or instabilities (serum TG>11.3mmol/L, serum cholesterol>25.9mmol/L[14,22], serum sodium concentration <125 mEq/L[23], etc); some disease states(severe liver or kidney failure[24,25], Pancreatitis[14,26,27], critical cardiovascular instability[28], etc); and propofol concurrent use or on propofol within 24 h[24,29]

2 Efficacy and safety of KD-PN on evidence-based perspective

In order to evaluate the efficacy and safety of KD-PN in refractory epilepsy on the evidence-based perspective, summarize the use protocols and influent factors of KD-PN, We performed a systematic review and a meta-analysis of the efficacy and safety of KD-PN in refractory epilepsy by RevMan5.4 software, analyzed date and the influent factors of KD-PN by SPSS25.0 software.

2.1 method

This study is jointly participated by doctors and pharmacists to strengthen cooperation. We screened patients according to the flow diagram of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Study selection searched The Cochrane Library, PubMed ,EMbase , Web of Science, Google Scholar, China National Knowledge Infrastructure(CNKI), WanFang Date (published between January 1, 1990, and March 1, 2021). The terms ketogenic, parenteral nutrition or intravenous KD, epilepsy or epilepticus were searched under the medical subject headings (MeSH) terms. Due to the comparison method is different, we divide patients into two groups by whether had an ongoing enteral KD before (table 2). the primary outcome of the study is maintaining or achieving a reduction in seizures frequency ≥50% [30]. The secondary outcome is maintaining or achieving target level for clinically relevant ketosis defined as β-hydroxybutyrate(β-HBA) plasma level of ≥2 mmol/L or urine ketones≥3+ during KD-PN. studies reported our primary outcome were included in the analysis. Safety outcomes included the proportion of adverse reactions(AEs), AEs which are too severe to stop treatment, and deaths.

table 1 the primary and secondary outcome of patients in 2 conditions

Group	the primary outcome	The secondary outcome
A: Patients who had an ongoing enteral KD before	maintaining the reduction in seizures frequency≥50%	maintaining target level for clinically relevant ketosis
B: Patients who initiated KD for the first time	reducing seizures frequency ≥50%	achieving target level for clinically relevant ketosis

2.2 Results

2.2.1 general condition

A total of 266 articles were retrieved, and 13 articles were included in the systematic review finally(5 retrospective studies[20,27,30-32] and 8 case reports[11,21,33-38]). The mean(±SE) age was 5.23±4.91years (range from 0.03 to 22 years). The mean(±SE) duration KD-PN was 8.00±9.00d (range from 1 to 41d), and the mean(±SE) follow-up duration was 10.75±7.44months (range from 4 to 29 months). Of all patients, 69.05% (29/42) patients were aim of maintaining the reduction in seizures frequency≥50% and ketosis the previously achieved. the KD-PN is applied for the initiation of the KD with the aim of reducing seizures frequency and achieving ketosis for the others.

2.2.2 Efficacy of KD-PN in epilepsy

We divide all patients into group A(who had an ongoing enteral KD) and group B(who initiated the KD) . The forest plots of the anti-seizure effect and level of ketosis before and after KD-NP therapy were shown in Figure 1 and Figure 2. No significant difference of the anti-seizure effect between before and after KD-NP therapy was found in group A [OR=2.31 ,95% CI(0.51, 8.94), P=0.30], and significant difference in group B [OR=0.11 ,95% CI(0.02, 0.51), P=0.005]. significant difference of the ketosis level between before and after KD-NP therapy in both of them. It means that KD-NP therapy can achieve the anti-seizure effect and ketosis effectively, but can only maintain ketosis in patients who initiated the KD.

