Evaluation of Bone Metabolism in Children Using Antiseizure Drugs: A Single-Center Experience and Review of the Literature

Emine Tekin[1] Ülkü Şiraz Gül[2] Sultan Köker Aydın[3] Adem Yasin Köksoy[4]

[1] Pediatric Neurology Division, Faculty of Medicine, Giresun University, Maternity and Children Hospital, Giresun, Turkey
[2] Department of Pediatric Endocrinology, Faculty of Medicine, Erciyes University, Kayseri, Turkey
[3] Division of Pediatric Hematology, Department of Pediatrics, Antalya Training and Research Hospital, Antalya, Turkey
[4] Division of Pediatric Nephrology, Department of Pediatrics, Van Training and Research Hospital, Van, Turkey

Address for correspondence Emine Tekin, MD, Pediatric Neurology Division, Faculty of Medicine, Giresun University, Maternity and Children Hospital, Giresun, Teyyaredüzü mh. Atatürk Bulvari No: 333 Merkez, Giresun 28200, Turkey (e-mail: dreminetekin@yahoo.com).

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Abstract

The effect of anti-seizure drugs (ASDs) on bone mineral density (BMD) is a controversial topic. This study investigated the effect of monotherapy and polytherapy drugs separately. Patients with a history of epilepsy treated with the same ASDs for more than 6 months were included in the study. Data regarding patient demographics, biochemical markers related to bone metabolism (calcium, phosphorus, alkaline phosphatase, parathyroid hormone, vitamin D), and BMD with dual-energy X-ray absorptiometry (DXA) were collected and compared. In total, 104 children with epilepsy using valproic acid (VPA), levetiracetam (LEV), carbamazepine (CBZ) alone or in combination and 22 healthy controls were evaluated. The ages of the children (64 boys, 62 girls) ranged between 2 and 17, with a mean of 9.50 ± 4.03 years. BMD or *Z*-scores did not differ among the monotherapy groups or between them and the polytherapy group. The lowest mean *Z*-score was in the VPA group but without statistical significance. Alkaline phosphatase levels were significantly higher in the group using CBZ. Calcium levels significantly differed between the groups ($p = 0.001$). The CBZ and LEV groups had the lowest calcium levels. However, phosphorus and vitamin D measurements did not significantly differ by ASDs used. Unfortunately, low vitamin D levels were evident in all children with epilepsy and even among controls. Physical activity, sun exposure, and calcium intake might be recommended in children treated with ACDs and in combination with additional risk factors monitoring via DXA should be considered. Further studies in a large population are necessary to judge which ASDs are more at risk to reduce bone mineralization than others.

Keywords
- bone mineralization
- bone mineral density
- dual-energy X-ray absorptiometry
- epilepsy
- vitamin D

Introduction

Epilepsy is one of the most common diseases for which children are referred to pediatric neurology outpatient clinics. International League Against Epilepsy defines epilepsy as two or more seizures occurring more than 24 hours apart. The first-line treatment of the disease is medical therapy with anti-seizure drugs (ASDs), first with monotherapy. If

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monotherapy is not sufficient, then polytherapy may be used according to the patient's age, seizure type, or epileptic syndrome. Other modalities, such as ketogenic diet, vagus nerve stimulation, and epileptic surgery, are preferred in refractory seizures.[1]

Various reports are available on bone mineralization of children with epilepsy. These generally recommend considering vitamin D and plasma calcium (Ca) status. In addition, bone mineral density (BMD) with dual-energy X-ray absorptiometry (DXA) may be considered if immobilization, polytherapy, or other severe comorbidity exist since these children are at risk of low BMD.[2,3] Low bone mineral mass or BMD is the preferred term for pediatric DXA reports when BMD *Z*-scores are less than or equal to −2.0 SD.[4]

The pathogenesis of the negative effects of ASDs on bone mineralization is not clear, especially for the new generation ASDs. Liver cytochrome c activation and the degradation of vitamin D by enzyme-inducing drugs and the disruption of Ca, phosphorus (P), and parathyroid hormone (PTH) metabolism may be responsible.[3,5]

