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Original article

Low glycemic index treatment in patients with drug-resistant epilepsy

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Abstract

Objective: Low glycemic index treatment (LGIT) is a newly developed dietary therapeutic option for epilepsy that is less restrictive than the ketogenic diet (KD). Our objective was to determine the efficacy and tolerability of LGIT.

Methods: From March 2014 to February 2015, 36 patients received LGIT at Severance Children's Hospital. One-year seizure outcomes and side effects were evaluated.

Results: A total of 36 patients were assessed. Fourteen were female. Common diagnoses were Lennox-Gastaut syndrome (33%, 12/36) and Dravet syndrome (14%, 5/36). The median age at the initiation of the LGIT was 12.6 years (min. = 1.5, max. = 28, interquartile range (IQR) 8–17). After 3 months of therapy, 20 (56%) patients experienced a 50% or greater reduction in seizure frequency, which was maintained in 19 (53%) patients for 1 year. Two (6%) patients became seizure-free after 3 months of LGIT; they remained seizure-free for 1 year. These two had Dravet syndrome and generalized epilepsy. Only three (8%) patients discontinued treatment within 1 year. Adverse events were rare, and two patients (6%) reported transient diarrhea.

Conclusions: LGIT effectively reduced seizure frequency in the present study, although seizure freedom was infrequently achieved. LGIT may be considered as a therapeutic option for patients with drug-resistant epilepsy, particularly those who find KD effective but intolerable.

Keywords: Low glycemic index treatment; Ketogenic diet; Epilepsy; Children

1. Introduction

The ketogenic diet (KD) is a high-fat, low carbohydrate diet that is an effective treatment option for patients with drug-resistant epilepsy [1–5]. A randomized clinical study showed that 38% of patients had a greater than 50% seizure reduction with three months of KD, while only 6% of patients did with placebo [1]. Therefore, experts have recommended early use of KD for patients with drug-resistant epilepsy [6]. KD is also generally well-tolerated in children of young age, even infants [7]. However, in older children and adults, KD is often poorly tolerated, and KD is rarely considered as a therapeutic option, mostly due to low palatability [8,9]. Recent data suggest that more liberal diets, such as a modified Atkins diet (MAD), may have higher tolerability than KD with comparable efficacy [10,11]. These liberalized KD-resembling diets may be good treatment options and worthy of consideration in older children and adults who cannot tolerate KD [9].

Low glycemic index treatment (LGIT) is the most liberal dietary treatment option developed for epilepsy. LGIT is similar to KD in that it encourages intake of

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fat; it is different from KD in that it allows higher daily intake of carbohydrates and protein. LGIT particularly focuses on stabilizing blood glucose levels by only allowing the consumption of carbohydrates that increase postprandial blood glucose slowly with small fluctuations [12]. Abrupt changes in blood glucose levels are known to reduce seizure threshold [13].

Our goal in this study was to assess whether LGIT shows tolerability and efficacy against epilepsy. We also evaluated which patient groups experience the optimum benefits from LGIT.

2. Materials and methods

Patients who were treated with LGIT at Severance Children's Hospital between March 1, 2014 and February 28, 2015 were included. All patients had drug-resistant epilepsy. Drug-resistant epilepsy was defined as failure of adequate trials with two tolerated, appropriately chosen, antiepileptic drug schedules to achieve sustained seizure freedom [14]. For inclusion, patients had to have drug resistant epilepsy, with seizures occurring more frequently than once per month, and no prior treatment with LGIT. Exclusion criteria included (1) patients who were directly transitioned from KD to LGIT, (2) patients who did not have any seizures for three months prior to LGIT initiation, (3) patients who never started LGIT, despite it being recommended, and (4) patients lost to follow-up. Age was not an exclusion criterion. Patients with previous uses of KD, modified Atkins diet, or a history of epilepsy surgery were not excluded.

Data were obtained by medical chart review. Antiepileptic drug adjustments were allowed, at the physician's discretion, during the diet therapy at 3 months from the day LGIT was initiated. This study was approved by the Institutional Review Board of Severance Children's Hospital (4-2015-0778).