Figure 1a Treatment response before and after KD-NP therapy in patients who had received the KD

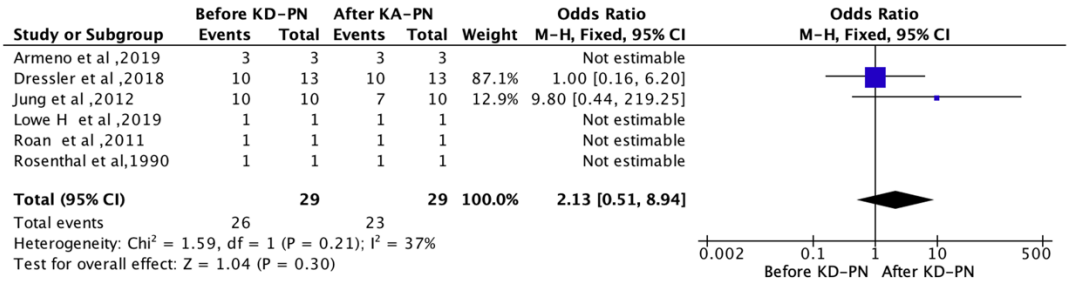

Figure 1b Treatment response before and after KD-NP therapy in patients initiated the KD

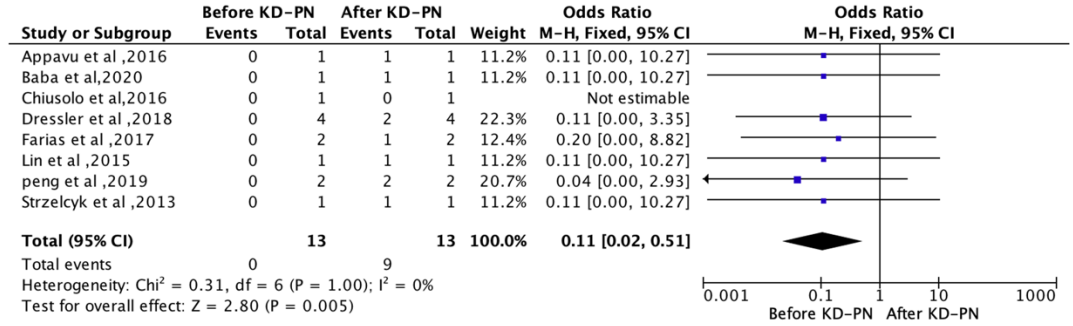

Figure 1 The forest plot of treatment response before and after KD-NP therapy

Figure 2a Clinically ketosis before and after KD-NP therapy in patients who had received the KD

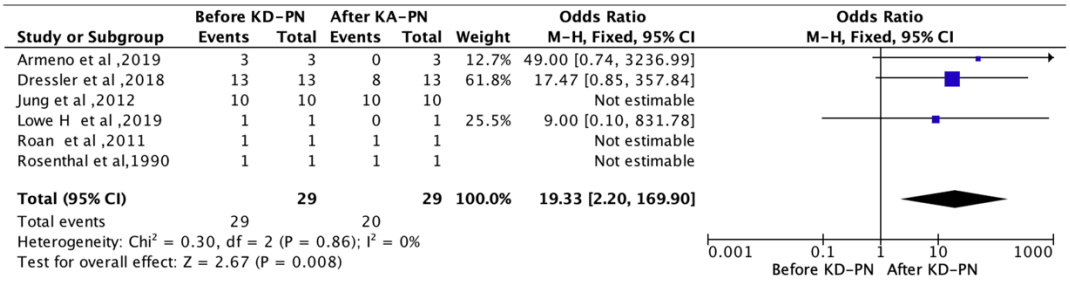

Figure 2b Clinically ketosis before and after KD-NP therapy in patients initiated the KD