The most common and reliable method for evaluating bone health is DXA which uses X-ray beams.[6,7] The use of T-score (SD score compared with young adults) is inappropriate for children. The *Z*-score (SD compared with persons of the same age), calculated according to normative data from children of the same chronological age, sex, and ethnicity, is more useful.[8]

The present study investigates the relationship between low bone mineralization and epilepsy in children. In addition, we consider whether there are differences between the drugs used as monotherapy and ASDs used as polytherapy. We also present a review of the current literature in Turkey and the world related to this topic.

Materials and Methods

The study was performed at the Pediatric Neurology Outpatient Clinic, Van Training and Research Hospital, Turkey, between August 2016 and June 2018. Children using the same anti-seizure medication/medications (mono/polytherapy) for more than 6 months were included in the study. The patients were divided into four groups according to the therapy administered as valproic acid (VPA), levetiracetam (LEV), and carbamazepine (CBZ), the three monotherapy groups, and VPA combined with levetiracetam (VPA + LEV), the only polytherapy group. Combinations like CBZ + VPA or LEV + CBZ are not commonly used, so these groups were not evaluated. The healthy control group consisted of patients presenting to the pediatric neurology outpatient clinic with a headache. These children had no bone pathology or systemic disease. Our analysis covered subject data regarding epilepsy assessed with DXA scan, biochemical parameters, and demographic variables in all groups (VPA, CBZ, LEV, VPA + LEV, and control).

All subjects were ambulatory, none having significant comorbidities such as cerebral palsy or severe psychiatric problems. There was no known history of fractures in any of the patients. Also, none of them were sedentary or involved in any extra sporting activities.

We compared demographic variables (age, gender, weight, height, body mass index), epilepsy type, cranial magnetic resonance imaging (MRI) results, and biochemical parameters, such as Ca, P, alkaline phosphatase (ALP), vitamin D, PTH, between the monotherapy, polytherapy, and control groups. BMD was measured by DXA scanning (Stratos-DR, DMS, France) of the lumbar spine. DXA was only studied in children with epilepsy and therefore compared among the monotherapy groups and between the monotherapy and polytherapy groups due to ethical reasons.

BMD *Z*-score values of the patient: aBMD (areal BMD) of their total L1-L4 vertebrae was calculated by subtracting their age-appropriate reference value and dividing by the standard deviation of that age. Since the DXA value may be much lower in cases with short stature, aBMD values were determined according to height age-appropriate references. The DXA *Z*-score data determined for Turkish children is taken as the source.[9]

Statistical Analysis

Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used in the data analysis. The conformity of quantitative data to normal distribution was tested by the Shapiro-Wilk test and graphical examinations. The Student's *t*-test was used to compare normally distributed quantitative variables between two groups, and the Mann-Whitney U test to compare non-normally distributed quantitative variables. Besides, the one-way analysis of variance (ANOVA) was used in comparisons of three or more groups with normal distribution and the Bonferroni test in binary comparisons. Furthermore, we conducted the Kruskal–Wallis test to compare three or more groups without normal distribution and the Bonferroni-Dunn's test for binary comparisons. Moreover, the Pearson's Chi-square and the Fisher-Freeman-Halton tests were performed to compare qualitative data. Statistical significance was accepted as $p < 0.05$. NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, United States) program was used for statistical analysis.

Ethical Issues

Informed consent was obtained from all individual participants included in the study. All procedures performed in this study 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 was approved by the Institutional Ethics Committee. (Date and no:November 07, 2019/11)

Results

The study included 126 children (104 with epilepsy and 22 controls), and 62 (49%) were girls. The ages of the children

ranged between 2 and 17, with a mean of 9.50 ± 4.03 years. ►**Table 1** shows the electroencephalography and MRI findings, and ASDs used. Medication dosages per kilogram were similar for each group. ►**Table 2** shows the demographic variables and comparison of biochemical parameters between the groups.

