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Factors Affecting Serum Vitamin D Level in Epilepsy

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Abstract

Objective: Our aim was evaluate the relationship between 25-Hydroxyvitamin D (25(OH)D) and old and new generation anti-seizure drugs (ASDs), seizure type and seizure frequency in epilepsy patients.

Method: A total of 96 individuals aged 18 years and older with epilepsy were included in this study who were followed up in the SBU Adana City Training and Research Hospital Epilepsy outpatient clinic between January 1, 2020 and November 1, 2022 and met the inclusion criteria. Patients were grouped by age, gender, seizure type, frequency, and ASDs usage (according to their relationship with cytochrome P450 enzymes). Complete blood count, kidney functions, serum ASD levels and calcium, magnesium, phosphate and parathormone levels, season when 25(OH)D were measured, and sun exposure time was also obtained from patient file scans.

Results: 55.2% of the patients were women and the mean age was 32.56±12.90 (Min:18 Max:71). 25(OH)D level was found to be deficient or insufficient in 95.8% of the patients. The 25(OH)D level was statistically significantly lower in patients with generalized and complex partial epilepsy who were exposed to the sun for less than one hour per week compared to the focal type and those exposed to the sun for more than one hour per week. $p<0.05$)

Conclusion: 25(OH)D levels should be closely monitored in patients with epilepsy who use ASD for a long time it should be aimed to provide effective seizure control and a positive effect on bone metabolism with appropriate replacement therapy.

Keywords: Epilepsy, seizure, anti-seizure medication, vitamin 25(OH)D

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Epilepside Serum D Vitamini Düzeyini Etkileyen Faktörler

Öz

Amaç: D vitamininin epilepsi hastalarında eski ve yeni jenerasyon nöbet önleyici ilaçlar (NÖİ), nöbet tipi ve nöbet sıklığıyla arasındaki ilişkiyi değerlendirmek amaçlandı.

Yöntemler: Çalışmaya 1 Ocak 2020- 1 Kasım 2022 tarihleri arasında SBU Adana Şehir eğitim ve Araştırma Hastanesi Nöroloji Kliniği Epilepsi polikliniğinde takip edilen ve dahil edilme kriterlerini karşılayan 18 yaş ve üzeri epilepsi tanılı 96 hasta alındı. Hastalar yaş, cins, nöbet tipi, nöbet sıklığı ve kullandıkları nöbet önleyici ilaçlarına göre gruplandırıldı. Nöbet önleyici ilaçlar (NÖİ) hepatik sitokrom P450 enzimlerini indükleme yeteneklerine göre gruplandırıldı. Tam kan sayımı, böbrek fonksiyonları, serum NÖİ ilaç düzeyleri ve kalsiyum, magnezyum, fosfat ve parathormon (PTH) düzeyleri, D vitamini ölçülen mevsim ve güneşe maruziyet süresi de ayrıca hasta dosya taramalarından elde edildi.

Bulgular: Hastaların %55.2 si kadın olup yaş ortalaması 32,56±12,90 (Min:18 Max:71) dir. %77,1'i Jenaralize epilepsi tanılı olup %60,4'ü (58 kişi) son üç ay içerisinde nöbet geçirdiğini belirtmiştir. Çalışmaya dahil edilen hastaların %95,8'inin serum (25-Hidroksivitamin D (25(OH)D) vitamini düzeyi eksik ya da yetersiz seviyede olduğu tespit edilmiştir. Jeneralize ve kompleks parsiyel epilepsisi olanların ve haftada bir saatten az güneşe maruz kaldıklarını belirtmiş olanların serum 25(OH)D vitamini seviyesi fokal tipe göre ve haftada bir saatten fazla güneşe maruz kalanlara göre istatistiksel olarak anlamlı düzeyde daha düşük çıkmıştır. (p<0,05)

Sonuç: Uzun süreli NÖİ kullanan ve jeneralize veya kompleks parsiyel epilepsisi olan ve güneşe maruziyeti haftada 1 saatten az olan hastaların serum 25(OH)D vitamini düzeyleri yakın takip edilerek uygun replasman tedavisi ile kemik metabolizmasına olumlu etkileri yanı sıra etkin nöbet kontrolü sağlanabilir.

