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The Early Response to Dietary Therapy can Predict the Late Outcome in Children with Intractable Epilepsy

Soo-young Lim
Mi-Sun Yum*
Hyunji Ahn
Min-Jee Kim
Han Na Jang
Tae-Sung Ko*

Department of Pediatrics,
Asan Medical Center Children's Hospital,
University of Ulsan College of Medicine,
Seoul, Korea

Background and Purpose Dietary therapy (DT), including the ketogenic diet (KD), is one of the nonpharmacological treatment options for patient with drug-resistant epilepsy. However, maintaining DT in patients without seizure reduction is very difficult, so it is critical for clinicians to decide when to stop this intervention.

Methods We retrospectively analyzed early clinical and laboratory findings and the clinical characteristics of children who received DT. The maintenance of DT and the clinical seizure frequency were assessed at 1, 3, 6, 12, and 24 months after KD initiation. Responders were defined as patients showing an overall reduction in seizure frequency of >50% relative to the baseline.

Results We included 67 patients who received DT, but only 23 (34.3%) of these patients remained on DT at 6 months. Only 1 (5%) of the 20 responders at 1 month became a nonresponder at 6 months. The response rate at 6 months was significantly higher among patients under 2 years of age (15/17, 88.2%) than older patients (2/6, 33.3%; p=0.021). Moreover, the 6-month responders were significantly younger (29.4±38.6 months, mean±SD) than the nonresponders (98.9±84.6 months, p=0.012) at the initiation of the diet. A high blood β-hydroxybutyrate (BHB) level at 1 month predicted a good DT response at 6 months.

Conclusions Most 1-month responders maintained their response on DT for up to 6 months. The blood BHB level at 1 month was significantly correlated with the 6-month seizure outcome. Confirming clinical and laboratory biomarkers for the efficacy of DT requires further studies with larger cohorts.

Key Words diet, ketogenic diet, drug resistant epilepsy, seizures, biomarkers.

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Correspondence
Mi-Sun Yum, MD, PhD
Department of Pediatrics,
Asan Medical Center
Children's Hospital,
University of Ulsan College of Medicine,
88 Olympic-ro 43-gil, Songpa-gu,
Seoul 05505, Korea
Tel +82-2-3010-3381
Fax +82-2-473-3725
E-mail misun.yum@gmail.com

Tae-Sung Ko, PhD
Department of Pediatrics,
Asan Medical Center
Children's Hospital,
University of Ulsan College of Medicine,
88 Olympic-ro 43-gil, Songpa-gu,
Seoul 05505, Korea
Tel +82-2-3010-3381
Fax +82-2-473-3725
E-mail tsko@amc.seoul.kr

*These authors contributed equally to this work as the corresponding authors.

INTRODUCTION

Refractory epilepsy is defined as "failure to achieve sustained seizure freedom with two appropriate and tolerated antiepileptic drugs" (AEDs) by the International League Against Epilepsy (ILAE).[1] Approximately one-third of children with epilepsy will be refractory to standard antiepileptic medication[2] despite the yearly expansion of AED availability. Among various alternative therapies for patients with refractory epilepsy, dietary therapy (DT) first reported as a treatment option in 1921.[3] The classic ketogenic diet (KD) consists of high fat, moderate protein, and low carbohydrate intakes, with a typical ratio of 3:1 or 4:1 for the ratio of fat to protein plus carbohydrate. The difficulty of maintaining the KD due to its unfamiliar taste and strict restrictions resulted in the introduction of the modified Atkins diet (MAD) and low-glycemic-index treatment.[4,5]

While the exact antiepileptic mechanisms of DT remain poorly understood, a KD combines several mechanisms including the peroxisome proliferator activated receptors mediated anti-inflammatory or antioxidative modulation, control of K_{ATP} channels, and

brain-derived neurotrophic factor signaling pathway, increased mitochondrial function, and epigenetic modification via DNA methylation that together reduce neuronal excitability.[6,7] A recent meta-analysis of five randomized controlled trials revealed that 35–56.1% of patients on a KD achieved a >50% reduction in seizures without severe adverse effects.[8]

Nevertheless, the use of DT for refractory epilepsy is restricted by its poor tolerability, insufficient feasibility for caregivers (due to diet complexity), and relatively poor compliance.[9] Diet maintenance is especially difficult in patients who do not experience definitive seizure reduction after DT. These characteristics indicate the need to determine the antiseizure efficacy of DT as early as possible.