There was no significant difference between the groups by age, weight, height, or BMI. We also observed no difference between the groups by lifestyle and physical activity. However, there were differences regarding gender, and girls were dominant in the VPA group, whereas boys in the other groups. Nevertheless, BMD or *Z*-scores did not differ among the monotherapy groups or between them and the polytherapy group. The lowest mean *Z*-score was in the VPA group but without statistical significance.

We observed a statistically significant difference between the ASD groups in terms of ALP ($p = 0.045$). Relevant binary comparisons revealed the significance originated from the CBZ group, which had higher ALP measurements than the VPA group ($p = 0.022$). No further significance was detected in the other binary comparisons. However, when we look at the ALP *Z*-score described by Turan et al,[10] we found that none of the epilepsy patients or healthy children had an ALP value above 2SD. ALP values were close to the mean in 32 of 104 epilepsy patients and in five healthy children, and were below −2SD in all other children. This situation was attributed to nutritional deficiency in children.

Although there was no statistically significant difference between the PTH measurements of the VPA, LEV, CBZ, VPA + LEV, and control groups ($p = 0.068$), the PTH levels were notably high in the CBZ group. Besides, Ca levels significantly differed between the groups ($p = 0.001$). The CBZ and LEV groups had the lowest Ca levels. However, P and vitamin D measurements did not significantly differ by ASDs used. Unfortunately, low vitamin D levels were evident in all children with epilepsy and even among controls.

Furthermore, there was no significant relationship among PTH, ALP, and *Z*-scores. However, vitamin D was found low (10.45 ± 5.20 ng/mL) in the group with high PTH (>65 pg/mL) with a significant difference ($p = 0.001$).

Moreover, among the children with epilepsy, 16 patients had low BMD, of which five were using VPA, five were using CBZ, four were using LEV, and two were using VPA +LEV. The patient with the lowest *Z*-score (−7,2) used VPA, with an 8 ng/mL vitamin D level. This patient was thought to have a defect in the bone mineralization.

All patients with low bone density had low vitamin D levels. Then we opted for correlation analysis to look for whether the BMI (anthropometry) or vitamin D deficiency do more than ASDs. There was no correlation between vitamin D and *Z*-score, but a significant statistical correlation was found between BMI and *Z*-score (p: 0.015). It was determined that the formulation as BMI × 0.1–2.6 = *Z*-score was valid for 57% of the patients.

No significance was found between vitamin D and *Z*-score by linear regression model. A low level of positive significant correlation was detected between BMI and *Z*-score (regression value: 0.23).

Discussion

BMD measurements have always been relevant for physicians prescribing ASDs. The present study aims to review the literature by summarizing the research done since the late 1900s. We present the articles chronologically, mainly including the studies conducted in Turkey. ►**Table 3**

Table 1 Gender, EEG, MRI findings and medications of the patients

		N	%
Patients	Girls	62	49
	Boys	64	51
Epilepsy	Generalized	62	60
	Focal	41	40
EEG	Normal	48	47
	Generalized epileptic	24	24
	Focal epileptic	31	30
MRI	Normal	42	40
	Abnormal	30	29
	No MRI/not available	32	31
ASD	VPA	37	36
	CBZ	19	18
	LEV	29	28
	VPA + LEV	19	18

Abbreviations: ASD, anti-seizure drug; CBZ, carbamazepine; EEG, electroencephalography; LEV, levetiracetam; MRI, magnetic resonance imaging; VPA, valproic acid.