Anahtar kelimeler: Epilepsi, nöbet, nöbet önleyici ilaç, vitamin, 25(OH)D vitamin.

MAIN POINTS

The aim of the research is to evaluate serum 25(OH)D vitamin levels and the factors affecting this level in epilepsy patients who are followed up regularly for one year or more.

• 25(OH)D levels were found to be deficient or insufficient in 95.8% of the patients included in the study.

• The 25(OH)D level was statistically significantly lower in patients with generalized and complex partial epilepsy who were exposed to the sun for less than one hour per week compared to the focal type and those exposed to the sun for more than one hour per week. p<0.05)

• Another important aim of this study is to inform clinicians dealing with epilepsy about the importance of appropriate replacement by closely monitoring 25(OH) D levels of patients who use long-term anti-seizure medication, have generalized or complex partial epilepsy, and are exposed to the sun for less than 1 hour per week.

INTRODUCTION

Vitamin D is important for bones and its deficiency causes many diseases. 7-Dehydrocholestriol turns into cholecalciferol, also called vitamin D, on skin exposed to sunlight UVB (290-315 nm). Cholecalciferol binds to vitamin D binding protein, an-globulin synthesized in the liver, and is converted to 25(OH)D' by cytochrome P450 enzymes in the liver and to its active metabolite, 1.25 α-hydroxyvitamin D, in the kidney[1]. The circulation and storage form of vitamin D is 25(OH)D[1].

Vitamin D is a neurosteroid with an important role in neuroprotection, brain development and immunomodulation, and it crosses the blood-brain barrier and plays a protective role in neurodegenerative diseases by regulating

neurotrophic factors[2–5]. Its role in the pathophysiology and treatment of epilepsy is quite complex.

Hollo et al. reported that vitamin D decreased the frequency of seizures in epilepsy patients[6]. In epilepsy patients taking anti-seizure drugs (ASDs) that induce cytochrome p450 enzyme system, vitamin D deficiency and thus osteoporosis risk are common[7,8]. Osteoporosis is associated with balance and risk of falling[9]. A recent meta-analysis reported an approximately 40% increased risk of femoral fracture for values less than 20 ng/mL (50 nmol/L)[10].

Although enzyme-inducing and non-inducing ASDs are known to affect bone density, there is still a lack of consensus on effective vitamin D dosing in epilepsy.

So, we planned to review the possible relationship between vitamin D levels, old and new generation ASDs, seizure type and seizure frequency in epilepsy patients from different perspectives.

METHODS

Between 1 January 2020 and 1 November 2022, 96 patients aged 18 years and older who were followed up in the Neurology Clinic of SBU Adana City Training and Research Hospital and met the inclusion criteria were included. Health Sciences University Adana Medical Faculty City Hospital Clinical Research Ethics Committee approved the study. (No:115/2227 and 2022-11-03).

Epilepsy was defined and managed in accordance with the practical clinical definition from the The International League Against Epilepsy (ILAE)[11]. Cadwell Sierra brand electroencephalography (EEG) device with 18 channels, banana mount, 7uV/mm sensitivity, 30 mm/sec sweep speed and 1-70 Hz filter was used in the diagnosis and follow-up of epilepsy.

Patients with transient ischemic attack (TIA), migraine, syncope, and psychogenic non-epileptic seizures (PNES) were not included in the study.

The study excluded the patients who were pregnant, had change in anti-seizure medication schedule in the three months before the study, took vitamin D supplements six months before the study or took medication that interferes with the metabolism of this vitamin. The study also excluded the patients with a diagnosis of a disease causing a disorder in the metabolism of this vitamin, liver and kidney dysfunction, hypercalcemia, kidney stones, parathyroid disease or stomach operation history, toxic habits such as alcohol, tobacco, and substance use, vegetarian or vegan diet habits.

