Original Article

Growth and nutritional status of pediatric patients treated with the ketogenic diet

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Background and Objectives: Ketogenic diet (KD), a well-known nonpharmacologic treatment of intractable epilepsy, could adversely affect growth and nutritional status; however, such data are limited in Thailand. This study aimed to assess growth and nutritional status of Thai children treated with KD together with dietary adherence and its related factors. **Methods and Study Design:** The records of children treated with KD for more than 1 month between January 2009 to September 2020 were reviewed. Weight, height, and biochemical indices were retrieved at baseline, 1, 3, 6, 12, 18, and 24 months. Type of KDs, compliance and adverse effects were extracted. **Results:** Forty-eight patients (21 male) were enrolled. Median age was 3.5 years (IQR 0.9, 10.1). There was no significant decrease in weight-for-age z-score (WAZ) despite a trend toward minimal reduction in WAZ at 3 months. Median follow-up time was 13 months (IQR 7, 29.5). Height-for-age z-score (HAZ) significantly decreased at 12 months [median -1.55 (IQR -3.35, -0.43) vs baseline median -0.6 (IQR -2.07, 0.29)]. Adherence of KD in tube feeding patients was better than oral feeding. Thirty seven percent (18/48) of the patients continued the diet beyond 2 years. Early discontinuation before 6 months was mostly due to poor compliance from patients and families (6/11, 55%). Common adverse effects were GI problems (77%), dyslipidemia (64%) and hypercalciuria (29%). **Conclusions:** Under close monitoring, KD can be administered in Thai children with minimal adverse effects on growth and nutritional status. Adherence depends on route of feeding, clinical response, and cooperation of the families.

Key Words: ketogenic diet, compliance, adverse effects, growth, nutrition

INTRODUCTION

Epilepsy affects approximately 0.5-1% of all children through the age of sixteen.[1] Although the major treatment for epilepsy is antiepileptic drugs, one-quarter of the patients suffered from unsuccessful response to multiple anti-epileptic drugs (AEDs).[2,3] Consideration of additional therapies, including epileptic surgery, neuromodulation or dietary therapy has been proposed to be a better option for drug-resistant epilepsy.[3,4]

The ketogenic diet (KD), a high-fat, low carbohydrate and adequate-protein diet has been established since 1921.[5] Wilder introduced the concept that high-fat diet can induce ketosis and ketone bodies is an alternative fuel source for the brain, which may be anticonvulsant.[5-7] There are currently 4 major ketogenic diet treatments: the classic KD, the modified Atkins diet, the medium chain triglyceride diet (MCT), and the low glycemic index treatment.[8] In the past, KD was reserved as a "last treatment option" for medical intractable seizure but nowadays, KD treatments could be considered earlier as an option for treatment of patients who fail 2 or more antiepileptic medications.[9-11] Currently KD is one of the most well-known non-pharmacologic treatment for children with intractable epilepsy.[8,12] Before starting KD, it is crucial to discuss family psychosocial status, complications, and co-morbidities of this treatment such as nausea and vomiting, constipation, kidney stones, dyslipidemia, and osteopenia.[8,13,14] Despite KD being proven as beneficial for seizure control, this treatment could adversely affect growth and nutritional status due to caloric restriction and prolonged ketosis.[15,16] Moreover, many children may have preexisting malnutrition from concurrent neurodisability which may be aggravated by the restrictiveness of the KD. Previous studies abroad found that KD had significant negative effects on weight-for-age z score (WAZ) and height-for-age z score (HAZ) in pediatric patients.[17-21] In Thailand, data regarding growth, nutri-

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Manuscript received 12 March 2021. Initial review completed 02 April 2021. Revision accepted 05 May 2021.
doi: 10.6133/apjcn.202106_30(2).0007

tional status, and long-term adverse effects of this treatment modality is still limited. The objectives of this study were to assess growth and nutritional status of children treated with KD and to determine adverse effects and factors affecting dietary adherence of this dietary treatment.

METHODS

Study participants were pediatric patients treated with KDs between January 2009 to September 2020 in the Pediatric Nutrition Division at King Chulalongkorn Memorial Hospital. This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB number 482/62). The study included all pediatric patients aged less than 18 years at the start of KD. Patients who were on the KD for less than 1 month were excluded.