Urine ketone (UK) levels have been used to monitor DT adherence due to their noninvasiveness. However, some studies have shown that blood β-hydroxybutyrate (BHB) levels are a more accurate indicator of seizure reduction.[10]

We hypothesized that early clinical and laboratory findings determine the final DT response in children with refractory epilepsy. We tested this hypothesis by examining DT-induced seizure reduction in a single-center cohort of children with refractory epilepsy. Furthermore, to identify early predictors of a DT-mediated response, clinical and laboratory data were compared between early responders and nonresponders.

METHODS

Patients population and data collection

From April 2004 to April 2019, 81 patients with epilepsy started receiving DT at Asan Medical Center in Seoul, South Korea. We excluded patients with insufficient clinical data (n=14).

We retrospectively reviewed clinical and laboratory data and collected information on 1) demographics (sex, weight, age at diagnosis, age at initiation of DT, number of AEDs prior to DT, and duration of DT), 2) epilepsy characteristics (etiology and baseline seizure frequency), 3) type of KD (KD formulation, classic KD, or MAD), 4) response rates to the diet at 1, 3, 6, 12, and 24 months, and 5) blood BHB levels. The ILAE classification divides the etiologies of epilepsy into structural-metabolic, genetic or presumed genetic, and unknown.[11] The clinical seizure frequency was obtained from caregivers' seizure diaries and evaluated at baseline (prior to DT) and at 1, 3, 6, 12, and 24 months after the initiation of DT. The blood BHB level was quantitatively measured using a test strip every other day during hospitalization and at 1, 3, 6, 12, and 24 months after the initiation of DT.

The study was approved by Institutional Review Board 2018-0021 of Asan Medical Center.

KD protocol and outcome assessment

Patients were admitted to the hospital for 1 week to receive an introduction about DT. In general, patients were advised to begin consuming one-third of the target calories, followed by a gradual increased in caloric input over the first 3 days. The target calories and ketogenic ratio were established by the department of nutrition at the hospital.

The responders were defined as patients with a reduction of >50% reduction in the predominant seizure frequency relative to baseline. The effects of DT at 6 months were evaluated in the 1-month responder and nonresponder groups.

We compared clinical variables and blood BHB levels between 6-month responders and nonresponders in order to

Table 1. Baseline demographics and clinical data for the study population

Variable	Value (n=67)
Sex	
Male	39 (58)
Female	28 (42)
Weight	
>90th percentile	7 (10)
10–90th percentiles	37 (56)
<10th percentile	23 (34)
Age at diagnosis, months	19.3±31.5 (0.0–170.0)
Epilepsy etiology	
Structural or metabolic	38 (57)
Malformation of cortical development	11
Hypoxic ischemic encephalopathy	8
Sequelae of encephalitis	7
Tuberous sclerosis complex	6
Periventricular leukomalacia	4
Metabolic disease	2
Genetic or presumed genetic	5 (7)
Unknown	24 (36)
West syndrome	37 (55)
Lennox-Gastaut syndrome	10 (15)
Baseline daily seizure frequency	
At least once	55 (82)
Less than once	12 (18)
Number of antiepileptic drugs prior to DT	
Fewer than three	21 (31)
At least three	46 (69)
Initial blood β-hydroxybutyrate level, mmol/L	2.6±2.0 (0.1–5.8)
Age at initiation of DT, months	44.9±54.1 (1.8–253.3)
Duration of DT, months	6.6±11.4 (0.0–82.0)
Type of DT	
Classic ketogenic diet	58 (87)
Modified Atkins diet	9 (13)

Data are mean±SD (range), n, or n (%) values.
DT: dietary therapy.

identify predictors of a DT-mediated response. Additionally, receiver operating characteristic curves with 95% confidence intervals for distinctions were calculated to determine the blood BHB cutoff for differentiating 6-month responders from nonresponders.

Statistical analyses

Categorical data were analyzed using Pearson's chi-square tests and numerical data were analyzed using independent Student's *t*-tests. Mann-Whitney U-tests were used to assess the relationships of urine and blood BHB levels with seizure reduction. Correlations with $p<0.05$ were considered significant in all tests.

RESULTS

Patient demographics

The baseline demographics and epilepsy characteristics of the 67 patients included in the study are listed in Table 1. The mean age at diagnosis was 19.3 months, and most of the patients were diagnosed with West syndrome (n=37) or Lennox-Gastaut syndrome (LGS) (n=10). Most of the patients (n= 55, 82%) reported daily seizures. The mean age at the initiation of DT was 44.9 months and the mean duration on the diet was 6.6 months. Overall, 58 and 9 patients were initiated on the classic KD and MAD, respectively.

