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Original Article

Ketogenic diet therapy map of Turkey

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ABSTRACT

Background. Although the ketogenic diet (KD) is a well-established non-pharmacologic treatment for intractable epilepsy in pediatric patients, it is still perceived as theoretical information contained within textbooks rather than implementation in daily clinical practice. The aim of the present study was to primarily determine KD implementation frequency in daily clinical practice, the number of pediatric patients with intractable epilepsy, the conditions that hindered or facilitated KD implementation, and to provide a roadmap to improve patient outcomes.

Methods. A total of 27 pediatric neurologists, who were experienced in intractable epileptic pediatric patients and the implementation of KDs, responded to a 24-question survey. The survey was structured to outline patient selection criteria for KDs, prevalent treatment approaches in daily clinical practice for intractable epilepsy, level of physician awareness and impediments in KD implementation.

Results. Intractable epilepsy was diagnosed predominantly in children within the 7 to 12-year age group (44%). KD implementation was hindered mainly by lack of an adequate number of personnel (53.8%), lack of a dietitian (52%), inadequate training of patients (24%), and inadequate experience of healthcare professionals (23.1%). Lack of guidance in treatment, physician's hesitations due to probable problems, inadequate time spent for each patient, lack of awareness for KD therapy, and loss of appetite in these patients were also emphasized by the participants (each 16.7%).

Additional drawbacks were non-appealing taste (76.9%), need for continuous supervision (76.9%), and low patient motivation (73.1%). The treatment failure causes for KDs were ranked as imprecise cooking of recipes (94%), inadequate family support (92.3%), inadequate consumption of meals (73%), incorrect indication (53.9%), and inefficiency of KD despite correct application (42.3%).

Conclusion. The panoramic view of KDs in Turkey indicates that a National Guideline would increase both physician awareness level for KD, and the rate of structured therapy implementation in pediatric patients, who suffer from inadequate treatment.

Key words: ketogenic, diet, epilepsy, child.

The ketogenic diet (KD), first defined in 1921 by Dr. Wilder,[1] is a well-established non-pharmacologic treatment for intractable epilepsy in pediatric patients. Classical KD was defined initially and later on three more types were qualified according to clinical requirements: the modified Atkins diet (MAD), the medium chain triglyceride diet (MCT), and the low-glycemic index treatment (LGIT).[2] It is still unclear how KD therapy (KDT) improves drug resistant epilepsy, but it is considered that high fat and low carbohydrate content induces biochemical response to starvation, thus energy for the brain is supplied by ketone bodies.[3]

For decades, KDT has been included in books as supplementary information but it was rarely implemented on pediatric patients as a part of clinical practice.[2] Instead increasing number of antiepileptic drugs (AEDs) were commonly preferred. In the early 2000s, KDT was first

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reported as an effective and safe approach in a small group of infants.[4] In the literature, it is reported that most of the pediatric patients with intractable epilepsy have been using at least two AEDs before they started KDT[2,5] and they typically discontinue one AED at a time during KDT.[2,6]

In December 2006, the Charlie Foundation invited 26 pediatric epileptologists and dietitians from nine countries with expertise in implementing the KDT for a panel, because KDT was used differently in various centers around the world, and standardized protocols were needed. After the consensus statement about patient selection, pre-KDT counseling and evaluation, specific dietary therapy selection, implementation, supplementation, follow-up management, adverse event monitoring, and eventual KDT discontinuation was published, it was supported by the Practice Committee of the Child Neurology Society.[7] In 2009, the first expert consensus guideline for the management of children on KDT was prepared for practical recommendations.[7] After nearly a decade, in 2018, the original committee members with more international experts gathered to evaluate new evidences in KDT.[2] The committee published key points about patient profiles for KDT, flexibility in initiation in this therapy, and recommendations for the ketogenic team.[2]

In the present survey study, we primarily aimed to determine KDT implementation frequency in daily clinical practice of pediatric neurologists who had expertise in this area; the number of pediatric patients with intractable epilepsy; the conditions that hindered or facilitated KD implementation; and also to discuss probable solutions, and to provide a roadmap so that KDT would become more prevalent for this patient group in Turkey.

Material and Methods

The present survey trial was performed on 27 pediatric neurologists who had expertise in KDT implementation, and were working in different affiliations in four main cities of Turkey; Adana (n= 3), Ankara (n= 12), Istanbul (n= 6) and Izmir (n= 6).