Table 2 Evaluation of descriptive properties and biochemical parameters according to ASDs used

Descriptive properties and biochemical parameters		Control (*n*: 22)	Patients with epilepsy ($n = 104$)				*p*-Value
			VPA ($n = 37$)	CBZ ($n = 19$)	LEV ($n = 29$)	VPA + LEV ($n = 19$)	
Age (year)	*Mean* ± *SD*	10.41 ± 3.54	9.86 ± 3.89	9.26 ± 3.71	7.97 ± 5.01	10.32 ± 3.04	*0.240*[d]
Gender; *n (%)*	Girl Boy	16 (72.7) 6 (27.3	23 (62.2) 14 (37.8)	6 (31.6) 13 (68.4)	12 (41.4) 17 (58.6)	5 (26.3) 14 (73.7)	*0.015*[a,c]
Height (cm)	Median (IQR)	133 (123–150)	136 (119–156)	130 (120–150)	117 (100–155)	140 (121–151)	*0.301*[d]
Weight (kg)	Median (IQR)	33 (23–43)	34 (21–48)	30 (21–38)	22 (15.5–49.5)	35 (22–40)	*0.194*[e]
BMI (kg/m^2)	Median (IQR)	17.22 (15.80–21.36)	17.36 (15.65–19.28)	16.29 (15.13–18.13)	16.29 (14.98–18.14)	17.26 (14.92–18.66)	*0.412*[e]
BMD	Median (IQR)		0.66 (0.46–0.80)	0.5 (0.4–0.6)	0.47 (0.42–0.76)	0.59 (0.51–0.75)	*0.106*[e]
Z-score	Median (IQR)		−0.51 (−1,65–0,45)	−1.3 (−2.1 to −0.6)	−0.73 (−1.57 to −0.27)	−1.06 (−1.38 to 0.43)	*0.394*[d]
Z-score	< − 2SD (*n*) > − 2SD (*n*)		5 32	5 14	4 25	2 17	
ALP (U/l) ($n = 124$)	Median (IQR)	225 (181–238)	181 (150–269)	260 (217–371)	222 (166–282)	205 (157–269)	*0.045*[a,d]
PTH (pg/mL) ($n = 121$)	Median (IQR)	34 (29–50)	43 (30–70)	46.5 (34–88)	36 (24.5–51)	37.5 (25.7–51)	*0.098*[e]
Ca (mg/dL) ($n = 124$)	Median (IQR)	9.8 (9,4–10)	9.8 (9.6–10)	9.2 (9–9,5)	9.3 (9–9.6)	9.5 (9.2–10.1)	*0.001*[d,b]
P (mg/dL) ($n = 124$)	Median (IQR)	4.4 (4–4.9)	4.7 (4.1–5.1)	4.8 (4.5–5.3)	5 (4.2–5.2)	4.4 (4–5)	*0.417*[d]
Vitamin D (ng/dL) ($n = 122$)	Median (IQR)	15 (11–25)	15 (9–22)	13 (10–15)	16 (11–21)	15 (11–25)	*0.455*[e]

Abbreviations: CBZ, carbamazepine; IQR, interquartile range; LEV, levetiracetam; VPA, valproate.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]Pearson Chi-square test.
[d]One-way ANOVA test.
[e]Kruskal–Wallis test.

Table 3 Summary of studies evaluating BMD in children with epilepsy regarding DXA and biochemical markers