Data collection

Data of all patients were extracted from retrospective review of medical records and electronic database. Clinical status, anthropometric data (weight and height), biochemical indices were collected at baseline, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months after treatment with KDs. Reduction in seizure frequency was assessed by the medical record review at baseline and 3 months visit. All patients had their seizure frequency recorded in the medical record from parents' interview as well as seizure diary. These extracted blood test results were analyzed according to the hospital standard protocol. Serum beta-hydroxybutyrate was measured by methodology electrochemical biosensor (FreeStyle Optium Neo, Abbott Laboratories before 2018 and XPER Technology Procheck Advance, TaiDoc Technology Corporation from 2018 onward). Urinary analysis was performed by automated urine chemistry analyzer UF 3500 (Systemex) for which urine ketones were tested by sodium nitroprusside.

KD regimens

Ketogenic diet administration followed the internal standard protocol of the Pediatric Nutrition Division. The different types of KDs in this study consisted of the classic KD, the medium chain triglyceride (MCT) diet as well as modified MCT KD. All patients were supplemented with sugar-free multivitamin, trace elements, calcium, magnesium, phosphorus, and other electrolytes. After consultation from the Neurology team, the decision whether each patient would receive a classic vs MCT KD was made by the Nutrition team according to clinical status and family circumstance. The caregivers were taught and trained on how to interchange food items within the prescription and to keep a seizure frequency and urine ketone diary to monitor the compliance and effect of KD. They were also trained on how to avoid extra carbohydrate intake from snacks and medications. The diets were fine-tuned according to the nutritional status and seizure control during each follow-up visit by the Nutrition and Neurology teams.

Statistical analysis

Weight-for-age z-score (WAZ), Height-for-age z-score (HAZ), and BMI-for-age z-score (BMIAZ) were calculated according to the WHO child growth standards and reference using WHO AnthroPlus program. All parameters were compared between the baseline, 1 month, 3 months, 6 months, 12 months, 18 months, and 24 months timepoints by using Generalized Estimating Equation (GEE) with linear model. Proportion of abnormal lipid and uric acid profiles during each follow-up were compared to baseline by Mc-Nemar's test. Probability of KD discontinuation was analyzed by Kaplan-Meier curve and the log rank test was used to compare between route of feeding. All the analyses were done by the STATA statistical software version 15.1. A p-value <0.05 was considered to be statistically significant.

RESULTS

Subjects

Sixty-two patients were identified from the records of the Pediatric Nutrition Division between January 2009 to September 2020. Fourteen patients were excluded from this study due to short duration (less than 1 month) of KD treatment (reasons: short-term parenteral KD, death unrelated to KD, loss follow-up, poor oral compliance and change to epileptic surgery). Therefore, forty-eight patients (21 male and 27 female) were reviewed in the study. Most patients were between 1 and 5 years old; median age was 3.5 years (IQR 0.9, 10.1). There was no difference in terms of gender and type of KD distribution between the different age groups. There was a trend towards a higher proportion of tube-fed patients among younger (<5 years old) age groups (23/28, 82.1% vs. 9/20, 45%; p <0.05). Table 1 presents composition of the ketogenic diet regimens that prescribed to the patients. Most patients reported to receive no less than 85% of their target energy requirement for age and gender whereas all patients had no less than 100% of their protein requirement according to the Thai Dietary Reference Intake (DRI). As expected, patients received classic KD had higher fat ratio and lower energy from carbohydrate than those received MCT KD. MCT KD allowed for increase carbohydrate and protein intake thus resulted in more food choices. Classic KD required higher KD ratio to achieve adequate ketosis [median of classic KD 3.27 (range 2.8, 4) vs. MCT KD 2 (1.2, 2.9) vs. modified MCT KD 2.1 (1.8, 2.3)]. Example of diet compatible with Thai dietary tradition are shown in Table 1. Two-thirds of the patients (16/48) were orally fed entirely. Nearly half of the patients (22/48) started the diet during an elective admission for the purpose of KD initiation whereas the rest were put on KD due to status epilepticus and uncontrolled seizure during other hospital admission. Diagnosis included Lennox-Gastaut Syndrome (n=10), unspecified intractable epilepsy (n=12), early infantile epileptic encephalopathy (EIEE) (n=7), focal cortical dysplasia (n=6), infantile spasm (n=2), herpes encephalitis (n=2), Hashimoto encephalitis (n=2), and each of the following: anti-NMDAR encephalitis, ADEM, tuberous sclerosis, pyridoxine dependent seizure, and ferro-cerebro-cutaneous syndrome. Two patients were put on KD due to inborn errors