A 24-question survey was prepared to gather information from each center about the percentage of patients with intractable childhood epilepsy and their follow-up, alternative treatment options such as KDT, epileptic surgery and vagal nerve stimulation (VNS) applied in the center, physician approach to start the KD and to determine underlying reasons for the low rate of KDT. The survey contained 15 quantitative, 7 qualitative questions and 2 open ended discussion questions. Participants completed a Likert scale for qualitative questions related to KDT: 1= "I definitely do not agree", 2= "I do not agree", 3= "I am uncertain about it", 4= "I agree", 5= "I definitely agree".

Between December 2018 and February 2019, the survey was distributed electronically to all centers, and participants were invited to a meeting in their city for further discussion about the place of KDT among other treatment modalities in Turkey.

In the present descriptive study, statistical analysis of interrupted data was shown by using frequency (n) and percentage (%). It was performed by using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) Program.

Results

In the first part of the survey, introductory characteristics of the participating centers were collected. More than half of the participants (51.9%; n= 14) examined 26-50 patients per day at the pediatric neurology outpatient clinic, and 16 out of 27 participants (59.3%) reported that %26-50 of patients applying daily were diagnosed with epilepsy. Of those diagnosed with epilepsy, <25% were diagnosed with intractable epilepsy by 63% of physicians (n= 17). Nearly half of pediatric neurologists

(n= 14) reported that they had >150 patients with intractable epilepsy in their systems. Of critical revision of the manuscript for important intellectual content; administrative support, study supervision recorded intractable epilepsy patients, 51-75% were followed regularly. The age range of patients with intractable epilepsy were ranked as 7-12 years (44%), 1-3 years (29.6%), and 4-6 years (25.9%). During daily clinical practice, 59.3% of physicians spent 11 to 20 minutes for each epilepsy patient. Of the participants 7.4% reported spending <10 minutes whereas 22.2% reported spending <30 minutes with each patient

The second part of the survey contained questions about intractable epilepsy treatment (Table I). Epileptic surgery and VNS were performed in 59.3% and 40.7% of participating centers, respectively.

The last part of the survey contained questions about KDT (Table II).

Physicians reported four leading reasons for KDT implementation in fewer patients as; lack of an adequate number of personnel (53.8%), lack of a dietitian (52%), inadequate training of patients (24%), and inadequate experience of healthcare professionals (23.1%). Physical environment specifications and low socio-cultural level (both 15.4%) were ranked as the fifth reason. Lack of guidance in treatment, physician's hesitations due to probable problems, inadequate time spent for each patient, physicians being mainly concentrated in the pharmacological treatment algorithms, and loss of appetite in these patients were also emphasized by the participants (each 16.7%).

For patient incompliance to the diet therapy, physicians reported that the taste of the diet would not be appealing for children due to the high fat content (76.9%); the patient would not have continuous supervision (76.9%), and that the physician or nurse or dietitian had inadequate time to motivate the patient (73.1%). Other causes were described as high cost (30.8%), frequent illness in children (23.1%), and low treatment success rate (7.7%). One fifth of participants (20%) agreed that parents would not be able to understand the significance of the diet, moods of parents would hinder therapy, disadvantage of taste, patients would not attend visits, and low parental education level.

Table I. Distribution of indications for treatment approaches in intractable epilepsy patients at the centers.

	Range	Number of physician (n)	Percentage (%)
Epileptic surgery indicated*	<10%	24	92.3
	11-20%	1	3.8
	21-30%	1	3.8
	>30%	0	0
VNS indicated	0-10%	19	70.4
	11-20%	5	18.5
	21-30%	1	3.7
	>30%	2	7.4
Mean number of concomitantly used antiepileptic agents	1	3	11.1
	2	2	7.4
	3	11	40.7
	>3	11	40.7
Maximum number of concomitantly used antiepileptics	1-3	3	11.1
	4-6	20	74.1
	>6	4	14.8

VNS: vagal nerve stimulation.
*: one physician did not answer this question

Table II. Data about attitudes and experiences of physicians about ketogenic diet therapy.