Efficacy and tolerability of DT

Figs. 1 and 2 present the overall efficacy and tolerability of DT over time. At 3 and 6 months after DT initiation, 42 (62.7%) and 23 (34.3%) patients were able to remain on the diet, respectively. Moreover, at 1 and 2 years after DT initiation, only 8 (11.9%) and 4 (6.0%) patients continued the diet, respectively (Fig. 1). Altogether, the data indicate that the DT retention rate had decreased to <50% after 6 months (Fig. 2).

Among the patients who remained on DT, the overall rates of response to DT were 34.5% (20/58), 57.1% (24/42), 73.9% (17/23), 87.5% (7/8), and 50.0% (2/4) at 1, 3, 6, 12, and 24 months after diet initiation, respectively (Fig. 1).

At 1 month, 58 of 67 patients remained on the diet, with the 9 patients discontinuing due to a lack of efficacy (n=1), adverse effects (n=7), or poor compliance (n=1). Twenty (34.5%) of the patients who remained on the diet exhibited >50% seizure reduction, and five (8.6%) also achieved the electroencephalographic improvement: three patients with hypsarrhythmia and two LGS patients with generalized fast activities

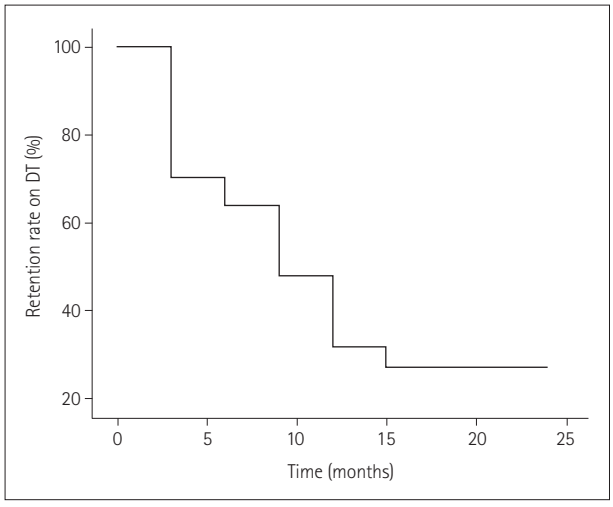

Fig. 2. Kaplan-Meier curve showing the retention rate on DT. DT: dietary therapy.

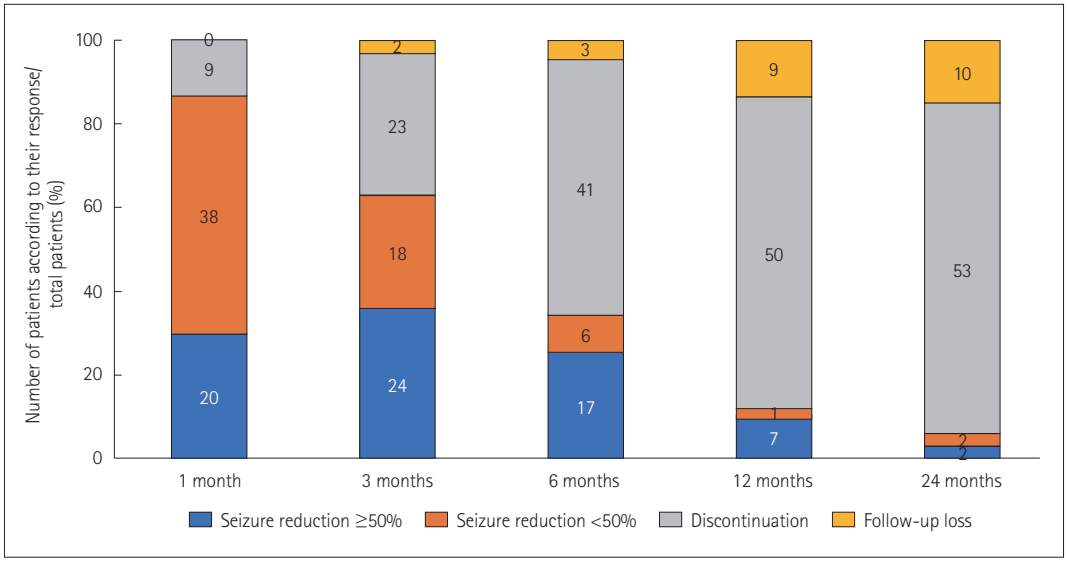

Fig. 1. Seizure outcomes of the patients on dietary therapy and dropouts at each time point.