Table 1. Composition of the classic and MCT KDs prescribed to the patients

Type of diet	% Energy from fat		% Energy from carbohydrate	Protein intake (g/kg/day)	Protein intake (%DRI)	Energy intake (% DRI)	Ketogenic ratio (K:AK)	Example of typical diets for Thai culinary culture
	MCT	LCT						
Classic KD (n=8, all tube-fed)	0	87.4 (81-90)	4.35 (1-7.2)	1.2 (1-2.4)	100 (83.3-160)	89.9 (78.2-104)	3.27 (2.8-4)	Blendarized fish meat, chicken breast, egg white, rice bran oil, vegetables
MCT KD (n=35)	50 (40-56)	32.4 (24-40)	9 (4.5-15)	1.7 (1-3.4)	114.2 (66.7-186)	91.9 (68.3-114)	2 (1.2-2.9)	Blendarized fish meat, chicken breast, egg, rice bran oil, MCT oil, vegetables for tube-fed patients OR Three meals of steam rice/porridge (half portion) together with stir-fried meats with vegetables/fried eggs Two servings of MCT containing sip drink (coconut milk substitute/cocoa) Minimal carbohydrate containing snacks such as fried seaweed/vegetable leaves, cashew nuts
Modified MCT KD (n=5)	38 (30-40)	42.2 (31.2-46.7)	10.5 (8.6- 12.5)	2 (1.6-2.4)	138.9 (115-142)	105.3 (61.4-125)	2.1 (1.8-2.3)	

MCT: medium chain triglyceride; LCT: long chain triglyceride; DRI: dietary reference intake; K: AK: ketogenic: anti- ketogenic; KD: ketogenic diet.
†All data were presented as median (range).

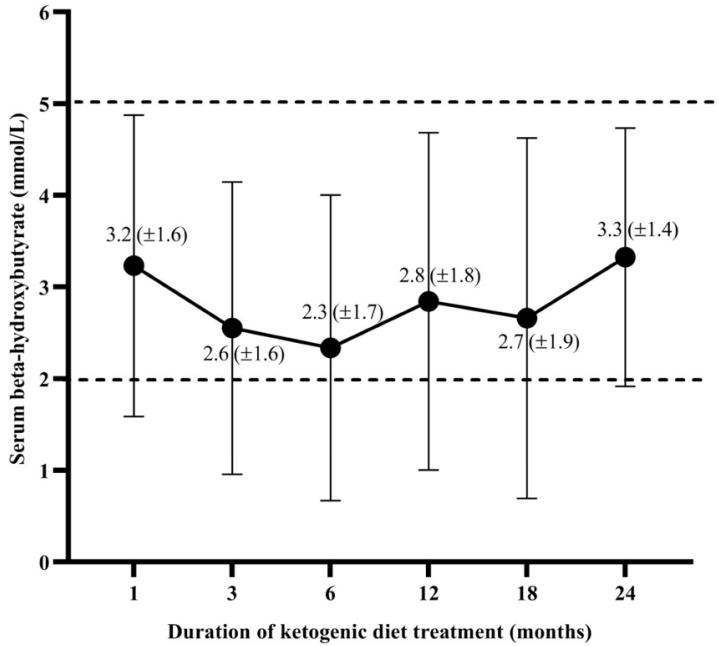

Figure 1. Means and SDs of serum beta-hydroxybutyrate during 2-year follow-up. Number of patients at 1, 3, 6, 12, 18, and 24 months were 20, 19, 13, 14, 8, and 7, respectively due to serum beta-hydroxybutyrate analysis has been available at KCMH after 2015. Dashed lines show expected therapeutic range of serum beta-hydroxybutyrate for KD treatments.

of metabolism namely, Glucose Transporter-1 (GLUT-1) deficiency and pyruvate dehydrogenase deficiency. Seventy-eight percent of patients (37/48) received more than 2 AEDs at the start of KD treatment. Four percent (2/48) started KD due to underlying disease and did not receive any AED.