		Number of physician (n)	Percentage (%)
If had optimum conditions, what percentage of your patients would you start on ketogenic diet therapy?	<25%	2	7.4
	26-50%	10	37.0
	51-75%	10	37.0
	>75%	5	18.5
What percentage of patients, do you think, would comply to ketogenic diet therapy?	<20%	3	11.1
	21-40%	10	37.0
	41-60%	10	37.0
	>60%	4	14.8
What percentage of patients with intractable epilepsy have you started ketogenic diet therapy?	<25%	22	84.6
	26-50%	3	11.6
	51-75%	1	3.8
	>75%	0	0
What percentage of your patients have responded to the ketogenic diet therapy?	0-30%	10	37.0
	31-60%	12	44.4
	61-90%	3	11.1
	>90%	2	7.4

Parameters defined for treatment response according to physicians are given in Table III.

Reasons of treatment failure among physicians who agreed and completely agreed were imprecise cooking of recipes (94%), inadequate family support (92.3%), inadequate consumption of meals (73%), incorrect indication (53.9%), and inefficiency of KD despite correct application (42.3%). It was also mentioned that limited cooperation with families, disbelief of parents to KD, lack of well-trained personnel, and children not being able to follow their meal plan at school or due to imitation of their siblings were other causes for treatment failure (each 16.7%).

Physicians discussed facilitating factors to implement KDT. The highest ranked factors defined for implementation were defined as presence of trained dietitians and physicians (69.2%), distribution of contact information of a dietitian (57.7%) and well-running ketogenic diet outpatient clinic (57.7%). The complete list is presented in Table IV.

Discussion

In this first survey study on KDT implementation in our country, we obtained a panoramic view of the main barriers in the widespread use of KDT in pediatric patients with intractable epilepsy, and how they could be overcome. In the four meetings held in different cities, the committee members, who were all pediatric neurologists, shared their experiences as well as insights both for daily practice and the requirement of a national KDT guideline.

As the birthplace of KD, the USA has the best-established facilities including many KD centers, the Charlie Foundation is particularly interested in providing all necessary information in KDT, and has a ketocalculator program to support parents' needs. In many European countries, KDT has been used for many decades now. From the United Kingdom (UK), Neal et al.[8] published the first randomized clinical trial of the KDT. The UK has also a parent-support group (the Matthew's Friends), which has been dedicated to providing information,

Table III. Parameters to define treatment response, (*according to physicians' reports*).

	I completely disagree (n, %)	I disagree (n, %)	I am uncertain (n, %)	I agree (n, %)	I completely agree (n, %)
No seizure	0	0	0	20 (76.9)	6 (23.1)
Decreased number of seizures	0	0	0	17 (65.4)	9 (34.6)
Decreased number of drugs	0	0	0	19 (73.1)	7 (26.9)
Improvement in cognitive functions	0	3 (11.5)	0	15 (57.7)	8 (30.8)
Improvement in success in school	0	2 (7.7)	1 (3.8)	16 (61.5)	7 (26.9)
Increased QoL	0	0	1 (3.8)	17 (65.4)	8 (30.8)
Improvement in motor functions	0	2 (7.7)	3 (11.%)	15 (57.7)	6 (23.1)
Improvement in EEG	0	1 (3.8)	2 (7.7)	18 (69.2)	5 (19.2)
Decreased number of hospitalizations	0	1 (3.8)	1 (3.8)	19 (73.1)	5 (19.2)

EEG: electroencephalography, QoL: quality of life.

Table IV. Factors to improve implementation of ketogenic diet therapy, (*according to physicians' reports*).

	I completely disagree (n, %)	I do not agree (n, %)	I am uncertain (n, %)	I agree (n, %)	I completely agree (n, %)
Detailed training of the child and parents	0	1 (3.8)	1 (3.8)	13 (50)	11 (42.3)
Contact information of a dietitian that parents can easily reach	0	1 (3.8)	0	10 (38.5)	15 (57.7)
Well-running ketogenic diet outpatient clinic	0	1 (3.8)	2 (7.7)	8 (30.8)	1 (57.7)
Ketogenic treatment algorithm	0	2 (7.7)	1 (3.8)	12 (46.2)	11 (42.3)
Ketogenic diet treatment guideline	0	2 (7.7)	1 (3.8)	10 (38.5)	13 (50)
Trained dietitian and physician	0	2 (7.7)	0	6 (23.1)	18 (69.2)
Other factors		N		Percentage (%)	
Financial support for the family (providing baseline devices, and transportation compensation etc.)		1		25	
Establishment of a patient association for KDT		1		25	
Experience sharing with new KDT starters		1		25	
Presence of a metabolism specialist		1		25	