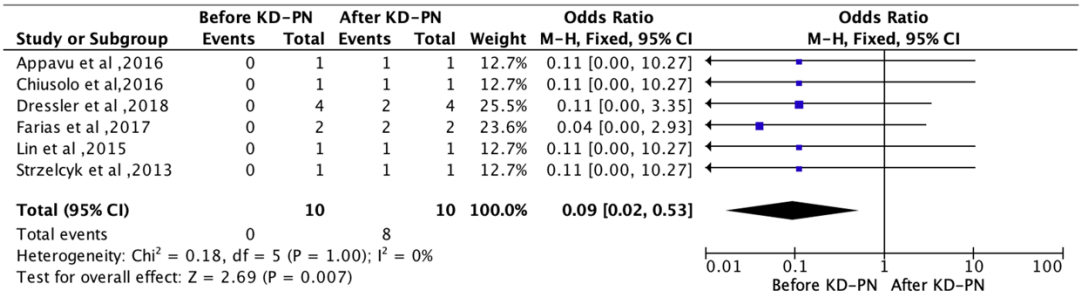

Figure 2 The forest plot of clinically relevant ketosis before and after KD-NP therapy

2.2.3 Safety of KD-PN in epilepsy

25 patients (62.5%) experienced hyperlipidemia, 4 patients of them are discontinuation for too high triglyceride(TG, >1000mg/dl) or pancreatitis. 7 patients (17.5%) had an increase in liver enzymes. 5 patients (12.5%) increased levels of amylase and lipase. 4 patients (10%) had an increase in lactate dehydrogenase. 1 patients (2.5%) had sepsis and finally died[33].

2.2.4 correlation between the degree of diet ratio and the anti-seizure effect

There is no significant correlation between the level of ketosis and anti-seizure effect in KD-PN

(correlation coefficient=0.138, p=0.384) in our review.

3 Formulas for accurate component calculating

To create a new computer based algorithm for accurate component calculating, with promotion value to use in clinical. we summarized ESPGHAN/ESPEN/ASPEN/GANM guidelines and the Chinese Parenteral Nutrition Clinical Pharmacy Consensus, optimal clinical management of children receiving KD for epilepsy and the studies above.

3. 1 Energy

Generally, basal metabolic rate(BMR) is the most important part for KD-PN patients, resting energy expenditure (REE) is usually applied BMR [39]. Indirect calorimetry(IC) is the most preferable way to estimate energy requirements, but the applicability of IC is limited in clinic by availability and cost. We recommended a formula REE(kcal/d) $=8.19\times V_{CO2}$ (ml/min) for mechanically ventilated patients(most mechanical ventilators provide the option to measure V_{CO2}) [40]; a weight-based formula for the others(table 2), and obese patients[body mass index(BMI)>30kg/m^2][41,42] should be corrected with ideal weight .

Table 2 Energy requirements (kcal/kg/day) for PN 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		20-25

3.2 fluid

In 1957, Holliday Segar proposed a rehydration method based on calorie consumption and still be used today[43-45] (Table 3). The volume of PN is limited by the volume required to dilute drugs.

Table 3 Holliday Segar formula

weight	goal
0-10kg	100mL/kg/d
10-20kg	1000mL+50mL/kg*(x-10)
>20kg	<50 year :1500mL+20mL/kg*(x-20)
	>50 year :1500mL+15mL/kg*(x-20)

3.3protein

The amino acids(AAs) intake of 1.0-2.0 g/kg/d may be considered for most patients. Calculating the amino acid dosage according to the different situation for patients[46] (table 4). An intake of 0.5g/kg to 0.8g/kg for short-term use might be acceptable[13,47].

Table 4 protein requirement in different patients

patient	protein requirements(g/kg/d)
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
older	1.2-2.0

3.4 Lipids

Lipids is them most important part in KD-PN. ESPEN[42,48,49]recommended that parenteral lipid intake should not exceed 4g/kg/d in infants,3 g/kg/day in children and 1.5-2g/kg/d in adults. the White Paper[13] and the guideline[15] agree that maximum of 4g/kg/d lipid in KD-PN. we recommends KD-PN starting with 1-2g/kg/d(or 50% of goal lipids) to 3g/kg/d advancing to 4g/kg/d, increase lipids every 1–2d.