Efficacy of the KD

Eighty-four percent of the patients (39/46) had more than 50% reduction in their seizure frequency after 3 months of KD treatment. Means and SDs of serum beta-hydroxybutyrate at any time-point of follow-up are shown in Figure 1. Most patients maintained serum beta-hydroxybutyrate within the therapeutic range. However, urinary analysis revealed that the proportion of patients who had urine ketone level greater than 2+ (80 mg/dL) during 1, 3, 6, 12, 18, and 24-months follow-up were 64%, 55%, 60%, 75%, 58%, and 56%, respectively.

Growth parameters

Figure 2 shows the comparison of WAZ, HAZ and BMIAZ at baseline and after KDs. There was a trend toward WAZ reduction at 3 months compared to baseline while WAZ after 3 months follow-up tended to increase after KD treatment. GEE showed no statistically significant changes in WAZ at baseline compared with any time-point during the 2-year follow-up. There was also a non-significant trend towards the decrease in HAZ from starting KD until the end of treatment. HAZ significantly decreased at 12 months compared to baseline [median -1.55 (IQR -3.35, -0.43) vs. -0.6 (-2.07, 0.29)]. BMIAZ significantly increased onwards from 12, 18 to 24 months follow-up [-0.09 (-1.25, 0.91), -0.11 (-1.4 to 0.18), -0.68 (-1.46 to 0.72) vs. baseline -1.19 (-1.88, -0.07)].

Biochemical indices and nutritional status

There was no significant change in hemoglobin (Hb), hematocrit (Hct), platelet number, BUN, creatinine, electrolytes, and liver function compared to baseline by GEE model. All types of diet had no statistically significant effect on lipid profiles (total cholesterol, LDL, HDL, triglyceride) analyzed by Mc-Nemar's test (data not shown). At baseline, 38% of patients had hypertriglyceridemia and after treatment with ketogenic diet, the proportion of patients with hypertriglyceridemia were elevated but not statistically significant. The highest proportion of those with hypertriglyceridemia was found at 3 and 6 months after the start of KD which were 14/22 (63.6%) at both time-points. There was an increase in prevalence of hyperuricemia (above cut-off for age, 10.9% at baseline) at 1 month and 18 months follow-up. [71.4% (10/14) at 1 month, p=0.04 and 46.2% (6/13) at 18 months, p=0.03). Hypercalciuria at any time-point was revealed in 29% (14/48) of the patients. None of their renal ultrasound surveillance demonstrated renal or ureteric stones.

Adverse effects and dietary adherence

The longest duration of KD treatments in this study is 129 months and median follow-up time was 13 months (IQR 7, 29.5). Dietary adherence of tube feeding patients was significantly better than oral feeding from start until the end of the study but there were no significant differences between type of KD treatments (Figure 3). Expected minor adverse effects included gastrointestinal side effects such as constipation, diarrhea, vomiting (77%) were reported. All were benign and resolved with minor dietary modification according to patient's specific conditions.

Eleven patients (23%) quit KD earlier than 6 months due to various reasons. Failed dietary compliance of children and caregivers was reported in 45% (5/11) of these patients. The remaining reasons were loss to follow-up (2/11), seizure improvement (2/11), death unrelated to KD (1/11) and miss diagnosis of GLUT-1 (1/11). Eighteen patients (37%) continued KD more than 2 years. Except one with the diagnosis of pyruvate dehydrogenase deficiency, the remaining 17 patients had significant seizure reduction contributable to KD.

