

Retrospective Study of the Effect of Ketogenic Diet Therapy on Vitamin D Levels in Children with Resistant Epilepsy

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Abstract

Aim: A ketogenic diet has proven to be very effective for childhood resistant epilepsies. Vitamin D deficiency affects all systems of the body and invites many diseases. The aim of our study is to compare the vitamin D status of children with resistant epilepsy, with and without ketogenic diet therapy.

Materials and Methods: Patients who were followed up in the Pediatric Neurology outpatient clinic with the diagnosis of resistant epilepsy treated ketogenic diet were included in the study. Our study was planned in case-control type, retrospective study. The study group was divided into two groups as those who applied ketogenic diet therapy and those who did not. The files of the patients were examined for demographic features, laboratory results, etiologic diagnosis and antiepileptic drugs were noted.

Results: A total of 129 patients (61 patients on ketogenic diet and 68 patients as control group) were included in the study. Of the total patient group, 71 (55%) were male and 58 (45%) were female. The mean age of all patients was 7.03 ± 7.06 (1 month - 18 years). Magnesium value was significantly lower in the ketogenic diet group ($p = 0.042$). Vitamin D deficiency was found to be significantly higher in the group receiving ketogenic diet ($p = 0.015$).

Discussion: Studies questioning the effect of ketogenic diet on vitamin D metabolism are limited to a very limited number of patient groups. In our study, considering the literature significant decrease was observed in the vitamin D and magnesium level after the third month in epileptic children receiving KD.

Conclusion: We would like to emphasize that the follow-up of vitamin D and magnesium deficiency in patients with resistant epilepsy who treated with KD may provide early diagnosis and treatment for complications that may arise.

Keywords: Ketogenic Diet; Resistant Epilepsy; Childhood; Vitamin D Level

Introduction

Despite adequate treatment and compliance with antiepileptic drugs (AED), 30 - 40% of patients with epilepsy develop resistant epilepsy [1]. Patients who are given alone or in combination and who do not reach long-term seizure free despite at least two suitable AEDs are defined as drug-resistant epilepsy according to International League Against Epilepsy (ILAE) 2010 criteria [2].

Ketogenic diet treatment is a high-fat and low-carb diet that has been used in epilepsy for more than a century. It was reported first time that, in 1921, epileptic seizures decreased following the fasting process by Rawle Geyelin. Similar to the fasting period, the ketogenic diet has a positive effect on epileptic seizures [3]. In the early 1930's, it was widely used, but later with the increasing number of new AEDs, ketogenic diet therapy remained in the background. The ketogenic diet has become popular again in the treatment of resistant epilepsy with studies from the 1990s [4].

Ketogenic diet treatment is not exactly sufficient in terms of nutrition. Ketogenic diet may be deficient some of vitamins and minerals, as the intake of foods containing carbohydrates and protein is restricted. There is an increased need for many nutrients in all forms of ketogenic diet treatment [5]. Before the ketogenic diet, the serum 25-hydroxyvitamin D (25-OHD) concentration of children with resistant epilepsy is low in 4% and insufficient in 55% [6]. However, AEDs can affect food metabolism, especially vitamin D. It has been suggested that the ketogenic diet causes a decrease in the level of 25-OHD together with the calcium (Ca) level as in many other nutrients, and therefore 200% more of the daily need of vitamin D should be given [7]. J Hahn., *et al.* detected lowered 25-OHD, Ca levels and high levels of alkaline phosphatase (ALP) levels of patients on a ketogenic diet in their study [8].

Aim of the Study

In our study, it was aimed to determine the effect of ketogenic diet on vitamin D level in children with resistant epilepsy.

Material and Methods

Subject selection

Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital. Patients between 1 month and 18 years of age who were diagnosed with resistant epilepsy who applied to University of Health Sciences Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Pediatric Neurology outpatient clinic were included. The study was planned retrospectively in case-control type. Patients who were followed up for resistant epilepsy were grouped as those who received ketogenic diet (patient group) and those who did not receive ketogenic diet (control group). As exclusion criteria; Patients who received ketogenic diet for less than three months, those who were excluded from follow-up for any reason or lacking laboratory tests were identified and those who used vitamin D at therapeutic dose except patients who used vitamin D prophylaxis.

Medical information of the patients included in the study were recorded on the case report forms. Age of patients, gender, type of epileptic seizure, etiological diagnosis, age of onset of seizure, number and type of AEDs used, whether ketogenic diet received (ketogenic diet group) or not (non-ketogenic diet group), electroencephalography (EEG) and cranial magnetic resonance imaging (MRI) findings, ambulation status, 25-OHD, Ca, P, Mg, ALP levels and the season when the examinations were carried out were recorded. The drugs used by the patients are divided into 2 groups as drugs that do enzyme induction and not. Between March and August taken as spring-summer, September-February; taken as autumn-winter.