2.1. Dietary protocols

To administer LGIT, we followed the Massachusetts General Hospital protocol that was proposed in 2005 [15]. LGIT was initiated without a fast in the outpatient clinic [16]. Patients were instructed to consume 10% of their caloric intake from carbohydrates, 30% from protein, and 60% from fat. For carbohydrates, patients were instructed to only consume foods with a low glycemic index (GI) of 50 or less. The approved low GI foods ($GI \leq 50$) were selected based on the International Table of Glycemic Index [12]. GI was defined as the incremental area under a blood glucose response curve after consumption of 50 g of carbohydrate, expressed as a percent of the comparative response to the consumption of 50 g of glucose. GI represents the postprandial glucose peak that occurs two hours after consumption of 50 g of carbohydrate, compared with that after consumption of 50 g of glucose [12]. Foods with GI values higher than 50 were restricted. Water intake was not restricted. Individual dietary plans were designed by our dietician [17]. Diets were supplemented with vitamins and minerals. The total caloric intake was determined based on the patient's daily activity, height, weight, and their habitual meal size. Patients received supplemental multivitamins and calcium.

2.2. Efficacy and related factors

The primary endpoint was the number of patients who had a 50% or greater seizure reduction after three months of therapy. Seizure outcomes after 3 months of treatment were assessed. Seizure frequency was compared with the mean seizure frequency that was reported by the children's parents or the patients themselves during the three-month baseline period prior to initiating LGIT. Efficacy was evaluated with respect to reductions in seizures, and patients were assigned to one of the following three groups: (1) seizure freedom, (2) seizure reduction of $\leq$50–99%, and (3) seizure reduction of $<$50%. The number of patients who showed urine ketosis was recorded.

To evaluate factors related to diet efficacy, patients who received LGIT were categorized as (1) good responders or (2) poor responders. Good responders included patients who experienced a 50% or greater reduction in seizures with the diet. Poor responders included patients who experienced a $<$50% reduction in seizures and patients who discontinued the diet before three months due to poor tolerability or side effects. The two groups were compared with respect to the following characteristics: age of seizure onset, age at initiation of the diet, epilepsy duration, epilepsy syndrome, etiology, epilepsy surgery, previous use of KD, and previous use of anti-epileptic drugs.

2.3. Diet tolerability and side effects

Diet tolerability, compliance, and side effects were closely monitored with regularly scheduled assessments according to our epilepsy center diet protocol [18]. The following side effects were assessed: hematuria, acidosis, diarrhea, vomiting, pancreatitis, hypercholesterolemia, hypertriglyceridemia, aspiration tendency, and seizure aggravation. Tolerability was assessed by recording early withdrawal, which was defined as discontinuation of the diet before 3 months.

For laboratory evaluation, complete blood count with platelets, liver function test, renal function test, electrolytes, serum bicarbonate, calcium, and phosphate were collected. Additionally, lipid profiles, urine calcium, creatinine, and urine ketone were assessed. Values obtained at 3 months after the LGIT was initiated were

collected. Any values out of their respective reference range were counted and reviewed.

2.4. Statistical analysis

To identify variables that were related to favorable seizure outcomes, patients who received LGIT were categorized as (1) good responders or (2) poor responders, and variables for these two groups were compared. Age of seizure onset and age at diet initiation were compared using Mann–Whitney *U*-test. Associations between responses to the LGIT and failure of epilepsy surgery or KD treatment, as well as previous favorable response to KD, were investigated using Pearson's Chi-square test. Numbers of previous anti-epileptic drug therapies for each group were compared using Student's *t*-test. In order to evaluate adverse effects, changes in the laboratory values occurring with LGIT were assessed. All laboratory values obtained after three months of LGIT were compared with those measured prior to the LGIT initiation using Student's *t*-test. All data were analyzed using SPSS version 23 (SPSS Inc., Chicago, IL, USA). Data are expressed as a mean ± standard deviation, median (minimum, maximum, interquartile range (IQR)), or median (IQR).

3. Results

3.1. Baseline characteristics

A total of 36 patients received LGIT. All patients had drug-resistant epilepsy, and the mean number of anti-epileptic drugs previously tried was 6 ± 2.4. Fourteen were female. The median age at the initiation of the LGIT was 12.6 years (min. = 1.5, max. = 28, IQR = 8–17). Many had previously received KD (58%, 21/36) but stopped due to restrictiveness of the KD. Of the 36 patients, 20 (56%) had received epilepsy surgery.