DISCUSSION

We reported the largest case series of pediatric patients treated with KD in Thailand. So far, the efficacy of KD in reducing seizure frequency has been confirmed and well established. In our study, 84 percent reported more than 50% seizure reduction, in accordance with other studies.[7,8,22] Our KD treatments seemed to show a small negative effect on weight, especially in the first 3 months, which may be due to diuresis from ketosis and reduced caloric intake. After 3 months however, there was a trend towards a non-significant increase in WAZ. Moreover, median HAZ was significantly lower at 12 months than baseline which might be interpreted as a slight adverse effect on linear growth. Although overall BMIAZ significantly increased after 12 months, it is difficult to assume that KD offers a positive effect on growth because BMI may increase as a result from decreasing HAZ and slight increase in WAZ. Moreover, due to the retrospective nature of data collection, some growth data were missing at some time-points which may affect the interpretation of the results.

Previous studies showed significant decrease of weight percentile in children treated with classic KD and decrease WAZ and HAZ at 6 and 12 months follow-up compared to baseline.[17,19-21] In contrast, Vining et al[23] reported results from a prospective cohort study where their pediatric patients also had initial weight loss in the first 3 months but WAZ reverted to baseline afterwards, which correspond with our study. Apart from diuresis, initial weight loss could be due to adverse GI side effects such as vomiting and diarrhea. Thereafter, WAZ most likely improved due to the energy and protein intake was adjusted and the gastrointestinal side effects were diminished.

Most patients in this study reported one or other adverse effects after starting the KD but all of them were minor as compared to previous studies which reported major adverse events leading to discontinuation of treatments such as severe diarrhea, lipoid pneumonia, recurrent hypoglycemia, bone fracture, and kidney stones.[24,25] Most patients only required minor dietary adjustment and nutritional supplement for the improvement of these gastrointestinal or metabolic side effects. Despite the fact that two-thirds of the patients showed hypertriglyceridemia at 3 and 6 months after the start of KD, we could not demonstrate any statistically significant trend due to