Patients were grouped by age, gender, seizure type, seizure frequency, and seizure medications they used. The seizure type was analyzed in three groups as focal, complex partial and generalized, and the frequency of seizures in three groups as those with seizures in the last 0-3 months, those with seizures between 4 and 12 months, and those without seizures for a year or more. Sun exposure was divided into two groups as less than one hour per week and one hour and more per week. The seasons of the year in which the measurements were made were grouped as spring, summer, autumn and winter. ASDs were grouped according to their ability to induce hepatic cytochrome P450 enzymes:

- Enzyme-inducing ASD users: EIASD (phenytoin, phenobarbital, carbamazepine, eslicarbazepine acetate, primidone, oxcarbazepine and topiramate >200 mg/day)

- Non-enzyme-inducing ASD users: non-EIASD (valproate, lamotrigine, gabapentin, levetiracetam, clobazam, pregabalin, zonisamide, lacosamide, perampanel, topiramate ≤200 mg/day and benzodiazepine)

- EIASD + NonEIASD

- Two NonEIASDs

- Two EINASDs

- Users of ASDs of 3 or more

Laboratory data (vitamin D, parathyroid hormone (PTH)etc.) were studied with the paramagnetic particle chemiluminescence immunoanalysis method on Beckman Coulter Access Immunoasay Systems-DXI 800 device, and complete blood count, kidney functions, serum ASDs levels and calcium, magnesium, phosphate and PTH levels obtained from patient file scans.

Statistical Analysis

Frequency, percentage, arithmetic mean, and standard deviation were used in the evaluation of socio-demographic data of individuals with epilepsy diagnosis included in the study. The normal distribution property of dependent variables was examined with Skewness and Curtosis values. Since the values were between -1.98 and + 1.98, it was accepted that the data showed a normal distribution[12]. Independent simple t test and one-way analysis of variance (ANOVA) were used to examine the effects of dependent variables on vitamin D, Calcium, Phosphorus and PTH. Tukey test was used to test the significance of groups because of ANOVA. The correlation between dependent variables was evaluated with Pearson correlation analysis. The significance value (p value) of the tests was considered significant if it was below 0.05.

RESULTS

Of the 96 patients participating in the study, 53 (55.2%) were female, and the mean age of the patients was 32.56±12.90 (Min:18, Max:71). 77.1% of the patients were diagnosed with generalized epilepsy, and 60.4% (58 people) stated that they had seizures in the last three months. 59.4% were using one or two drugs that did not induce enzymes. 86.3% of the patients stated that they were exposed to the sun less than 1 hour a week. Descriptive characteristics of the patients are given in Table 1.

Table I: Descriptive characteristics of the patients

Descriptive characteristics (N:96)	Number	%
Gender		
Female	53	55.2
Male	43	44.8
Age		
18-24 years	32	33.3
25-34 years	29	30.2
35 years and older	35	36.5
Epilepsy type		
Focal	4	4.2
Complex partial	18	18.8
Generalized	74	77.1
Seizure frequency		
Seizure in the last 3 months	58	60.4
Seizure in 4-12 months	11	11.5
Seizure-free for more than 1 year	27	28.1
ASD		
EİASD	7	7.3
Non-EİASD	41	42.7
Dual ASDs (EİASD+Non-EİASD)	14	14.6
Dual ASDs (Both Non-EİASD)	16	16.7
3 or more ASDs	18	18.8
Sun Exposure		
< 1 hour per week	83	86.5
1 hour or more per week	13	13.5

ASD: Anti-seizure drug, EİASD: Enzyme inducing anti-seizure drug, Non-EİASD: Non- enzyme inducing anti-seizure drug,

25(OH)D levels were found to be insufficient or deficient in 95.8% of the patients. Calcium levels in 6 patients, Phosphorus levels in 7 patients were below the reference values, and PTH values in 7 patients were above the reference values (Table 2).