(Figs. 1 and 3). At 6 months, 23 patients remained on DT, with 41 patients discontinuing due to a lack of efficacy (n=12), adverse effects (n=24), poor compliance (n=4), or discontinued production (n=1); 3 patients were lost to follow-up.

Only one of the 1-month responders became nonresponsive to DT after 6 months (Fig. 3). Importantly, six of the 1-month nonresponders achieved seizure reductions of >50% at 6 months; their clinical characteristics are listed in Table 2. One of these six patients started on a 4:1 classic KD, but their caregiver had difficulty making the diet properly, thereby inhibiting its effectiveness. The other five patients were on a 3:1 classic KD or the MAD, with two reporting poor tolerance or compliance. Moreover, 2 days after DT initiation, these two patients had blood BHB levels of 1.2 and 0.2 mmol/L. All these six patients achieved seizure reduction of >50% at 3 months.

Among the 23 patients remaining on DT at 6 months, 17 (73.9%) showed >50% seizure reduction and 5 (21.7%) with infantile spasms also showed disappearance of hypsarrhythmia. When clinical characteristics were compared between responders and nonresponders after 6 months of DT (Table 3), there were significantly more responders under the age of 2 years (15/17, 88.2%) than older responders (2/6, 33.3%; p=0.021). Moreover, 6-month responders were significantly younger (29.4±38.6 months, mean±SD) than the nonresponders (98.9±84.6 months, p=0.012) at the initiation of the diet. Finally, there was no significant difference of diet types between 6-month responders and nonresponders (p=0.089).

Adverse events of DT

Several adverse events were reported while receiving DT (Table 4). During DT initiation, 40 (60%) of the 67 patients experienced adverse events, including food refusal (n=14), vomiting (n=12), and hypoglycemia (<50 mg/dL, n=10). After discharge, anorexia (n=17) and vomiting (n=15) were the most frequent difficulties, and hypertriglyceridemia (≥200 mg/dL, n=46) was the most common abnormal laboratory finding.

Blood BHB levels according to responsiveness to DT

A blood BHB test was performed in 21 of the 58 patients receiving DT at 1 month (Fig. 4). After the initiation of DT, blood BHB levels of 1-month responders were significantly higher than those of nonresponders at both 2 days (4.4±1.3 mmol/L vs. 2.0±1.7 mmol/L, p=0.031) and 1 month (5.1±0.9 mmol/L vs. 2.2±1.7 mmol/L, p=0.011) (Fig. 4). Blood BHB levels were measured in 10 of the 23 patients who were still receiving DT at 6 months (Table 3 and Fig. 4). The blood BHB level was significantly higher in 6-month responders than in nonresponders at both 1 month (4.8±1.0 mmol/L vs. 1.2±1.0 mmol/L, p=0.016) and 3 months (5.2±1.3 mmol/L vs.