Study	Number (*n*) of patients and anti-epileptic drugs	DXA region	Biochemical markers	Significance
Sheth et al,1995	VPA *n*:13, CBZ *n*:13, control *n*:27	Distal radius, L2-L4 vertebrae		CBZ caused non-significant reduction (<5%) at both sites but VPA caused 14% reduction at L2–4 ($p = 0.003$), 10% reduction at distal one-third radius ($p = 0.005$).
Akın et al, 1998	VPA *n*:25, CBZ *n*:28, control *n*:26	L2-L4 lumbar vertebrae	Ca, P, ALP, albumin, transaminase, renal function tests	Bone mineral density values of VPA and CBZ were not statistically different from that of the control group ($p > 0.05$).
Kafali et al, 1999	CBZ *n*:13, VPA *n*:6, control *n*:57	Proximal and middle one-third radius	Ca, P, ALP, ALT, AST	The difference in BMD at the proximal and middle third of the radius-ulna was statistically significant ($p < 0.05$). VPA had 8% ($p < 0.04$), CBZ had 4.5% ($p =$ NS) reduction in bone mineral at the middle radius-ulna region, as compared with the control group.
Erbayat Altay et al, 2000	CBZ *n*:21, VPA *n*:15, control *n*:22	Femoral neck, lumbar spine (L2–4).	Ca, calcitonin, PTH, ALP, osteocalcin	BMD values at both the femur neck and lumbar spine in VPA, CBZ groups were not significantly different from the control group. Serum calcium was low in CBZ group. Calcitonin, PTH was normal. ALP was high in both CBZ and VPA groups. Osteocalcin was high in CBZ group. Urinary calcium and phosphorus were significantly lower in treatment groups.
Öner et al, 2004	VPA *n*:33, control *n*:33	L2–4, femoral neck, and trochanter regions		Duration of therapy was longer ($p < 0.01$) and doses were higher ($p < 0.01$) in the seven osteopenic patients. Osteocalcin significantly increased in VPA group. Serum Ca, P, ALP showed no significant difference between patient and control groups.
Ecevit et al, 2004	CBZ *n*:17, VPA *n*:16, Control $n = 31$	Femoral neck, Ward's triangle, greater trochanter		BMD values were lower at all sites in the CBZ group compared with controls, but not significant. VPA group had significant reduction at trochanter (−11.4%); other sites lower than controls, but not significant. There were three and four hypocalcemic and six and eight hypophosphatemic patients in the CBZ and VPA groups, respectively.
Tekgul et al, 2005	Monotherapy *n*:41 patients [CBZ *n*:21,VPA *n*:9, PB *n*:6, DPH *n*:4, PRM *n*:1] Polytherapy *n*:15 patients [PB + DPH: 4, PB + CBZ: 3, PB + VPA: 2, PB + VPA + CBZ: 2, CBZ + PRM: 2, CBZ + VPA: 1, BZ + VPA + PRM+ VGB: 1], 400 IU vitamin D was given	L2-L4 lumbar vertebrae	Ca, P, ALP	Three patients (5%) had a BMD *Z*-score less than −1.5. No significant difference in mean BMD values from lumbar spine (L2-L4) between monotherapy or polytherapy groups.
Kumandaş et al, 2006	CBZ *n*:33, VPA *n*:33, control *n*:22	L1-L4 lumbar vertebrae	Ca, P, ALP, PTH, vitamin D	Significant decrease in BMD with both CBZ and VPA, hyperparathyroid status with VPA and low vitamin D with CBZ.
Babayigit et al, 2006	CBZ *n*:23, VPA *n*:31, OXC *n*:14, control:30	L1-L4 lumbar vertebrae	Ca, P, ALT, AST, albumin, ALP, PTH, vitamin D	No significant change in Ca, P. Higher ALP and low BMD compared with healthy subjects. VPA, CBZ, or OXC induces a state of decreased BMD.

(*Continued*)

Table 3 (*Continued*)