Biochemical parameters in our study were studied with Abbott c16000 device and turbidimetric method. On the other hand, 25-OHD has been studied in the hormone laboratory of our hospital with the Abbott i2000 device using CMIA technology with the test protocols called Chemiflex. According to the ESPGHAN (European Pediatric Gastroenterology, Hepatology and Nutrition Society), defined the "Vitamin D deficiency" if the serum 25-OHD level is < 20 ng/ml, the "severe Vitamin D deficiency" if the serum 25-OHD level is < 10 ng/ml, according to 2013 report [9].

Statistical analysis

The data obtained as a result of the research were evaluated in SPSS 22.0 program. Tables showing absolute and percentage numbers were prepared for the study data and arithmetic averages were taken where necessary. For statistical analysis, chi-square test and independent sample student t-test were used when necessary. Numerical variables are summarized with mean ± standard deviation or median (minimum-maximum) values.

Results

A total of 129 patients were included; including 61 patients as ketogenic diet group (patient group) and 68 patients as non-ketogenic diet group (control group). Seventy one (55%) of the patient group were male and 58 (45%) were female. In the patient group 27 of the patients were boys (44.3%) and 34 were girls (55.7%). Of the control group, 44 were male (64.7%) and 24 were female (35.3%). The mean age of all patients included in the study was 7.03 ± 7.06 (min-max 1 month-18 years). It was 6.4 + 4.2 in the patient group, and 7.7 + 4.9 in the control group. There was no statistically significant difference between the patient groups in terms of age (p = 0.076) (Table 1).

	Patient group (Ketogenic diet group) n (%)	Control group (non-ketogenic diet group) n (%)	Total n (%)
Gender			
Male	27 (44,3)	44 (64,7)	71 (55)
Female	34 (55,7)	24 (35,3)	58 (45)
Age (years)	6,4+4,2	7,7+4,9	7,03 ± 7,06
Etiological diagnosis			
Idiopathic	15 (24,6)	13 (19,1)	28 (21,7)
Symptomatic	33 (54,1)	23 (33,8)	56 (43,4)
Cryptogenic	13 (21,3)	32 (47,1)	45 (34,8)
EEG findings			
Hypsarrhythmia	4 (6,6)	4 (5,9)	8 (6,2)
Burst Suppression	2 (3,3)	3 (4,4)	5 (3,8)
Focal	21 (34,4)	25 (36,8)	46 (35,6)
Generalized	16 (26,2)	27 (39,7)	43 (33,3)
Multifocal	18 (29,5)	9 (13,2)	27 (20,9)
MRI Abnormality			
Present	52 (85,2)	43 (63,2)	95 (73,6)
Absent	9 (14,8)	25 (36,8)	34 (26,3)
Mobilization			
Mobil	25 (41)	30 (44,1)	55 (42,6)
İmmobil	36 (59)	38 (55,9)	74 (57,3)
Number of antiepileptics			
1AED	3 (4,9)	0 (0)	3 (2,3)
2 AEDs	31 (50,8)	33 (48,5)	64 (49,6)
3 AEDs	19 (31,1)	33 (48,5)	52 (40,3)
4 ≤ AEDs	8 (13,1)	2 (2,9)	10 (7,7)

Table 1: Characteristics of intractable epilepsy patient and control groups.

When the classification was made according to the etiological diagnosis of patients in the ketogenic diet group, 15 of the patients were idiopathic (24.6%), 13 were cryptogenic (21.3%) and 33 were symptomatic patients (54.1%). In the non-ketogenic diet group, 13 patients were idiopathic (19.1%), 32 were cryptogenic (47.1%), and 23 were symptomatic (33.8%). When the etiological diagnoses of the patients included in our study were examined, symptomatic epilepsy was significantly higher in the ketogenic diet group, and cryptogenic epilepsy was significantly higher in the non-ketogenic diet group ($p = 0.008$).

In the ketogenic diet group, 11 of the patients (18%) had their first seizure in the neonatal period, 37 of them between 1 and 24 months (60.7%) and 13 of them after 24 months (21.3%). In the non-ketogenic diet group, 15 had their first seizure in the neonatal period (22.1%), 43 were between 1 and 24 months (63.2%), and 10 were after 24 months (14.7%).

Although there is no significant difference between the groups in terms of EEG abnormalities ($p = 0,199$); when we evaluated the subgroups, the multifocal EEG abnormality was found to be significantly higher in the ketogenic diet group ($p = 0.004$).