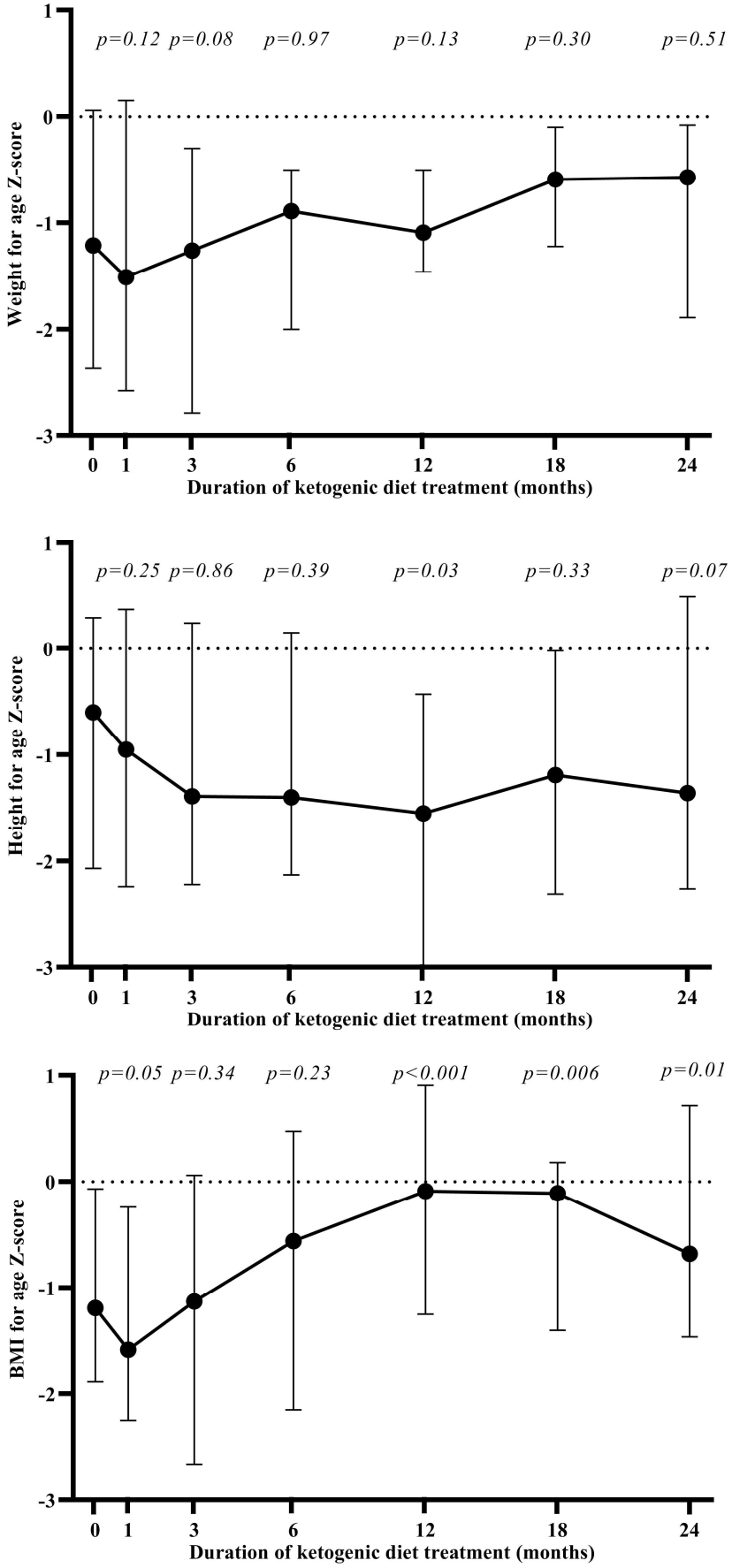

Figure 2. Comparison between median (error bar represented IQR) weight-for-age Z-score (WAZ), height-for-age Z-score (HAZ), and BMI-for-age Z-score (BMIAZ) during 24-month follow-up. WHO anthroplus was used to calculate Z score; p-value was generated from Generalized Estimating Equation (GEE) with linear model comparing each time-point with baseline. GEE showed no statistically significant changes in WAZ at baseline compared with any time-point during the 2-year follow-up. HAZ at month 12 was significantly different compared to baseline [median -1.55 (IQR -3.35, -0.43) vs. -0.6 (-2.07, 0.29)]. BMIAZ at month 12, 18 and 24 were significantly different compared with baseline [-0.09 (-1.25, 0.91), -0.11 (-1.4 to 0.18), -0.68 (-1.46 to 0.72) vs. baseline -1.19 (-1.88, -0.07)].

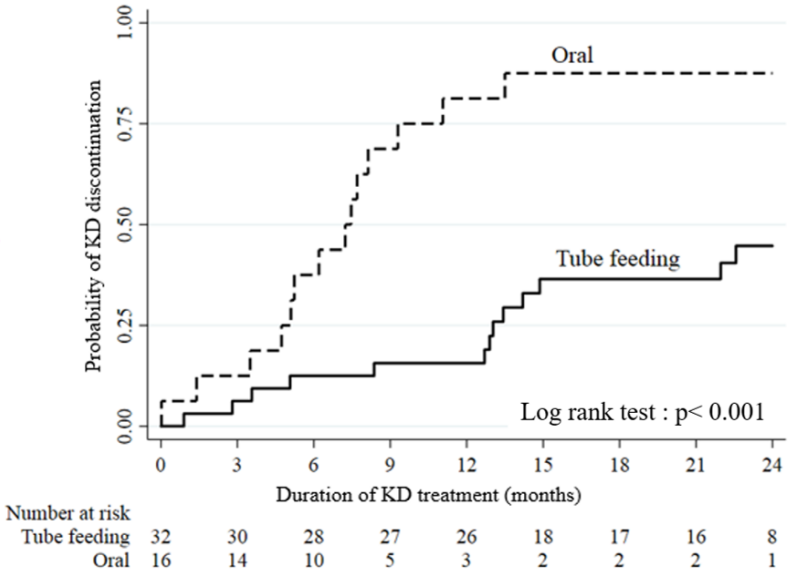

Figure 3. Kaplan-Meier curves showed dietary discontinuation of ketogenic diet (KD) treatment comparing between tube feeding and oral feeding patients.