3.5 Carbohydrates

In the first 2 days of KD-PN, in order to achieve ketosis as soon as possible, it is not recommended to add additional glucose when serum glucose>50mmol/L[6,24,34,50] fat emulsions(FEs) contain glycerol, which contributes to the carbohydrate content of the PN. IV drugs such as phenobarbital (PB), diazepam(DAP), lorazepam(LAP), phenytoin (PHT) which deliver carbohydrates by dissolvent should also be considered, they contain propylene glycol and alcohol and deliver about 30kcal/d by carbohydrate.[13] we find it is feasible and encode it in our computer-based algorithm.

3.6 Electrolytes, vitamin and mineral

Electrolytes such as serum sodium(Na),calcium(Ca), potassium(K), magnesium(Mg), chlorine(Cl) and phosphorus(P), and vitamins which can be divided into the lipid soluble (vitamin A, D, E, K) and water soluble (vitamin B and C) are essential for a body. they should be administered daily if possible except vitamin K which can be given weekly. Trace minerals are inorganic micronutrients with main 9 kinds: namely, zinc, copper, selenium, iron, molybdenum, chromium, manganese, iodine and fluorine. supplementation of trace minerals is considered unnecessary for generally short-time of KD-PN. the actual requirements must be adjusted according to the clinical situation, such as gastrointestinal loss, kidney failure dehydration, excessive water losses or some laboratory index[51].

3.7 Infusion route and osmolar

PN's infusion route can be divided into peripheral venous catheter (PVC) and central venous catheter (CVC). CVC is generally required to maintain long term venous access (>2 weeks[45]). PVC is suitable for short-term treatment of nutrient solution with lower osmotic concentration(≤900 mOsm/L for all patients)[52,53]. the osmolarity of the PN solution (mOsm/L) =[(glucose (g) × 5mOsm/g + fat (g) × 1.3~1.5 mOsm/g + AA (g) × 10 mOsm/g + alanyl glutamine (g) × 5 mOsm/g

+ electrolytes (mEq)×1mOsm/mEq + elements×19 mOsm/ bottle]/total liquid volume (L)[45]. our computer-based algorithm incorporates detailed data from the drug insert.

3.8 Infusion times

The KD-PN infused continuously over 16 h and then interrupted for 8 h during the night with glucose-free solution such as half saline everyday in most studies[11,18,27,54], while the others infused continuously over 12h[34], 20h[20,31] and 24h[21,38](Figure 5c). In KD-PN, total infusion rate is limited by the infusion rate of FEs(< 0.15[6,34] to 0.2[38] g/kg/h) and glucose (< 0.12g/kg/h) [34]. Infusion time of FEs should be administered over at least 12 hours each day[22], slower infusion rates such as continuous infusion over approximately 24 hours when a more critical metabolic situation[22].

4 monitoring and modification

According to the guidelines and studies above, we have summarized examination of effectiveness and safety, and treatment methods(table 5).

Table 5 baseline examination and monitoring during KD-PN

item	examination	treatment
Blood gas(serum CO2)	Y(qd)	bicarbonate 1~3mEq/kg/d, split bid[30]for patients whose < 16mmol/L[32,54]
Electroencephalogram (EEG)	Y(qd)	the main criteria for evaluating the effect of KD-PN
comprehensive metabolic panel		
serum glucose	Goal range:55-79mg/dl	
	<50mg/dl, repeat in 3h	0.25 g/kg dextrose 10% solution
	<45mg/dl, repeat in 1h	
serum β-HBA	Y(qd), Goal range: 2-5mmol/L[32]	
	<1.5mmol/L	increase FE[15]
	>6.5mmol/L	reduce FE[11,15]
AST ,ALT	Y (biw-tiw), >3 upper normal limit	reduce FE[55]
γ-glutamyl transpeptidase(GGT)	Y (biw-tiw), >1.5 upper normal limit	reduce FE[55]
direct bilirubin	Y (biw-tiw), > 2 mg/dL	reduce FE[55]
amylase/lipase, pancreatic enzymes	Y (qw)	reduce FE[55]
Na, K, Cl,Mg,PO4,Ca	Y(qd)	dosage is determined as required
Lipid profile(TG,HDC-C)	Y (qd)	
	TG > 1000 mg/dl	stop KD-PN
	TG > 400 mg/dl	reduce FE
	TG >200mg/dL	carnitine 50mg/kg ,<1g/d[56]