Study	Number (*n*) of patients and anti-epileptic drugs	DXA region	Biochemical markers	Significance
Coppola et al, 2009	Monotherapy *n*: 36 [VPA *n*:15, CBZ *n*:10, LEV *n*: 1, PB *n*: 5, VGB *n*: 2, LTG *n*: 2, OXC *n*: 1] Combination therapy *n*: 60 (two drugs *n*: 20; >2 drugs *n*: 40) included children with cerebral palsy and mental retardation.	L2-L4 lumbar vertebrae	Ca, P, albumin, ALP, PTH, vitamin D, total proteins, transaminases, GGT, urea, creatinine, glucose, CBC, iron, transferrin, osteocalcin, calcitonin, 24-h urine excretion of calcium and phosphorus	Abnormal BMD in 56 patients (42 osteopenia, 14 osteoporosis). BMD was abnormal in 7/15 (%47) for VPA and 5/10 (%50) for CBZ monotherapy. Abnormal BMD correlated significantly with the absence of autonomous gait ($p = 0.005$).
Aksoy et al, 2011	VPA *n*:53, CBZ *n*:23, control *n*:50	L2–L4 lumbar vertebrae	Ca, P, ALP, vitamin D, glucose, insulin, C-peptide, leptin, osteocalcin, C-telopeptide	Bone formation and resorption markers increased with CBZ, decreased with VPA. BMD and vitamin D were not affected.
Serin et al, 2015	LEV *n*:20, CBZ *n*:11, VPA *n*:28, control *n*:20	Total femur and L1–4 vertebra	Ca, P, ALP, PTH vitamin D	No statistically significant difference between the groups by Ca, P, ALP, PTH and vitamin D levels. There was no significant change in *Z*-scores between LEV, CBZ and VPA, but BMD was slightly lower in the LEV group.
Yaghini et al, 2015	Group 1 (*n*:60): enzyme inducers; PB, primidone, CBZ; group 2 (*n*:30): VPA; group 3 (*n*:30): no treatment	Lumbar spine (L1–4), and femoral neck	Ca, P, ALP, PTH vitamin D	BMD found low in group 1 and 2, vitamin D low in all groups - especially in group 1. ALP was also high in group 1.
Osman et al, 2017	Monotherapy *n*:41, polytherapy *n*:19, control *n*:60 old ASDs: VPA, CBZ, new ASDs: LEV, ETX)	Lumbar spines (L1–4)	Ca, P, ALP	ALP was significantly high in the patient group; Ca, P were not different. 17 patients with epilepsy had low BMD, VPA is significant, LEV found less adverse compared with VPA and CBZ. Polytherapy caused more decrease in BMD than monotherapy ($p < 0.001$).
Shin et al, 2018	OXC *n*:31, VPA *n*:16, LEV *n*:13	Spine and femur every 6 mo of treatment		Reduction of bone mineral density in 8/31 patients with OXC ($p = 0.10$), 9/16 with VPA ($p = 0.04$) and 4/13 with LEV ($p = 0.50$).
Fong et al, 2018	Total *n*:87, >2 ASDs *n*:11 EIASD: CBZ, PB, DPH, OXC, TOP Non-EIASDs: VPA, CLB, LTG, GBP, LEV, ZON, VGB	L1-L4 lumbar vertebrae	Ca, P, ALP, PTH vitamin D polymorphism	Polytherapy found to cause low BMD

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ASDs, anti-seizure drugs; AST, aspartate aminotransferase; Ca, calcium; CBC, complete blood count; CBZ, carbamazepine; CLB, clobazam; DPH, diphenylhydantoin; EIASD, enzyme inducing ASDs; ETX, ethosuximide; GBP, gabapentin; GGT, c-glutamyl transpeptidase; LEV, levetiracetam; LTG, lamotrigine; NS, non-significant; OXC, oxcarbazepine; P, phosphate; PB, phenobarbital; PRM, primidone; PTH, parathormone; VGB, vigabatrin; VPA, valproate; ZON, zonisamide.

summarizes the studies with their respective significance.[11–26] As seen in the Table, some studies report lower BMDs due to ASDs, while others indicate no significant difference. Unfortunately, the available body of work does not allow an objective evaluation due to the nonequivalent formation of groups (e.g., regarding BMD assessment from different areas), the generally low vitamin D levels of children, the heterogeneity of some groups (e.g., including patients with comorbidities or non-ambulatory status), and the absence of information on eating habits.

Studies mostly report adversely affected BMD as a result of polytherapy and the duration of epilepsy. However, these studies typically did not have homogenous polytherapy groups, included patients using two or more ASDs, and did not specify the drugs used. In the present study, we specifically indicated the polytherapy group as VPA + LEV but could not do the same for the other groups due to the low number of drug combinations. Our evaluation of the drugs in the monotherapy groups among themselves and with the polytherapy group yielded no difference in terms of BMD.

