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The Effect of Ketogenic Diet on Serum Selenium Levels in Patients with Intractable Epilepsy

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Abstract The aim of the present study was to evaluate serum selenium levels in children receiving olive oil-based ketogenic diet (KD) for intractable seizures for at least 1 year. Out of 320 patients who were initiated on KD, patients who continued receiving KD for at least 12 months were enrolled. Sixteen patients who had selenium deficiency at the time of starting KD were excluded. Finally, a total of 110 patients (mean age 7.3 ± 4.2 years) were included. Serum selenium levels were measured at baseline and at 3, 6, and 12 months after treatment initiation by using atomic absorption spectroscopy. Selenium deficiency was defined as a serum selenium level <48 μg/L at each visit. Repeated measure ANOVA with post hoc Bonferroni correction was used for data analysis. Mean duration of KD was 15.3 ± 4.3 months. Mean serum selenium levels were significantly lower at 6 and 12 months of KD treatment (66.2 ± 23.3 and 57.2 ± 16.2 μg/L, respectively) compared to pre-treatment levels (79.3 ± 25.7 μg/L) ($p = 0.001$). On the other hand, selenium levels did not show any significant difference at 3 months of KD treatment (70.0 ± 21.2 μg/L) compared to baseline levels ($p = 0.076$). A total of 54 patients (49.1%) were diagnosed with selenium deficiency, and oral selenium medication was initiated for these patients. No relevant clinical findings were detected, and echocardiographic findings were normal in all patients. The decline of the serum selenium concentrations after 6 and 12 months of ketogenic diet suggests that patients on this highly prescriptive dietary treatment need close monitoring of this trace element.

Keywords Children · Epilepsy · Ketogenic diet · Selenium

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Introduction

High-fat ketogenic diet (KD) is one of the most effective therapies for intractable epilepsy and the sole treatment modality for glucose transporter protein-1 (GLUT-1) deficiency and pyruvate dehydrogenase complex deficiency [1]. Moreover, this dietary treatment has been increasingly used in recent decades for the treatment of obesity, inflammation, and diabetes [2–4], cancer [5, 6], migraine [7], and autism spectrum disorders [8] in addition to refractory epilepsy. Together with the expanding utilization rates of this therapy, some side effects related to this highly strict diet have been increasingly reported in recent years. The well-established complications of this diet include hyperlipidemia [9], protein-losing enteropathy and hypoalbuminemia [10, 11], gastrointestinal disturbances (nausea/vomiting, diarrhea, constipation, etc.) [12], and renal stones [13] in addition to other acute or chronic side effects.

Selenium is a trace element which is essential for vital metabolic functions. Selenium exerts its effects mainly through incorporation into different selenoproteins. The well-known functions of this element are protecting the body against free radicals and cancer, modulation of thyroid functions, regulation of inflammatory response and fertility, and protection of cardiac muscle cells [14, 15]. The main sources of selenium in human diet are cereals, meat, seafood, eggs,

and dairy products [16]. Selenium deficiency has been well described in elderly population [17], in patients with inflammatory bowel disease [18], in obese children [19], in obese adults after bariatric surgery [20], in women with polycystic ovary syndrome [21], in children with nutritional deprivation [22], and in children receiving parenteral nutrition [23].

In the literature, coexistence of selenium deficiency and cardiomyopathy has been reported in a number of epileptic patients receiving KD treatment [24–26]. However, only three studies have evaluated the serum selenium levels in epileptic patients during KD treatment [26–28]. The aim of the retrospective study presented herein was to evaluate the serum selenium levels in children receiving olive oil-based KD for intractable seizures for at least 1 year.

Methods

Study Population

Patients aged 6 months to 18 years who had multidrug-resistant epilepsy were recruited for the study. Inclusion criteria were (a) at least two seizures per week despite the use of at least two antiepileptic drugs and (b) strict compliance to KD and attendance to all required clinic visits for follow-up purposes. Exclusion criteria were (a) use of medications other than antiepileptic drugs such as multivitamin-mineral supplementations or fish oils within the last 6 months, (b) severe malnutrition, and (c) parents' unwillingness about their child's participation to the study. Metabolic contraindications for KD (primary carnitine deficiency, beta oxidation defects, and pyruvate carboxylase deficiency) were ruled out. Out of 320 patients who were initiated on KD, patients who remained on KD for at least 12 months were enrolled. Sixteen patients who had selenium deficiency at the time of starting KD were excluded. Finally, a total of 110 patients (mean age 7.3 ± 4.2 years, 58 boys, 52.7%) were included in the study.