Table II: General Evaluation of 25-(OH) Vitamin D, Calcium, Phosphorus and Parathormone Levels of Patients

(N:143)	Number	%
25(OH) vitamin D		
<20 µg/L (Deficient)	72	78.1
20-30 µg/L (Insufficient)	20	17.7
≥30 µg/L (Normal)	4	4.2
Calcium		
<8,8 mg/dl (Low)	6	6.3
≥8.8 (Normal)	90	93.8
Phosphorus		
<2,5 mg/dl (Low)	7	7.3
≥2,5 mg/dl (Normal)	89	92.7
Parathormone		
<12 ng/L (Low)	0	0.0
12-88 ng/L (Normal)	89	92.7
≥88 ng/L (High)	7	7.3

There was no statistically significant difference between the gender variable and serum 25(OH)D, phosphorus and PTH levels of the patients, while the calcium levels were higher in favor of male patients. (p<0.05) (Table 3).

There was no significant difference between the age groups of the patients and 25(OH)D, phosphorus and calcium levels (p>0.05), but a significant difference was found between the PTH levels and age groups (p<0.05). In the post hoc analysis performed to evaluate which groups the significance stemmed from, it was determined that PTH levels were higher in the group over 35 years of age than in the 25-34 age group (Table 3).

Table III: 25(OH) Vitamin D, calcium, phosphorus and parathormone values by age and gender

		25(OH) vitamin D		Calcium		Phosphorus		Parathormone	
	(N)	**Mean**	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**	**Mean**	**S.D**
Gender	**Female (53)**	15,39	8,17	9,30	,62	3,44	,74	55,95	27,45
	Male (43)	18,26	7,75	9,76	,44	3,50	,76	48,73	30,84
	Test Values	t: -1,750 p:0,083		t:-3,997 p:0,000		t:-0,407p:0,685		t:1,212 p:0,229	
Age	**18-24 years[a] (32)**	18,51	10,64	9,69	,42	3,72	,85	47,20	29,63
	25-34 years[b] (29)	15,70	5,95	9,45	,85	3,36	,73	45,77	23,30
	35 years and older[c] (35)	15,81	6,70	9,38	,41	3,32	,60	63,52	30,45
	Test Values	F:1,246 p:0,292		F:2,472 p:0,090		F:2,979 p:0,056		F:4,056 p:0,020 c**>b**	

t:İndependent Simple t Test F: One way ANOVA p:Significant Value SD: Standard deviation

There was no difference between epilepsy type and phosphorus, calcium and PTH levels (p>0.05). (Table4.) However, 25(OH)D levels were found to be significantly lower in individuals with generalized and complex partial epilepsy compared to individuals with focal epilepsy, and this decrease was much more pronounced in patients with generalized epilepsy than in patients with partial epilepsy (p<0.05) (Table 4).

There was no statistically significant difference in 25(OH)D, phosphorus, calcium and PTH levels with the anti-seizure medication used by the patients (p>0.05) (Table 4).

There was no difference between the patients' sun exposure and phosphorus, calcium and PTH levels (p>0.05). However, 25(OH)D vitamin

levels were significantly lower in patients who were exposed to the sun for less than one hour per week compared to those exposed more than one hour per week (p <0.05) (Table 4).

Table IV: Evaluation of Factors Affecting 25(OH) Vitamin D, Calcium, Phosphorus and Parathormone Levels of Patients