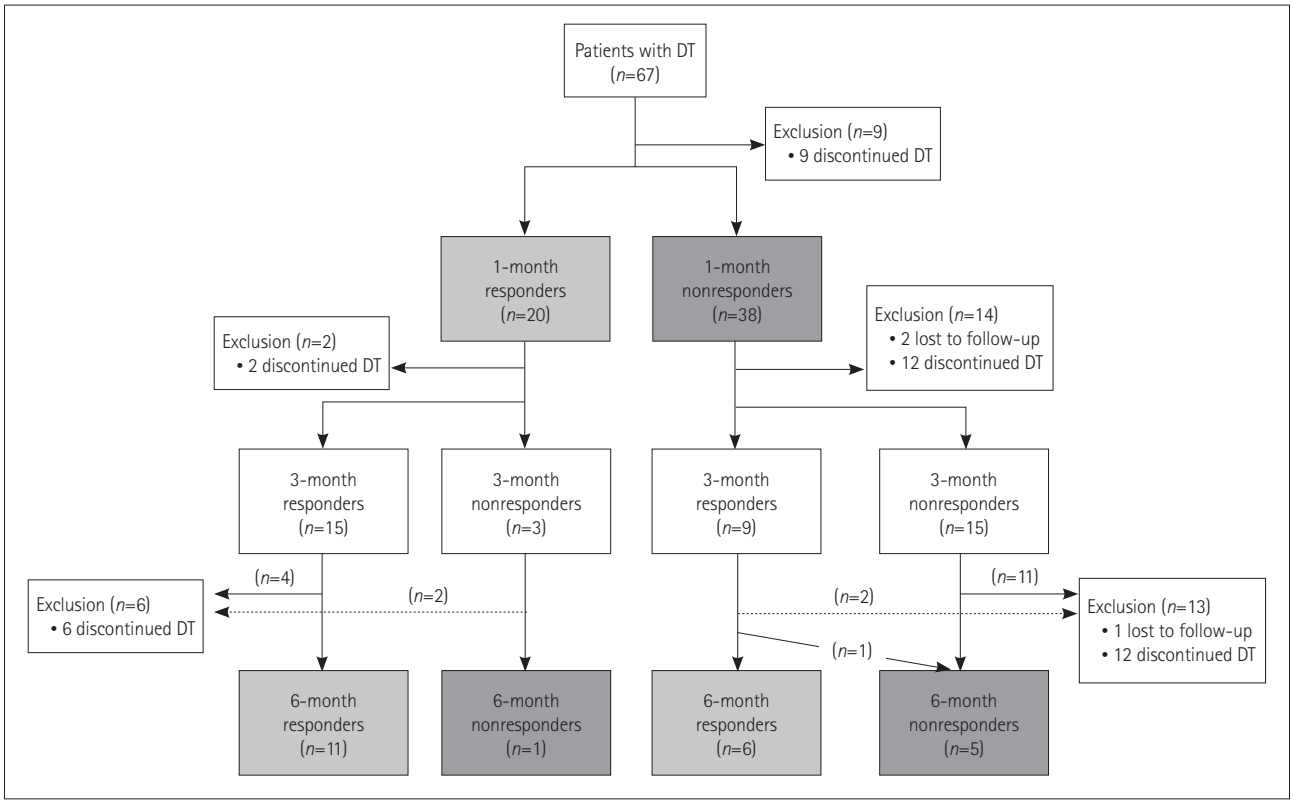

Fig. 3. Flow chart of patients at 1 and 6 months after DT. DT: dietary therapy.

Table 2. Clinical characteristics of late responders who had no response at 1 month

Diagnosis	Age at diagnosis (months)	Age at initiation of DT (months)	Response at 3 months	DT type	Type of DT formula	Blood β-hydroxybutyrate level at 2 days after DT (mmol/L)	Daily seizure frequency	Seizure type	Number of antiepileptic drugs	Adverse effects	Reasons for poor response at 1 month
Tuberous sclerosis, IS	10	16	+	Classic KD (4:1)	Homemade weaning food	-	Once+	Spasms	1	Vomiting, diarrhea	Poor parental education
Perinatal HIE, IS	0	10	+	Classic KD (3:1)	Homemade weaning food+ketogenic milk	-	Once+	Spasms	1	-	None
Perinatal HIE, IS	2	4	+	Classic KD (3:1)	Ketogenic milk	-	Once+	Spasms	3	Diarrhea	None
Encephalitis, focal seizures	135	140	+	MAD	Homemade Atkins diet	-	Once+	GTCS	5	-	None
Lissencephaly, IS, Lennox-Gastaut syndrome	5	78	+	Classic KD (3:1)	Homemade DT	1.2	Once+	Head drops	3	Hypoglycemia	Poor tolerance
Dravet syndrome, generalized seizure	8	97	+	MAD	Homemade Atkins diet	0.2	<Once	GTCS	3	-	Poor compliance

DT: dietary therapy, GTCS: generalized tonic-clonic seizure, HIE: hypoxic-ischemic encephalopathy, IS: infantile spasms, KD: ketogenic diet, MAD: modified Atkins diet.

1.7±1.7 mmol/L, p=0.036) (Table 3 and Fig. 4). Additionally, for 6-month responders, a blood BHB cutoff at 1 month after DT of 3.9 mmol/L yielded a sensitivity and specificity of 80%. Overall, the blood BHB levels of patients on a 4:1 and 3:1 classic KD were higher than those on the MAD (Supplementary Table 1 in the online-only Data Supplement and Fig. 4).