Urine analysis	
Urine ketones	Y(qd), Goal range>3+

5 Discussion

5.1 KD in epilepsy

KD was first applied in 1921 by Wilder[57], gradually developed during the 100 years(figure 3).

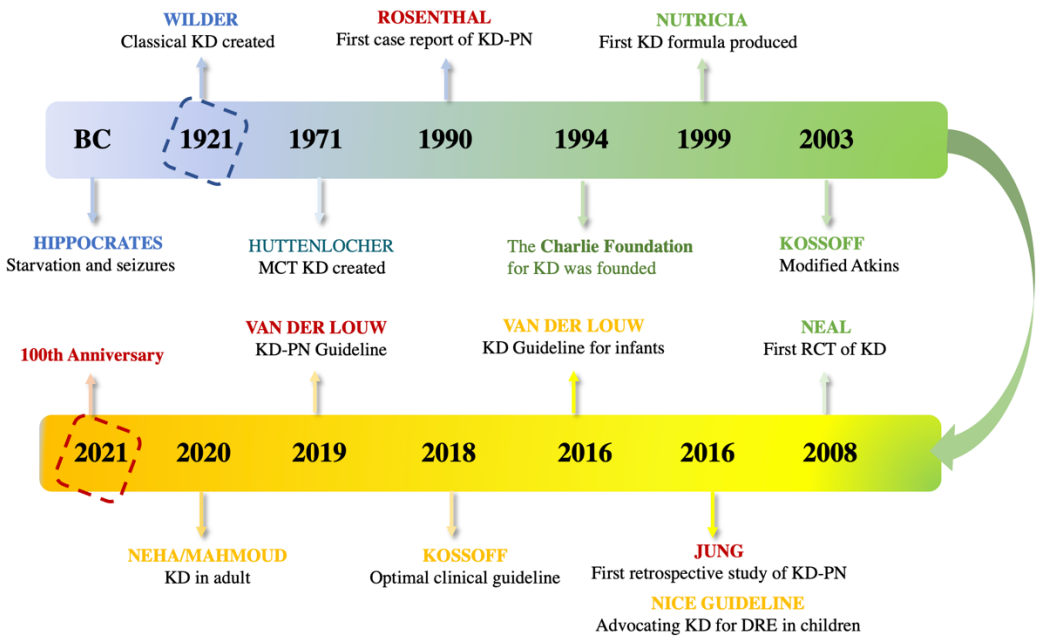

Figure 3 the history of KD

5.2 correlation between the degree of diet ratio and the anti-seizure effect

The principle of KD is the ketone bodies(KBs) by FFAs oxidation can penetrate into brain as major source [58]. so there could be a significant correlation between the degree of ketosis and seizure reduction in theory. But our result shows there is no significant correlation between the level of ketosis and anti-seizure effect in KD-PN (correlation coefficient=0.138, p=0.384). The literatures about the direct correlation of them are conflicting. More studies are needed to prove this.

5.3 The diet ratio of KD-PN

Providing more than 60% of total energy as fat in PN increases likelihood of ketosis[34],the goal ratio for the KD(4:1) may be difficult to achieve in most KD-PN patients[5,11]. The diet ratio of each studies vary widely, and the mean(±SE) diet ratio is 2.78(±1.35):1(range from 0.57:1 to 4:1). We divided the patients into 3 groups according to the diet ratio(Figure 4), there was no correlation between the degree of diet ratio and the anti-seizure effect (correlation coefficient = 0.036; p = 0.822) , but was a significant correlation with TG level (correlation coefficient = 0.559; p = 0.031) . That may due to KD-PN leads to a greater effectivity of IV lipids than enteral KD without fat absorption and increases the risk of transient elevation of TG, liver enzymes, lipid profiles, and pancreatic enzyme concentrations than enteral PN [11,32]. So the goal ratio for the enteral KD(4:1) is not necessary in most KD-PN patients[5,11]. We recommended KD-PN began with a 1:1 ratio by weight at the first day with 50% of the EENs, increase every 1–2 day to the highest ratio in a week[15].