		25(OH) vitamin D		Calcium		Phosphorus		Parathormone	
	(N)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Epilepsy Type	**Focal[a] (4)**	28,37	8,47	10,07	,22	3,42	1,21	38,67	9,74
	Complex partial[b] (18)	16,90	5,81	9,47	,42	3,28	,62	58,75	35,03
	Generalized[c] (74)	15,99	8,12	9,48	,63	3,51	,75	52,01	28,13
	Test Values	F:4,826 p:0,010 a>b/a>c		F:1,915 p:0,153		F:0,664 p:0,517		F:0,872 p:0,422	
Seizure Frequency	**Seizure in the last 3 months [a] (58)**	17,2	8,69	9,38	,65	3,50	,74	56,71	32,16
	Seizure in 4-12 months [b] (11)	16,62	7,49	9,72	,36	3,53	,90	47,28	19,90
	Seizure-free for more than 1 year [c] (27)	15,58	7,01	9,68	,47	3,36	,72	46,37	24,14
	Test Değerleri	F:0,365 p:0,695		F:3,202 p:0,045 b>a		F:0,381 p:0,684		F:1,390 p:0,254	
ASD	**EİASD (7)**	15,61	6,81	9,57	,31	3,50	,53	61,71	46,52
	Non-EİASD (41)	17,16	7,70	9,56	,77	3,42	,82	44,70	16,15
	Dual ASDs (EİASD+Non-EİASD) (14)	16,98	12,15	9,56	,42	3,44	,73	66,35	39,55
	Dual ASD (Both Non-EİASD) (16)	16,77	6,27	9,40	,42	3,46	,50	54,80	17,64
	3 or more ASDs (18)	15,68	7,64	9,42	,47	3,58	,89	55,05	39,11
	Test Values	F:0,135 p:0,969		F:0,336 p:0,853		F:0,135 p:0,969		F:1,825 p:0,131	
Sun Exposure	**<1 hour per week (83)**	14,54	5,41	9,49	,61	3,47	,73	53,69	30,05
	1 hour or mor eper week (13)	30,35	9,02	9,63	,47	3,40	,88	46,53	21,90
	Test Values	F: -8,334 p:0,000		F:0,779 p:0,438		F:0,319 p:0,751		F:0,823 p:0,413	

t:İndependent Simple t Test F: One way ANOVA p:Significant Value SD: Standard deviation ASD: Anti-seizure drug, EİASD: Enzyme inducing anti-seizure drug, Non-EİASD: Non- enzyme inducing anti-seizure drug,

DISCUSSION

Although 25(OH)D deficiency varies according to geographical regions, it is below 20% in Northern Europe, while it reaches 60% in other parts of Europe and even up to 80% in Middle Eastern countries[13]. In Turkey, it has been stated that there is vitamin D deficiency up to 74.9%.

This study revealed that 25(OH) D deficiency (78.1%) was more common in epileptic patients using ASD than in previous studies[7,14]. This may be due to geographical and ethnic differences or clothing style.

The most important finding of our study is that many epilepsy patients treated with ASDs are deficient in vitamin D, even if good seizure control is achieved. Although vitamin D deficiency was more common in patients with EIASDs and polytherapy, it was also found to be very common in epilepsy patients who received non-EIASDs. As the type and severity of epilepsy increased, vitamin D deficiency was observed to be higher. Patients with less than one hour of sun exposure per week had lower vitamin D levels, indicating the well-known role of UV radiation on vitamin D synthesis. Considering that the risk of fracture may increase due to seizures and decreased coordination caused by the underlying brain disease or ASDs, close monitoring of vitamin D levels and appropriate replacement are especially important in epilepsy patients.

Many studies support that vitamin D deficiency is more common in older EIASD use[15–20]. Most studies support that non-enzyme-inducing drugs do not alter vitamin D metabolism[21,22]. The results for valproic acid are controversial[23,24].

It has previously been reported that chronic ASD use is an independent factor for lowering plasma vitamin D levels, regardless of the type of ASDs[25]. In our study, it was noted that vitamin D deficiency was also high in epilepsy patients using non-enzyme-inducing ASDs. This may be due to the nature of epilepsy itself, as well as to the use of ASDs, or to the different mechanisms underlying the undesirable effects of ASDs on bone health, and to chronic use of ASDs. For this reason, we recommend close monitoring of vitamin D levels of epilepsy patients, regardless of the treatment they receive.