The most common diagnoses were Lennox-Gastaut syndrome (33%, 12/36) and Dravet syndrome (14%, 5/36). Many patients (22%, 8/36) had a structural cause for seizures, including focal cortical dysplasia, polymicrogyria, schizencephaly, and heterotopia. Three had genetic mutations: *SCN1A* in two patients and *MT-ND1* (Leber hereditary optic neuropathy) in one patient (Table 1).

3.2. Efficacy

After three and six months of LGIT, 56% (20/36) and 58% (21/36) experienced a ≥50% reduction in seizures, respectively. Overall, after one year of LGIT, 53% (19/36) of patients achieved a 50% or greater seizure reduction (Table 2). A total of two (6%) patients became seizure-free with LGIT after three months of LGIT and remained so for one year. The two LGIT patients who became seizure-free had Dravet syndrome and generalized epilepsy not otherwise specified. Seven patients showed urine ketosis.

To determine factors associated with a favorable outcome for LGIT patients, we compared characteristics of the good responder group (20/36) with those of the poor responder group (16/36). The characteristics of the good responders did not differ from those of poor responders with respect to age of seizure onset (3 years old, IQR = 1–7 vs. 4 years old, IQR = 1–9; $p = 0.4$), age at diet initiation (13 years old, IQR = 8–18 vs. 15 years old, IQR = 9–17; $p = 0.6$), previous epilepsy surgery (55%, 11/20 vs. 56%, 9/16; $p = 0.9$), previous KD treatment (50%, 10/20 vs. 69%, 11/16; $p = 0.3$), and number of previous anti-epileptic drug therapies (6 ± 2.6 vs. 7 ± 1.9; $p = 0.2$). Meanwhile, however, among patients who received KD prior to LGIT, patients who previously responded favorably to KD were more likely to be good responders to LGIT than those who did not respond well to KD (69%, 9/13 vs. 25%, 2/8; $p = 0.049$). Responder rates of LGIT were high in Dravet syndrome and in Lennox-Gastaut syndrome: 80% (4/5) in Dravet syndrome and 75% (9/12) in Lennox-Gastaut syndrome. Also, responder rates varied according to etiology: hypoxic-ischemic encephalopathy (0%, 0/2), genetic (33%, 1/3), structural (50%, 4/8), and metabolic (67%, 2/3).

3.3. Tolerability and adverse effects

By six months of LGIT, three (8%) patients discontinued the diet due to ineffectiveness and difficulty in adhering to the diet. No additional patients discontinued the LGIT between six months and one year of the therapy. Adverse events were rarely reported by LGIT patients (6%, 2/36). Reported adverse events were transient diarrhea not related to the diet. Vomiting, constipation, abdominal pain, and kidney stone did not occur. Seizure aggravation did not occur in any of the patients.

When laboratory values were assessed, no significant difference was observed between the baseline values and the values obtained after three months of LGIT. Several laboratory values exceeded reference ranges after three months of LGIT (16 patients, 44%). Nevertheless, these abnormalities occurred transiently and none required additional management or medication. The most common abnormal finding was reduced serum total carbon dioxide (tCO2), which ranged between 18 and 23 mmol/L in 13 patients (36%). Hypercholesterolemia was the next most common laboratory abnormality and was found in five patients (14%). In these five patients (14%), cholesterol levels ranged between 200 and 250 mg/dL. No medication was prescribed, and abnormal values improved after life style modification. Other minor laboratory abnormalities included

Table 1
Patient characteristics.

		LGIT $N = 36$	
Female: Male		14: 22	
Age at seizure onset, *y*, median (IQR, min., max.)		3.9	(1–7, 0, 14)
Duration of epilepsy, *y*, median (IQR, min., max.)		7.5	(5–12, 1, 18)
Age at the initiation of the diet, *y*, median (IQR, min., max.)		12.6	(8–17, 2, 29)
Epilepsy surgery, *n*		20	
Previous ketogenic diet, *n*		21	
Number of attempted AEDs, *n*		6 ± 2.4	
Epilepsy syndrome	Lennox-Gastaut syndrome	12	
	Dravet syndrome	5	
	Focal epilepsy	4	
	West syndrome	1	
	Epilepsy with myoclonic-astatic seizures	0	
	Epilepsy, NOS	14	
Cause	Structural	8	
	Mitochondrial	4	
	Genetic	3	
	Vascular	3	
	Inflammatory	3	
	Unknown	15	

LGIT, low glycemic index treatment; IQR, interquartile range; Min., minimum; Max., maximum; AEDs, antiepileptic drugs; NOS, not otherwise specified; *y*, year; *n*, number.