Dietary Characteristics and Data Collection

Olive oil-based KD was introduced using a non-fasting gradual initiation protocol. Ketogenic diets were started at a 3:1 or 4:1 ratio (fat/protein plus carbohydrate), and the protein content was generally kept at the minimum requirements for age. Diets were prepared with common, locally available food and modified according to the child's food preferences. The initial energy contents were estimated based on the subject's average pre-diet intake and level of physical activity, and generally, 75–85% of the recommended energy requirements were given. Extra virgin olive oil was used as the primary fat source (80–85% of the daily fat consumption) [9]. Blood glucose and ketone levels were measured twice a day until blood ketone concentrations stabilized between 4 and 5 mmol/L. Ratio of the diet was adjusted according to blood ketone levels and seizure control rates.

Demographic and etiologic data, seizure frequency, antiepileptic drug usage, complications, and compliance to the diet were recorded before and after 3, 6, and 12 months of treatment. Patients who were seizure-free and had >50% seizure reduction were accepted as KD responders.

Biochemical Analysis

Blood samples were drawn into plain tubes from all participants in the morning after an overnight fast. Serum selenium levels were measured at baseline and at 3, 6, and 12 months of treatment. Selenium concentrations were determined by atomic absorption spectroscopy (Perkin-Elmer 1100B, Waltham, MA, USA). Selenium deficiency was defined as a serum selenium level <48 μg/L at each visit [29].

Statistical Analysis

SPSS version 15.0 for Windows was used for all statistical analyses. The data derived from a normally distributed population (Kolmogorov-Smirnov test, $p > 0.05$) were reported as mean ± standard deviation. Variables which were not normally distributed (Kolmogorov-Smirnov test, $p < 0.05$) were expressed as median (25–75 interquartile range (IQR)). Categorical variables were reported as numbers (%).

Mann-Whitney U test was used to compare the average values of the two groups (patients with selenium deficiency vs. without deficiency). All p values were two-tailed, and group differences with $p < 0.05$ were considered to be statistically significant.

Univariate repeated measure analysis of variance (ANOVA) with a Greenhouse-Geisser correction was performed to analyze changes in serum selenium levels over time (prior to and at 3, 6, and 12 months after KD treatment). Repeated measure ANOVA was performed for all groups and also for these two groups (patients with selenium deficiency vs. without deficiency), separately. To identify the source of the significant differences among mean values, post hoc analysis was performed using the Bonferroni test. The significance level for post hoc multiple comparisons was set at 0.005.

Results

Table 1 summarizes baseline characteristics of the patients and etiology of the seizures. The mean duration of KD was 15.3 ± 4.3 months. Initial KD ratio was 3:1 in 103 children (93.6%) and 4:1 in 7 children (6.4%). At 3rd, 6th, and12th months of the treatment, 53 (48.1%), 48 (43.6%), and 46 (41.8%) children were on 3:1 ketogenic diet ratio,

Table 1 Demographic features and baseline characteristics of the patients

Characteristics	Number (%)
Age (years)[a]	7.3 ± 4.2 6.5 [4.0–8.0]
Gender (F/M)	52/58
Etiology	29 (26.4)
Idiopathic	16 (14.5)
Perinatal hypoxia	11 (10.0)
Malformation of cortical development	10 (9.1)
Tuberous sclerosis	10 (9.1)
Idiopathic West syndrome	7 (6.4)
GLUT-1 deficiency	4 (3.6)
Dravet syndrome	4 (3.6)
Encephalitis	19 (17.3)
Other	
Number of antiepileptic drugs at baseline[a]	2.8 ± 0.7 3 [2.0–3.0]
Age at epilepsy onset (years)[a]	0.8 ± 1.9 0.6 [0.1–1.0]
Age at the beginning of the diet (years)[a]	5.8 ± 4.3 5.0 [3.0–7.0]

[a] mean ± SD, median [IQR]

respectively; 57 (51.9%), 62 (56.4%), and 64 (58.2%) children were on ≤2:1 ratio, respectively. No patient received 4:1 ketogenic diet ratio after 3 months of therapy. Daily protein intake was between 1 and 1.5 g/kg of patients. Outcomes of KD were as follows: 52 (47.3%) patients became seizure-free; 36 (32.7%) had ≥50% decrease in seizures; and the remaining 22 (20.0%) patients had < 50% decrease in seizures during KD treatment.