When the cranial MRI findings of the brain were analyzed, the frequency of structural abnormality of the ketogenic diet group was statistically significantly higher ($p = 0.004$).

In the ketogenic diet group, 25 of the patients were evaluated as mobile (41%) and 36 (59%) as immobile. Of the non-ketogenic diet, 30 were mobile (44.1%) and 38 were immobile (55.9%). No significant difference was found between the two groups ($p = 0.428$) in terms of mobility.

Tonic seizures were found to be the most common seizure type (54.4%, 42.6%) in both groups. Atonic type of seizures were found to be less common in the ketogenic diet group ($p = 0.026$). Compared to the number of AEDs used by the patients, the use of four or more AEDs was higher in the ketogenic diet group ($p = 0.018$).

Considering the AEDs used by the patients, the most frequently used drugs were levetiracetam, valproate and topiramate in both groups, respectively. The number of patients using levetiracetam was found to be significantly higher in the non-ketogenic diet group ($p = 0.025$). The number of patients using clobazam was significantly higher in the ketogenic diet group ($p = 0.006$).

In the laboratory results of the patients, Ca, P, ALP, 25-OHD there was no significant difference between the two groups. The magnesium value was significantly lower in the ketogenic diet group ($p = 0.042$). No significant difference was found between the laboratory values according to the seasons.

According to the patients using AEDs inducing and not inducing liver enzymes there was no statistically significant difference between the groups in terms of their Ca, P, Mg, ALP, 25OHD levels. While vitamin D deficiency was found significantly high in the ketogenic diet group ($p = 0.015$). There was no significant difference between the groups in terms of severe vitamin D deficiency (Table 2).

Vitamin D deficiency	Ketogenic diet group n (%)	Non-ketogenic diet group n (%)	P value
Yes	35 (57,4)	25 (36,8)	0,015
No	26 (42,6)	43 (63,2)	
Severe vitamin D deficiency			
Yes	7 (11,5%)	9 (%13,2)	0,487
No	54 (88,5%)	59 (86,8%)	

Table 2: Distrubution of patients with vitamin D and severe vitamin D deficiency.

Discussion

Approximately one-third of epilepsy patients have resistant epilepsy. It is reported in the literature that resistant epilepsy is more common in male patients [10]. In a study in which 442 intractable childhood epilepsy patients were taken in Pakistan in 2008, it was found that resistant epilepsy was higher in males [11]. Considering the distribution of patients in terms of gender in our study, male patients were found to be higher in patients with total resistant epilepsy, and female gender was higher in the ketogenic diet group ($p = 0.02$).

Berg, *et al.* [12] found that 52.2% of patients with resistant epilepsy had symptomatic epilepsy. Chawla, *et al.* [13] reported this rate as 80%. In our study, when looking at the total resistant epilepsy patients, symptomatic epilepsy was found to be the most common type of epilepsy in accordance with the literature. Cryptogenic epilepsy was found statistically higher in the non-ketogenic diet group, and symptomatic epilepsy was higher in the ketogenic diet group ($p = 0.008$).

In the study conducted by Karen, *et al.* the onset of seizure before the age of 1 was found to be a risk factor for resistant epilepsy [14]. Studies in children with resistant epilepsy showed that 52.6-66% had seizures before the age of 1 [13,15,16]. In other studies in the literature, the onset of the first seizure before the age of 1 was found to be a risk factor for resistant epilepsy [17,18]. In our study, it was found that most of the patients both patient and control groups (60.7% and 63.2%, respectively) had their first seizures before two years of age. When all patients with resistant epilepsy were evaluated, it was found that 82.2% of the patients had their first seizure under 2 years of age in accordance with the literature.

In one study, the most common seizure type in the resistant epilepsy group was myoclonic seizure [19], while in another group it was found to be focal onset seizure [20,21] and in another study as generalized tonic seizure [5,16,22]. In our study, tonic seizures were found to be the most common seizure type. The reason for these differences between the most common seizure types in children with resistant epilepsy may be the heterogeneous epilepsy types of the cases included in the study and different etiological reasons.

While Berg and Shinnar found that the focal epileptiform pattern is the most common EEG abnormality in patients with resistant epilepsy [23], Yoshinaga H., *et al.* found mostly generalized abnormalities [24]. In our study, generalized EEG abnormality (39.7%) was found in the non-ketogenic diet group and multifocal (34.4%) in the ketogenic diet group as the most common EEG abnormality.