DISCUSSION

This study has demonstrated the difficulty of maintaining DT in children with epilepsy, as evidenced by the low retention rate of 34.3% after 6 months. The mean duration of DT was 6.6 months, which was shorter than those described in other reports.[12-14] Many epileptic patients have difficulty remaining on DT due to side effects, lack of efficacy, or poor compliance.

Table 3. Responders versus nonresponders at 6 months after DT

Variable	Responders at 6 months (n=17)	Nonresponders at 6 months (n=6)	p
Sex			0.408
Male	8 (47)	4 (67)	
Female	9 (53)	2 (33)	
Weight			0.134
<10th percentile	4 (24)	4 (67)	
Age at diagnosis			0.021*
<24 months	15 (88)	2 (33)	
≥24 months	2 (12)	4 (67)	
Epilepsy etiology			0.715
Structural/metabolic	9 (53)	3 (50)	
Genetic or presumed genetic	1 (6)	1 (17)	
Unknown	7 (41)	2 (33)	
Baseline daily seizure frequency			0.576
At least once	14 (82)	4 (67)	
Less than once	3 (18)	2 (33)	
Number of antiepileptic drugs prior to DT			0.058
Fewer than three	8 (47)	0 (0)	
At least three	9 (53)	6 (100)	
Age at initiation of DT, months	29.4±38.6	98.9±84.6	0.012*
Type of DT			0.089
Classic ketogenic diet	15 (88)	3 (50)	
Modified Atkins diet	2 (12)	3 (50)	
Blood β-hydroxybutyrate level, mmol/L			
2 days	3.2±2.2	1.4±1.4	0.257
1 month	4.8±1.0	1.2±1.0	0.016*
3 months	5.2±1.3	1.7±1.7	0.036*

Data are mean±SD or n (%) values.
*p<0.05.
DT: dietary therapy.

However, the overall efficacy of DT was 73.9% at 6 months, with most of the 6-month responders also showing responsiveness after 1 month. A few 1-month nonresponders became 6-month responders, but those patients failed to benefit from the full strength of the classic KD and ketosis, since they had difficulty remaining on DT during the first month and only reported seizure reduction 2–3 months later. This illustrates the importance of the successful induction of early ketosis and strict DT for achieving the effective control of seizures. Considering the poor DT retention rate, an early decision about DT maintenance can be made since the efficacy can be predicted during the initiation period of DT.

To identify other clinical factors affecting DT responses, the clinical characteristics of 6-month responders and nonresponders were compared. Six-month responders were diagnosed with epilepsy and initiated DT at a significantly lower age than did nonresponders. This group also showed significantly higher blood BHB levels at 1 and 3 months after DT initiation. The DT efficacy did not vary with sex, weight, epilepsy etiology, baseline seizure frequency, or number of AEDs. In line with our findings, previous studies have suggested that initiating DT at a lower age results in better outcomes.[15,16] It seems that young children, especially those younger than 2 years, can tolerate DT better, which is probably due to their eating habits being more flexible. Although not statistically significant, the classic KD seemed to be more effective than the MAD. However, this result is inconsistent with recent findings,[17,18] which is probably due to the younger age and higher seizure burden of our patient group, as well as the inclusion of fewer patients on the MAD.

Recent studies have shown that blood BHB levels are more strongly correlated with seizure reduction than are UK levels.[10] Van Delft et al.[10] reported that UK levels were merely indicative of the compliance with DT, rather than accurately

Table 4. Adverse events of DT

Variable	Value (*n*=67)
Adverse events during DT initiation	
Food refusal	14 (21)
Vomiting	12 (18)
Hypoglycemia (BST <50 mg/dL)	10 (15)
Diarrhea	7 (10)
Constipation	4 (6)
Fever	4 (6)
Adverse clinical events after discharge	
Anorexia	17 (25)
Vomiting	15 (22)
Seizure aggravation	11 (16)
Infection	9 (13)
Weight loss	6 (9)
Constipation	4 (6)
Adverse chemical events after discharge	
Hypertriglyceridemia (triglyceride ≥200 mg/dL)	46 (69)
Hyperuricemia (uric acid >7 mg/dL)	41 (61)
Hypercholesterolemia (total cholesterol ≥200 mg/dL)	30 (45)
Metabolic acidosis	21 (31)
Hypoglycemia (BST <50 mg/dL)	18 (27)
Hypomagnesemia (magnesium <1.8 mg/dL)	13 (19)
Hypercalcemia (total calcium >10.2 mg/dL)	11 (16)
Hypocalcemia (total calcium <8.6 mg/dL)	6 (9)

Data are *n* (%) values.
BST: blood sugar test, DT: dietary therapy.