missing data. One of the reasons that our study found no significant increase in dyslipidemia during KD treatment may be due to early detection and dietary adjustment. However, we found a greater proportion of children with hyperuricemia after commencing KD. This can partly be explained by persistent acidosis and dehydration which can together lead to increased risk of renal stones.[8,24,26] A recent systematic review of prospective studies on the safety and tolerability of KD by Cai et al[27] reported the incidence of hyperuricemia to be only about 5 percent which was much less than our study. The explanation for this could be that in our study the available uric acid results were only from those who were already detected with hyperuricemia and the number was rather small. Moreover, nearly one-third of the patients demonstrated hypercalciuria despite alkalization therapy which could also increase risk of renal stones. This was similar to a previous cohort study in United states where half of the patients had hypercalciuria and 7% developed kidney stones.[27] Another study from Johns Hopkins reported that 6 of 112 patients developed kidney stones during follow-up, 3/6 had uric acid stones and others had mix calcium oxalate and uric acid stones (0.8 cases of urolithiasis/100 patient-months at risk).[28] Therefore, surveillance renal ultrasound should be performed in all cases and more frequently in those with hyperuricemia or hypercalciuria.

In our study, one-third of patients continued KD treatment beyond 2 year. Most patients maintained serum beta-hydroxybutyrate within therapeutic levels that showed good compliance and tolerability. Hosain et al[29] showed that liquid KD via gastrostomy had absolute compliance with good ketosis and it appeared to be the most important predictor of dietary adherence. In our study, the main factor predicting dietary adherence was also route of feeding like another previous study.[23] This was expected because tube feeding was more convenient for the caregivers and the patients' ability to find extra 'forbidden' carbohydrate-containing food was diminished. Nevertheless, we did not use any commercial KD formula. All KD were modularly made according to Nutrition team calculations. The compliance to KD did not differ between the classic and MCT KD. This finding was perhaps caused by proper case selection for LCT diet (exclusive tube-fed patients). As shown in the results, some families choose to discontinue KD despite improvement of seizure control. Some children received high carbohydrate food during school time which cause distress to their caregivers. Some parents felt that their children did not have enough 'meals' since they were allowed to only consume small amounts of rice which is a staple food in Thailand. Therefore, pre-diet counselling is paramount to the success of long-term KD since the caregivers must put forth a great deal of effort for meal preparation and to be beware of forbidden food.

This study pointed out that KD can be administered long-term in pediatric patients with epilepsy or other indications without serious negative effect on growth and nutritional status. However, the multidisciplinary team must closely monitor and customize the diet to suit individual needs. Therefore, it can be considered in early medical-resistant epileptic syndrome despite the lack of commercially available KD formula. Dietary adherence depended on route of feeding as well as good collaboration of multidisciplinary team and caregivers. Our study presents the largest cohort of pediatric patients treated with the ketogenic diet in Thailand which showed good compatibility with Thai dietary traditions. However, the limitation of this study was the missing data due to its retrospective nature. Therefore, some longitudinal trends cannot be clearly demonstrated, particularly the metabolic complications. In addition, the proportion of those with abnormal lipid profiles or hyperuricemia may seem high due to the selection bias.

Conclusion

The ketogenic diet can be administered in Thai children with minimal adverse effects on growth and nutritional status. Under close monitoring, ketogenic diet can be successfully implemented without serious side effects. Adherence of ketogenic diet depends on route of feeding,

clinical response and cooperation of parents and patients. Further prospective research should focus on fine-tuning the diets to increase adherence and palatability in Thai population.

ACKNOWLEDGEMENTS

We would like to thank Assistant Professor Orapa Suteerojntrakool from the Ambulatory Division, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University and Ms. Nuntaporn Charoenphol from the Pediatric Nutrition Division, King Chulalongkorn Memorial Hospital for providing valuable information and patient records. We would like to thank Ms. Jiratchaya Sophonphan, Statistician of the HIV Netherlands Australia Thailand research collaboration for her invaluable help with statistical analyses. Lastly, we would also like to thank Associate Professor Patcharapa Thaweekul from the Nutrition Division, Department of Pediatrics, Thammasat University for her valuable comments on the manuscript.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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