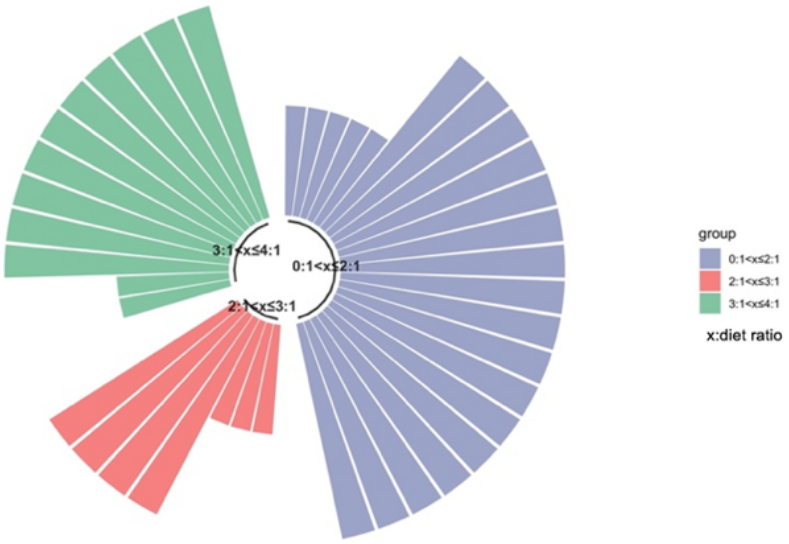

Figure 3 The diet ratio and anti-seizure effect in patients

Remarks: group1 with diet ratio range from 0:1 to 2:1, group2 with diet ratio range from 2:1 to 2:1,and group3 with diet ratio range from 3:1 to 4:1. Each line represents a patient. The blue line represents diet ratio between 0:1 to 2:1(including 2:1); The red line represents diet ratio between 2:1 to 3:1(including 3:1); The green line represents diet ratio between 3:1 to 4:1(including 4:1). The long line represents seizures controlled, the short line represents no improvement

5.4 the protocols of KD-PN

There are about 2 protocols for KD-PN. The calorie intake was always restricted to 50% of the estimated energy needs(EENs) due to the worrisome development of hypertriglyceridemia with increased infusion of lipids in 4 studies[11,21,27,33]; while the others restricted to 50% or 1/3 of the EENs initially, then increased gradually[18,20,31,34,38,54].

Most studies don't list the detailed calculation method and protocol of KD-PN, so our data is incomplete. Our result found that patients who initiated KD are more likely to increase over the next few days from a small dose. Avoiding over-nutrition is important(full targeted medical nutrition therapy is considered to be 70%-100% of resting energy expenditure, especially in acute phase)[42,59]. And the energy goal should be achieved progressively.

The duration of infusion of KD-PN is at least 12h, The duration depends on infusion rate and the total dose daily. in acutely ill patients, lipid infusion should be administered over at least 12h, and with a more critical metabolic situation, slower infusion rates such as continuous infusion over approximately 24 hours are recommended[22].

6 conclusion

Our review show promising results for the use of KD-PN in epilepsy. And the composition of the KD-PN was calculated individually for each patient using a computer-based algorithm(Appendix S1) based on guidelines and the studies. However, the small sample sizes, limited number of studies with short-term follow-up, result in a low to very low overall quality of evidence. Due to these reasons, the detailed information of KD-PN protocol need further large-scale and prospective

studies to confirm.

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