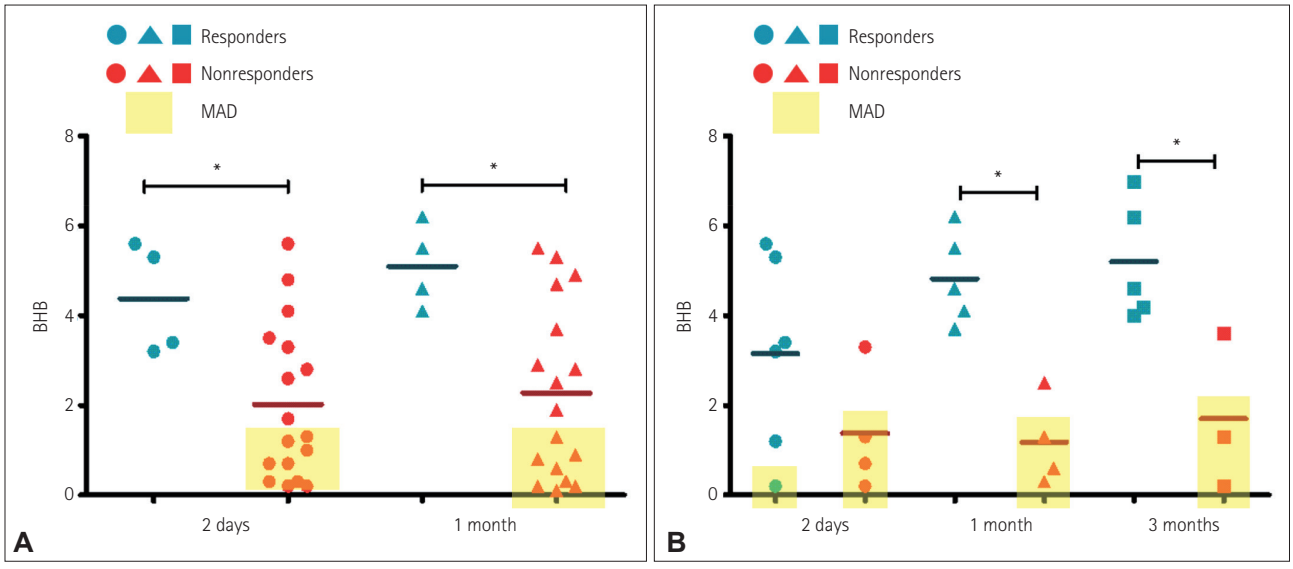

Fig. 4. Scatter plots of BHB level in responders and nonresponders at each time point. A: 1-month responders vs. nonresponders. B: 6-month responders vs. nonresponders. *p<0.05. BHB: β-hydroxybutyrate, MAD: modified Atkins diet.

reflecting treatment efficacy. For this reason, the present study measured blood BHB levels rather than UK levels. We found that the blood BHB levels at 1-month after DT initiation were higher in 6-month responders than in nonresponders. Moreover, high blood BHB levels were significantly correlated with reductions in DT-mediated seizures. These data suggest that the 6-month response can be predicted by measuring the blood BHB level at 1 month, allowing direct decisions to be made regarding the continuance of the diet as early as 1 month after initiating DT.

Overall, DT was found to be safe with no severe effects on mortality or intensive care unit admissions during the study period, which may have been due to the flexible DT applied at our center and the low retention rate. During the initiation of DT, 60% of the patients displayed side effects, the most common of which were food refusal and vomiting.

Our study was subject to some limitations, including its retrospective design with the seizure frequencies being reported by caregivers, the relatively short duration of DT maintenance, and the lack of data on blood BHB levels for patients who began DT before 2015. However, since the DT protocol remained consistent, it is unlikely that the blood BHB levels of patients would have differed between before and after 2015.

Notwithstanding these limitations, this study has revealed the critical value of the early prediction of DT efficacy in reducing DT-related side effects, which can help medical professionals to make decisions regarding DT for children with refractory epilepsy. Moreover, our data illustrate the usefulness of blood BHB levels as an early biomarker for DT efficacy.