In the overall study population, mean serum selenium levels were significantly lower at 6 and 12 months of KD treatment (66.2 ± 23.3 and 57.2 ± 16.2 μg/L, respectively) compared to pre-treatment levels (79.3 ± 25.7 μg/L) ($p = 0.001$). On the other hand, selenium levels did not show any significant difference at 3 months of KD treatment (70.0 ± 21.2 μg/L) compared to baseline levels ($p = 0.076$). A total of 54 patients (49.1%) were diagnosed with selenium deficiency (Fig. 1); 9, 17, and 28 patients were diagnosed at 3, 6, and 12 months, respectively. Oral selenium medication was initiated (2 μg/kg/day) for all patients diagnosed with selenium deficiency [30]. Age (median [IQR]: 6.0 [4.0-7.0] and (7.0 [4.0-10.0], respectively, $p = 0.287$), gender (males: 24 [48.5%] and 34 [56.1%], respectively, $p = 0.640$) and KD duration (median [IQR]: 15 [12–18] and 15 [12–24], $p = 0.356$) did not show any difference between the patients with and without selenium deficiency. Selenium deficiency was detected in 10 patients (34.4%) with idiopathic epilepsy, 10 (62.5%) with perinatal hypoxia, 6 (54.5%) with cortical malformation, 6 (60.0%) with tuberous sclerosis, 4 (57.1%) with GLUT-1 deficiency, 3 (30.0%) with idiopathic West syndrome, 2 (50.0%) with Dravet syndrome, 2 (50.0%) with encephalitis, and 11 (57.8%) with other etiological groups. There was no significant difference between groups regarding the rate of selenium deficiency ($p > 0.05$). We found no clinical evidence of cardiomyopathy, and all patients had normal echocardiographic findings before and after 12 months of KD treatment.

Despite appropriate treatment, serum selenium levels in patients with selenium deficiency were significantly lower compared to the other group at 3, 6, and 12 months of treatment (Table 2). In the selenium deficiency group, selenium levels were significantly lower at all follow-up time points compared to pre-treatment measurements (Table 2). Moreover, even in the second group in which there was no deficiency, serum selenium levels were significantly lower at 12 months of KD treatment compared to baseline and 3 months of treatment (Table 2).

All patients were on different combinations of multiple antiepileptic drugs at the beginning of treatment, including valproic acid, phenobarbital, carbamazepine, oxcarbazepine, topiramate, levetiracetam, benzodiazepines, and zonisamide. Since the use of carbamazepine and valproate has been previously shown to be associated with selenium deficiency [31], we stratified the patients according to their antiepileptic drug combinations: the first group was receiving medications including carbamazepine and/or valproate (72 patients, 65.4%) and the second group was receiving treatment with other combinations (38 patients, 34.6%). There was no significant difference between these two groups regarding selenium levels at baseline (82.1 ± 28.6 and 87.2 ± 22.2 μg/L, respectively, $p = 0.580$).

Discussion

In the present study, we investigated serum selenium level alterations in epileptic children treated with KD. The main finding of this study is the decreased selenium levels observed at 6 and 12 months of the diet in patients who were treated with olive oil-based KD.

In this study, nearly half of the children receiving ketogenic diet were diagnosed with selenium deficiency. In the literature, selenium deficiency and related cardiac dysfunction have been reported in three cases in patients on KD treatment [24–26]. However, only three studies appear to have evaluated the serum selenium levels in epileptic patients during KD treatment [26–28]. Hayashi et al. [27] investigated serum trace element levels in six patients after 6 months of KD treatment, and Christodoulides et al. [28] investigated these parameters in 91 patients after 12 months of treatment. Both of these studies found that serum selenium levels decreased along with the ketogenic diet treatment similar to other trace elements. Bergqvist et al. [26] evaluated 40 children and