In the studies of Sanjay C and Tae-Sung Ko, it has been shown that structural abnormalities are higher in patients with resistant epilepsy on cranial MRI [13,25]. In our study, structural abnormality was detected in MRI results of a significant number of patients in both groups (85.2% and 63.2%, respectively). Structural abnormality was found to be statistically significantly higher in the MRI results of the ketogenic diet group ($p = 0.004$).

Unfortunately in patients with resistant epilepsy, medication and its doses are increased over time, as adequate seizure control cannot be achieved. In the study of Sung, *et al.* the number of AEDs used by patients with resistant epilepsy was significantly higher [25]. In our study, the number of patients using four or more AEDs was found to be significantly higher in the ketogenic diet group ($p = 0.018$).

It has been suggested AEDs which induces enzyme in the liver to prevent hepatic transformation between 25-OHD with vitamin D. They suggested that vitamin D and 25-OH-D. were formed by inducing hepatic microsomal enzyme systems that accelerate the conversion of polar, biologically inactive products, or directly by inhibiting hepatic 25-hydroxylation of vitamin D [8]. In this study, patients were divided into two groups according to AEDs of their enzyme induction. However, there was no significant difference in terms of D-vitamin. D and other lab values between the two groups.

Treatment options for patients with resistant epilepsy are limited. Over the past decade, the use of a ketogenic diet has become widespread as another option. Adequate vitamins and minerals are normally present in a well-balanced diet. Foods containing fruits, vege-

tables, grains and calcium are restricted in the ketogenic diet [5]. The relationship between low vitamin D levels and epilepsy has been shown in several studies [26]. Vitamin D is thought to have an anticonvulsant effect [27]. Both AEDs and ketogenic diet have effects on vitamin D level [28]. There is little vitamin D and calcium in ketogenic diet food and evidence for decreased Vitamin D levels in children with epilepsy, and therefore both vitamin D and calcium should be supplemented [29]. In the literature review Bergqvist, *et al.* detected a significant decline in the level 25-OHD from the 3rd month to the 15th month in resistant epilepsy patients receiving ketogenic diet [23]. Similarly, Hahn, *et al.* found low levels of 25-OHD in patients receiving ketogenic diet for more than 1 year. In our study, vitamin D deficiency (< 20 µg/L) was found to be significantly higher in the ketogenic diet group ($p = 0.015$). When evaluated in terms of severe vitamin D deficiency (< 10 µg/L), no significant difference was found between the groups. We believe that this should be investigated with larger patient groups.

In the past ketogenic diet has been shown to provide insufficient magnesium levels [30]. Cross, *et al.* examined micronutrient status in children with intractable epilepsy treated with the ketogenic diet because there were no ketogenic diet specific supplement. They detected decline in magnesium status suggest that micronutrient status may be suboptimal in this group and that available formulations for ketogenic diet supplementation may need reviewing [31]. Consistent with the literature, we found that magnesium level was significantly lower in the children with resistant epilepsy who used ketogenic diet therapy compared to the control group without using a ketogenic diet.

In the studies of Bergqvist and Hahn, patients' bone density was also investigated and bone mineral density of patients who received ketogenic diet was found to be significantly lower [8,29]. Since our study was a retrospective study, bone densitometry measurements of patients could not be evaluated. However, in future studies, we believe that performing bone densitometry will significantly contribute to the evaluation of patients' bone health.

One of the important factors that determine the level of vitamin D is the sunlight that vary according to the seasons and environmental conditions. The main source of vitamin D (90%) for humans is sunlight. Lehtonen, *et al.* found that the deficiency of vitamin D was 9.1% in summer, while this rate was 13.4% in winter [32]. In our study, no significant difference was found between laboratory parameters between seasons.

There are many studies in the literature that question the relationship between vitamin D and AEDs [33,34]. However, studies questioning the effect of ketogenic diet on vitamin D metabolism are limited to a very limited number of patient groups. The fact that our study was planned retrospectively caused some data to be limited. Therefore, having received ketogenic diet treatment for at least 3 months as a criterion for inclusion in the study has caused a limitation in showing how the effect of the ketogenic diet on vitamin D and bone health varies with time. If we planned a study to look at vitamin D levels before the ketogenic diet was started and quarterly we could also examine the effects of ketogenic diet temporally. Also, it has not been evaluated what type of ketogenic diet treatment used and which supplements taken apart from vitamin D.

Conclusion

In conclusion, we would like to emphasize that the ketogenic diet used in the treatment of patients with resistant epilepsy causes vitamin D deficiency, in time. It is important to evaluate vitamin D levels in the controls of patients receiving ketogenic diet treatment and to start treatment of patients with deficiency early.

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