DXA was generally measured from the lumbar vertebral region in the literature, but some studies used the femoral neck and forearm, obtaining lower BMDs. Nevertheless, this result should not be considered significant since the lumbar region is the most proper for BMD measurement in children.[4,8]

We also reviewed studies on biochemical markers related to BMD and biomarkers related to bone metabolism. McNamara et al[27] investigated the metabolic abnormalities caused by ASDs and reported decline in BMD with PB, phenytoin, VPA, CBZ, OXC, gabapentin, TOP, and clonazepam, but mixed results with LEV and LTG.[27]

In another study, Durá-Travé et al[28] compared the biochemical parameters between VPA (*n*:59), LEV (*n*:31) monotherapy groups, and healthy controls (*n*:244) in Spain. They indicated that the Ca and P levels in the monotherapy groups were within the normal range but significantly lower than the controls. Besides, they found no significant difference between the groups by ALP and PTH. However, vitamin D deficiency was higher in the ASD groups. Although LEV causes lower BMD depletion, the highest rate of vitamin D impairment was seen in the LEV group.[28]

In the present study, the serum Ca level was lower in the CBZ and LEV groups, and ALP higher in the CBZ group, but no statistical significance was evident concerning *Z*-scores and ALP, PTH.

Vitamin D deficiency is an important cause of low bone mineralization. This deficiency may be extrinsic (inadequate dietary intake, decreased exposure to sunlight), intrinsic (obesity or gastrointestinal system disorders..) or acquired (increased catabolism or metabolic clearance) similar to that by anti-seizure drugs.[5]

Vitamin D status and the need for supplementation in children using ASDs are other important considerations regarding BMD. A recent meta-analysis revealed that vitamin D levels decreased in children using VPA and CBZ. Thus, routine monitoring of vitamin D levels and supplementation should be considered for children with epilepsy.[29] Turan et al[30] compared VPA, CBZ, and PB monotherapy groups and healthy controls and reported no significant difference in vitamin D levels.[30] Elsewhere, Tekgul et al[17] administered daily 400 IU vitamin D to 56 children with epilepsy. Only three patients (5%) had a BMD less than −1.5, a score relatively lower than the rates in the previous studies concerning ambulatory children on long-term ASD treatment without vitamin D supplementation.[17] In contrast, an Iranian report cited less vitamin D deficiency with 50,000 U per month vitamin supplement in children with epilepsy (26.7% of 90 children with epilepsy and 76.7% of 90 healthy children had vitamin D deficiency), but no significant difference in terms of lumbar BMDs.[31] Our study population was recruited from children living in the province of Van located in Eastern Turkey, near the Iranian border. Thus, the low vitamin D status among our subjects is consistent with the above report.

Ambulatory status, physical activity, Ca intake, vitamin D status, and ASDs have varying influences on BMD in children with epilepsy. As seen in Table 3, studies have investigated the effect of ASDs on BMD with reference to the drugs' enzyme-inducing properties, individual or combined regimens, and duration of therapy.

The presence of numerous ASDs makes evaluation of varying combinations of medications difficult in a single study. In the present study, we only included patients receiving VPA, CBZ, and LEV monotherapy since the number of patients using other drugs was small. We also excluded polytherapy combinations other than VPA + LEV for similar reasons. This is the main limitation of our study. However, the primary strength of the study lies in the homogeneity of the groups, i.e., participation of subjects from the same geographic region and similar socioeconomic backgrounds, with similar eating habits, and physical activity and sun exposure characteristics.

Conclusion

Epilepsy is the most commonly seen disease in pediatric neurology outpatient clinics. There is an ongoing interest in BMD and vitamin D levels of patients with epilepsy, not only with regard to ASDs but also with respect to underlying comorbidities (mental retardation, cerebral palsy, and other systemic disorders), amount of sun exposure, physical activity, diet as well as ambulatory status.

The present study, along with the previous ones, has shown that ASDs are not solely responsible for low bone mineralization, but other factors may play a role. Vitamin D status must be considered in all patients and DXA in patients with disabilities. Besides, sunlight exposure, physical activity, and good nutrition are recommended to improve the patients' quality of life.

Conflict of Interest
None declared.

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