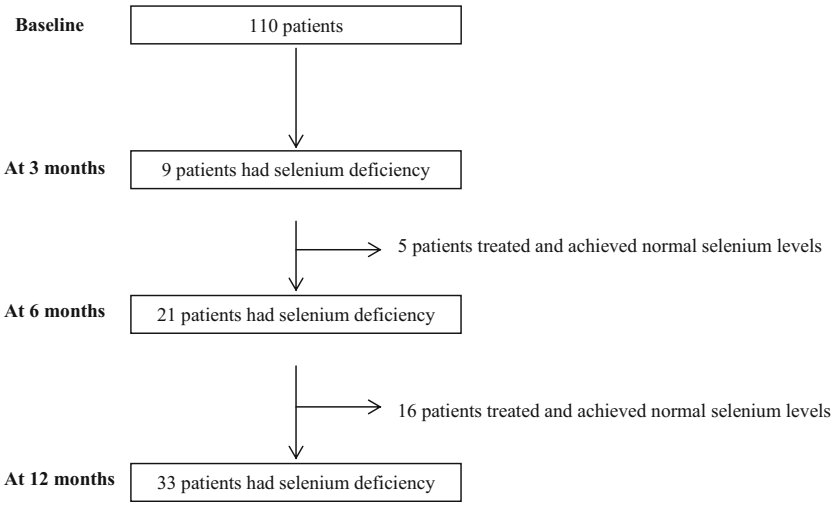

Fig. 1 Selenium status of the patients during ketogenic diet treatment

found selenium deficiency in eight (20%) of the patients. We detected selenium deficiency in half of our patients. The reasons for the different selenium deficiency ratios between these two studies may be the different geographical regions (as the dietary selenium content depends on the soil selenium content), different cutoff values for selenium deficiency (48 vs. 60 μg/L), different KD contents, and lastly, different KD ratios. Furthermore, different treatment doses of selenium (2 μg/kg/day vs. 20 μg/day plus daily Brazil nuts) were used in these two studies. Ketogenic diet, even in different contents (olive oil-based, medium chain triglyceride-based, classical, etc.), provides limited selenium-rich food as proteins are restricted. High-fat products are low in selenium. We initiated KD with the 3:1 ratio in majority of our patients. This ratio was further reduced in most of the patients due to high blood ketone concentrations and adequate seizure control during follow-up. Using lower KD ratios means that protein content of the diet is increased. Even though protein content of diets was relatively increased, these patients could not reach to healthy children's measures regarding daily protein consumption. Moreover, since constipation is a commonly seen complication of the ketogenic diet treatment, we treated constipated patients with more vegetable-contented menus rather than animal protein resources. All of these factors may contribute selenium deficiency in patients with ketogenic diet treatment.

In this study, oral selenium medication was initiated to all patients who were diagnosed with selenium deficiency. In recent studies, presence of selenium deficiency has been found to be related to anemia and poor cognitive performance in healthy children [32, 33]. Although the medical treatment of healthy population with asymptomatic selenium deficiency or selenium supplementation of healthy children in current literature is not clear [34, 35], we started oral selenium medication to all of our patients due to their great number of medical comorbidities (malnutrition, multidrug use, selenium-deficient ketogenic diet, etc.) and risk of cardiomyopathy. Five patients' serum selenium levels remained low despite 2 μg/kg/day oral

Table 2 Serum selenium levels of patients with and without selenium deficiency at baseline and during ketogenic diet treatment (mean ± SD, median [IQR])

Groups	Serum selenium levels (μg/L)				*p* value[a]
	Baseline	3rd month	6th month	12th month	
Patients with selenium deficiency (*n* 54)	79.4 ± 23.8 74.0 [57.3–95.8]	68.2 ± 24.6 63.9 [48.6–85.2]	61.1 ± 25.4 51.8 [45.1–73.2]	47.5 ± 13.6 45.4 [39.7–58.0]	<0.05[b]
Patients without selenium deficiency (*n* 56)	80.2 ± 27.3 73.8 [56.1–98.2]	79.6 ± 24.3 73.7 [61.4–93.3]	71.5 ± 20.4 66.1 [53.9–86.0]	65.5 ± 13.7 60.3 [56.3–70.5]	<0.05[c]
p value[d]	0.841	0.024	0.008	0.000	

[a] Univariate repeated measure ANOVA with Bonferroni correction was used to compare the changes in selenium levels of the patients in each group over time

[b] Baseline vs. all other months ($p = 0.049$, $p = 0.005$, and $p = 0.001$, respectively)

[c] Baseline vs. 12 months ($p = 0.014$) and 3 months vs. 12 months ($p = 0.003$)

[d] Mann-Whitney *U* test was used to compare the differences between the two groups at the same time

selenium supplementation, but all of them were asymptomatic. Low selenium levels can be caused by insufficient dose of medication in these patients. In a recent pediatric study, it was found that although daily dietary selenium mean intake was above the recommended level in 99.4% of healthy school children, 19.5% of these children had selenium deficiency [36]. Therefore, higher doses can be tried for reaching higher serum selenium levels in our patients. Another reason for the lower serum selenium level is said to be mutations or polymorphisms in the genes that are responsible for the transport of selenium [37]. We could not perform genetic evaluation of our patients. On the other hand, since the selenium levels in all of the patients were normal before the diet, lower selenium levels were attributed to restricted diet other than genetic factors.

This study has some limitations. The first limitation is the short follow-up period of the patients. It would have been useful to have further data on serum selenium levels after 18 and 24 months, particularly for the cases where micronutrients had a decreasing trend through the course of treatment. Although this is the largest series in the literature, the relatively small sample size of the study group is the second limitation. A larger study may compare different age groups, different etiologic groups, and different antiepileptic combinations regarding selenium levels of the patients. The third limitation is the lack of selenium-dependent enzyme activity measurements (such as glutathione peroxidase) in this study. The final limitation is the lack of data regarding the daily selenium consumption of our patients.

In conclusion, serum selenium concentration tends to fall during the ketogenic diet treatment. Although no relevant clinical or echocardiographic findings were observed in our patients, it is known that selenium deficiency may result in impaired myocardial function, which has previously been reported in children on KD as mentioned above [24–26]. The decreased serum selenium levels suggest that patients on this strict diet need close monitoring as well as supplementation of this trace mineral during the treatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study has received ethical approval (Number of ethical approval: 2016/19-15) from the Ethics Committee of Dokuz Eylul University Faculty of Medicine. Written informed consent was obtained from parents of the children enrolled to the study.

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