KDT: ketogenic diet therapy.

training, support and education on all aspects of dietary treatments for epilepsy.[9] The Charlie Foundation, the Matthew's Friends, results of clinical randomized trial and efforts of experts to prepare practical guidelines have raised awareness for KDT worldwide. Thus, adapting KD to the local culture, life-style and nutrition had been tried sometimes with limited resources.[9,10]

In the present survey study, pediatric neurologists reported a high number of intractable epilepsy patients in their databases, and a great workload in their daily outpatient clinics. The time for comprehensive evaluation of the patient for KDT initiation and selecting the most suitable diet type was very limited (11-20 minutes/patient). Similar to the literature, pediatric neurologists emphasized primarily

on limited resources such as inadequate staff and the lack of dietitians.[9,11] It is evident that if neurologists decide to implement KDT, then they should be involved not only in treatment and follow-up, but also in dealing with preparing a diet list, or hospitalizing patients in order to train mothers for recipe preparation. In some institutions, physicians sometimes receive help from dieticians from other departments. A majority of centers do not have a kitchen applied for training mothers. Lack of information about KD, and the loss of a patient's appetite are additional complicating issues at the initiation. Pediatric neurologists indicated that they hesitate in KD implementation, because of probable problems during the therapy, and the lack of consensus or an algorithm or guideline.

During discussions for solutions, it is described that health authorities, specialty associations and non-profit organizations should cover all aspects of problems related to KDT implementation. The Turkish Ministry of Health is expected to establish KDT centers with trained KD team members and required supplies; systematic extensive healthcare should be planned, and initiated in our country. This should include an increasing number of trained dietitians, complete reimbursement of ready-to-use keto-products, building a national database for children with intractable epilepsy, and financial support for the families traveling to the center for visits.

It is considered that specialty associations should prepare standard training programs and support participants with hard-copy material such as patient and/or parent leaflets, posters in KDT centers, and cook-books for parents. Moreover, specialty associations should be proactive in training pediatric neurologists in KDT by holding workshops at academic meetings. Training programs should contain practical recommendations rather than theoretical content. Consequently, trained physicians would approach their patients with more confidence, and KDT would reach more patients. Additionally, such training programs would increase communication between physicians with common interests. Physicians would be able to improve their practice, they may refer patients, and share experiences in specific situations readily. One of the most effective solutions for pediatric neurologists is to introduce a national guideline for KDT.

The establishment of non-profit organizations, such as the Charlie Foundation, would help patients and parents to feel that they are not alone, and reinforce effective interactions and experience-sharing among them. They may define common concerns of the Turkish patients and parents, which would provide more target-oriented training for all parties. Participants underlined that support from the pharmaceutical industry is necessary to cover some of the needs. Donations to organizations or associations would increase the quality of healthcare services provided for patients.

Parents and/or patients can be easily demotivated and break the diets due to meticulous efforts in preparation of meals, poor palatability due to high-fat content, pediatric age group, difficulty in understanding KDT recipes, and having limited supervision after the first training. Treatment success depends on a good interaction between the KD team, the patient, and the family. The patient and family should be encouraged to attend follow-up visits (current attendance rate is around 50%), whereas additionally parents must have a firm grasp on not only of the diet, but also how to identify and act quickly to minimize adverse events and complications.

In conclusion, in the first study concerning KDT in Turkish pediatric patients with intractable epilepsy, concrete decisions were made for the better implementation of KDT in Turkey. Priory, a consensus has been reached concerning the preparation of a National Guideline in KDT. Following that, continuous training programs will be planned at academic meetings to increase the knowledge level and KDT awareness among pediatric neurologists. The Turkish healthcare authorities will be informed about the challenges that these patients and

their parents are faced with. Participants of this study have decided to pool their databases to design and conduct clinical trials in the future.

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Author contribution

All authors confirm their contribution with data input and interpretation, drafting the manuscript. EPA; contributed for survey planning, data acquisition, data analysis and interpretation, supervision for drafting the manuscript. AS; contributed for study concept and design, critical revision of the manuscript for important intellectual content; administrative support, study supervision. All authors reviewed and approved the final version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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