In conclusion, maintaining DT is very difficult in children with refractory epilepsy. Moreover, most patients with DT-mediated clinical responses exhibited effects at 1 month or at least until 3 months after initiating DT. Blood BHB levels at 1 month are reliably predictive of the 6-month seizure outcome in patients on DT for a cutoff of 3.9 mmol/L. Further studies are needed to confirm clinical and laboratory biomarkers for the efficacy of DT.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.1.33.

Author Contributions

Conceptualization: Mi-Sun Yum, Tae-Sung Ko. Data curation: Soo-young Lim, Hyunji Ahn, Han Na Jang. Formal analysis: Soo-young Lim, Min-Jee Kim. Investigation: Soo-young Lim, Min-Jee Kim. Methodology: Mi-Sun Yum, Soo-young Lim. Project administration: Mi-Sun Yum, Tae-Sung Ko. Supervision: Mi-Sun Yum, Tae-Sung Ko. Validation: Soo-young Lim, Min-Jee Kim. Visualization: Soo-young Lim, Min-Jee Kim. Writing—original draft: Soo-young Lim, Min-Jee Kim. Writing—review & editing: Mi-Sun Yum.

ORCID iDs

Soo-young Lim https://orcid.org/0000-0001-6744-3568
Mi-Sun Yum https://orcid.org/0000-0002-5986-5258
Hyunji Ahn https://orcid.org/0000-0003-0736-6585
Min-Jee Kim https://orcid.org/0000-0002-8081-6522
Han Na Jang https://orcid.org/0000-0003-2770-6946
Tae-Sung Ko https://orcid.org/0000-0002-8213-8964

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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None

REFERENCES

1. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069-1077.
2. Hao XT, Wong IS, Kwan P. Interrater reliability of the international consensus definition of drug-resistant epilepsy: a pilot study. *Epilepsy Behav* 2011;22:388-390.
3. Wheless JW. History of the ketogenic diet. *Epilepsia* 2008;49 Suppl 8: 3-5.
4. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia* 2006;47:421-424.
5. Pfeifer HH, Thiele EA. Low-glycemic-index treatment: a liberalized ketogenic diet for treatment of intractable epilepsy. *Neurology* 2005; 65:1810-1812.
6. Boison D. New insights into the mechanisms of the ketogenic diet. *Curr Opin Neurol* 2017;30:187-192.
7. Seo JH, Lee YM, Lee JS, Kang HC, Kim HD. Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios--comparison of 3:1 with 4:1 diet. *Epilepsia* 2007;48:801-805.
8. Sourbron J, Klinkenberg S, van Kuijk SMJ, Lagae L, Lambrechts D, Braakman HMH, et al. Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis. *Childs Nerv Syst* 2020;36:1099-1109.
9. Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. *Cochrane Database Syst Rev* 2016; 2:CD001903.
10. van Delft R, Lambrechts D, Verschuure P, Hulsman J, Majoie M. Blood beta-hydroxybutyrate correlates better with seizure reduction due to ketogenic diet than do ketones in the urine. *Seizure* 2010;19:36-39.
11. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010;51:676-685.
12. Baby N, Vinayan KP, Pavithran N, Grace Roy A. A pragmatic study on efficacy, tolerability and long term acceptance of ketogenic diet therapy in 74 South Indian children with pharmacoresistant epilepsy. *Seizure* 2018;58:41-46.
13. Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 1998;102:1358-1363.
14. Jagadish S, Payne ET, Wong-Kisiel L, Nickels KC, Eckert S, Wirrell EC. The ketogenic and modified Atkins diet therapy for children with refractory epilepsy of genetic etiology. *Pediatr Neurol* 2019;94:32-37.
15. Kossoff EH, Pyzik PL, McGrogan JR, Vining EP, Freeman JM. Efficacy of the ketogenic diet for infantile spasms. *Pediatrics* 2002;109:780-783.
16. Nordli DR Jr, Kuroda MM, Carroll J, Koenigsberger DY, Hirsch LJ, Bruner HJ, et al. Experience with the ketogenic diet in infants. *Pedi-*

atrics 2001;108:129-133.
17. Rezaei S, Abdurahman AA, Saghazadeh A, Badv RS, Mahmoudi M. Short-term and long-term efficacy of classical ketogenic diet and modified Atkins diet in children and adolescents with epilepsy: a systematic review and meta-analysis. *Nutr Neurosci* 2019;22:317-334.
18. Kossoff EH, Cervenka MC, Henry BJ, Haney CA, Turner Z. A decade of the modified Atkins diet (2003–2013): results, insights, and future directions. *Epilepsy Behav* 2013;29:437-442.