Table 2
Seizure outcomes at 3, 6, and 12 months after starting a low glycemic index diet.

	3 months $N = 36$ (%)	6 months $N = 36$ (%)	12 months $N = 36$ (%)
Free	2 (6)	2 (6)	2 (6)
≤90–99% reduction	8 (22)	7 (19)	7 (19)
50–<90% reduction	10 (28)	12 (33)	10 (28)
<50% reduction	16 (44)	12 (33)	14 (39)
Withdrawal	0	3 (8)	3 (8)

increased alanine aminotransferase (ALT, 59 IU/L) in one patient, increased lipase (126 U/L) without increased amylase in a patient, and increased blood urea nitrogen without increased blood creatinine (BUN, 20 mg/dL) (Table 3).

4. Discussion

LGIT successfully controlled seizures in approximately half of our patients with drug resistant epilepsy. LGIT appeared to be an effective alternative dietary option for patients who cannot tolerate KD. Our study results are consistent with those of previous studies. Studies have reported that 38–83% of patients respond positively to LGIT after different periods of treatment [15,19–23]. In our study, approximately 50% of patients experienced a greater than 50% reduction in seizures after one year of LGIT. Our study showed that the efficacy of LGIT may be comparable to that of KD as a treatment option for drug-resistant epilepsy.

Nevertheless, although the seizure reducing ability of LGIT was demonstrated, LGIT seems to be inferior to KD with respect to complete seizure freedom. In our study, only two LGIT patients became seizure-free after one year. Similar low rates of seizure freedom were reported in previous studies of LGIT, which reported that no patients or only few patients became seizure-free with LGIT [19,20,22]. In comparison to KD, metabolic alterations and side effects are suspected to occur to a less degree in LGIT [11]. In our study, only seven patients showed ketones in the urine. Our result suggests that the anti-epileptic effects of LGIT, as well as metabolic alterations, may be weaker than those of KD and may involve anti-epileptic effects not solely based on ketosis.

The two LGIT patients who became seizure-free were diagnosed with Dravet syndrome and generalized epilepsy not otherwise specified. Previous studies reported good outcomes for LGIT therapy in treating epilepsy syndromes that are known to respond favorably to KD, including tuberous sclerosis [21], Angelman syndrome [23], and mitochondrial epilepsy [24]. LGIT appears to share some anti-epileptic effects with KD by stabilizing blood glucose levels. LGIT resembles KD with respect to its restriction of total daily calories and carbohydrate intake, although LGIT is less restrictive than KD.

The greatest benefits of LGIT are its increased tolerability and a lower occurrence of side effects, compared with KD. Patients were unlikely to discontinue the diet early and reported fewer side effects. Only two of our patients reported side effects during LGIT. Previous

Table 3
Laboratory abnormalities at 3 months after the low glycemic index treatment.

	Baseline	(SD)	After 3 months	(SD)	Reference range	Unit	p – value	N of values out of reference range
White blood cell count	6.5	2.3	6.1	1.8	4–10.8	$10^3/\mu L$	0.7	0
Hemoglobin	13.7	1.4	13.8	1.6	13–17.4	g/dL	0.7	0
Platelet count	256.0	56.1	224.0	42.8	150–400	$10^3/\mu L$	0.7	0
Total protein	6.8	0.6	6.9	0.5	6–8	g/dL	0.4	0
Albumin	4.3	0.3	4.4	0.3	3.3–5.3	g/dL	0.4	0
Aspartate aminotransferase (AST)	20.4	8.3	18.4	7.0	13–34	IU/L	0.3	0
Alanine aminotransferase (ALT)	13.1	6.7	14.9	11.5	5–46	IU/L	0.6	1
Total bilirubin	0.3	0.1	0.4	0.2	0.2–1.0	mg/dL	0.6	0
Alkaline phosphatase	196.8	87.2	169.4	91.6	75–379	IU/L	0.5	0
Amylase	59.8	15.2	62.3	14.2	30–115	U/L	0.7	0
Lipase	45.8	53.3	34.5	23.6	5–60	U/L	0.5	1
Cholesterol	169.8	39.7	181.4	42.9	70–160	mg/dL	0.6	16
HDL cholesterol	57.6	13.5	58.8	17.1	40–75	mg/dL	0.9	2
Triglycerides	70.1	27.5	81.7	44.3	48–200	mg/dL	0.5	0
Blood urea nitrogen	11.3	4.7	12.1	3.6	8–18.5	mg/dL	0.6	1
Creatinine	0.4	0.1	0.5	0.2	0.45–0.98	mg/dL	0.4	0
Uric acid	4.0	0.9	4.3	1.2	3.0–7.6	mg/dL	0.4	0
Sodium	141.4	2.0	141.1	1.9	135–145	mmol/L	0.7	0
Potassium	4.3	0.3	4.4	0.4	3.5–5.5	mmol/L	0.7	0
Chloride	104.3	4.0	104.5	3.0	98–110	mmol/L	0.9	0
Phosphate	4.7	0.6	4.3	0.5	3.8–5.9	mmol/L	0.2	2
Calcium	9.5	0.3	9.2	0.4	8.5–10.5	mg/dL	0.2	0
Total carbon dioxide (tCO2)	23.9	3.5	23.0	3.8	24–30	mmol/L	0.6	13
Glucose	93.1	9.8	91.5	10.8	70–110	mg/dL	0.7	0

studies also reported a limited number of side effects for LGIT [15,19–23]. In our study, many of the patients who discontinued the KD due to low compliance or side effects were able to successfully maintain LGIT for one year. The mean age at initiation of LGIT in our study was 12.6 years. Our results suggest that LGIT is tolerated well as a dietary treatment option for adolescents, whereas KD therapy is often not even considered for these patients due to its severe dietary restrictions.

Overall, our results suggest that treatment with LGIT in place of KD may be applicable in the following instances: First, after failure of KD, LGIT appears to be a good alternative treatment option that should be considered. LGIT appears to be a good alternative for patients who found KD effective but intolerable due to side effects or low palatability. LGIT would be particularly effective for those who previously responded favorably to KD. Second, after successful KD therapy, LGIT may be used. A patient can be directly transitioned from KD to LGIT. Patients are likely to maintain seizure freedom after transitioning to LGIT. As reported in other studies, patients are likely to continue their previously achieved seizure freedom or seizure reduction after being transitioned from KD to LGIT [15,25]. In some cases, KD is the only effective anti-epileptic treatment for patients with drug-resistant epilepsy, and physicians have to consider recommending long-term use of the diet. LGIT provides an effective transitional step for these cases. Similar transitions from KD to MAD have been reported as successful [10]. Nevertheless, the optimal duration of KD before transition, the indications for transition, or the means of transitioning the diet would have to be determined with future studies. Third, LGIT may be applied as a primary diet therapy for patients who have KD-responsive epilepsy syndromes, such as Dravet syndrome. LGIT may be initiated before KD for this patient group. LGIT may achieve seizure freedom in these KD-responsive epilepsy syndromes. If the outcome is not satisfactory, the diet therapy can be transitioned from LGIT to KD.

This study has several limitations. It was a retrospective study and included patients with diverse etiologies. Also, patients were highly selected. Physicians initiated LGIT when they thought patients were likely to respond well to LGIT based on their previous responses to KD or their underlying diagnoses. On the other hand, as Severance Children's Hospital is a tertiary referral center for epilepsy, all included patients had severe drug resistant epilepsy that was unresponsive to antiepileptic drug therapy or surgery. Responses to LGIT may be different in different patient populations. Randomized, blinded studies with larger sample sizes are needed to compare the efficacy of the treatment to other more commonly available diet therapies. However, because it is a diet therapy, randomized or blinded study would be difficult to perform.

It should also be noted that anti-epileptic drug adjustments were allowed after 3 months of LGIT. This can also challenge our interpretation of the results. However, no one achieved additional seizure freedom or marked improvement after 3 months, except one patient who experienced a transient 50% seizure reduction at 6 months, but not at 3 or 12 months. This finding suggests that 3 months is usually a sufficient time point at which to assess responses to LGIT in individual patients and to emphasize the fact that additional drug treatment has limited efficacy in drug-resistant epilepsy.

The current study emphasizes the potential value of LGIT in patients with drug-resistant epilepsy. LGIT appears be an effective dietary therapy, although the ability to achieve seizure freedom may be limited to certain populations. LGIT would be a beneficial alternative dietary option to KD, especially for older patients who find KD intolerable.

Conflict of interest

Authors of this manuscript have no conflicts of interest to disclose.

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