According to the Turkish Endocrine and Metabolism Society, the minimum daily vitamin D level required for bone and muscle health in adults aged 19-70 is 600 IU, and 1500-2000 IU to keep it at 30 ng/ml[26]. In a study conducted in Denmark, it was observed that 64% of patients could not reach adequate vitamin D levels despite 15 months of vitamin D supplementation up to 1200 IU/day[27]. In a Portuguese epilepsy cohort, A 79.3 percent of 25(OH) vitamin D deficiency was detected, and it was stated that with 8 weeks of 6670 IU/day cholecalciferol treatment, 98.9% of the patients achieved an adequate increase in their 25(OH) vitamin D levels[14]. This indicates that appropriate replacement doses should be reconsidered, especially in epilepsy patients. Therefore, future studies should research the effective vitamin D level in epilepsy patients and the dose of adequate vitamin D replacement. Although there are many studies pointing to the neurogenesis and neuroprotective role of vitamin D, our knowledge about the effect of vitamin D deficiency on cellular and neural tissues is limited. It seems that a good investigation of the process that causes the neural tissue to turn into epileptiform flow and whether this pathological process can be corrected after vitamin D replacement will be the subject of future research.

Relatively small sample size, lack of follow-up and treatment doses are the limitations of our study.

CONCLUSION

25(OH)D levels should be closely monitored in patients with epilepsy who use ASD for a long time it should be aimed to provide effective seizure control and a positive effect on bone metabolism with appropriate replacement therapy.

Author Contributions: Concept – P.B.B Design - P.B.B ; Supervision – P.B.B; Resources – P.B.B; Materials – P.B.B Data Collection and/or Processing – P.B.B; Analysis and/or Interpretation – P.B.B; Literature Search – P.B.B; Writing Manuscript – P.B.B Critical Review – P.B.B; Other – P.B.B

Ethics Committee Approval: Health Sciences University Adana Medical Faculty City Hospital Clinical

Research Ethics Committee approved the study. (No:115/2227 and 2022-11-03).

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REFERENCES

1. Bertoldo F, Cianferotti L, Di Monaco M, et al. Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS). Nutrients. 2022; 14(19): 4148. doi:10.3390/nu14194148

2. Zelzer S, Meinitzer A, Herrmann M, Goessler W, Enko D. A Novel Method for the Determination of Vitamin D Metabolites Assessed at the Blood-Cerebrospinal Fluid Barrier. Biomolecules. 2021; 11(9): 1288. doi:10.3390/biom11091288

3. Tuckey RC, Cheng CYS, Slominski AT. The serum vitamin D metabolome: What we know and what is still to discover. J Steroid Biochem Mol Biol. 2019; 186: 4-21. doi:10.1016/j.jsbmb.2018.09.003

4. Vanherwegen AS, Gysemans C, Mathieu C. Regulation of Immune Function by Vitamin D and Its Use in Diseases of Immunity. Endocrinol Metab Clin North Am. 2017; 46(4): 1061-94. doi:10.1016/j.ecl.2017.07.010

5. Gil Á, Plaza-Diaz J, Mesa MD. Vitamin D: Classic and Novel Actions. Ann Nutr Metab. 2018; 72(2): 87-95. doi:10.1159/000486536

6. Holló A, Clemens Z, Kamondi A, Lakatos P, Szűcs A. Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. Epilepsy Behav. 2012; 24(1): 131-3. doi:10.1016/j.yebeh.2012.03.011

7. Teagarden DL, Meador KJ, Loring DW. Low vitamin D levels are common in patients with epilepsy. Epilepsy research. 2014; 108(8): 1352-6.

8. McNamara NA, Romanowski EMF, Olson DP, Shellhaas RA. Bone Health and Endocrine Comorbidities in Pediatric Epilepsy. Semin Pediatr Neurol. 2017; 24(4): 301-9. doi:10.1016/j.spen.2017.10.005

9. AK Türkyılmaz, EE Kurt, G Devrimsel. The effect of serum vitamin D level and bone mineral density on balance and the risk of falling in postmenopausal women. Diclemedj. 2013; 40(3): 391-5. doi:10.5798/diclemedj.0921.2013.03.0295

10. Feng Y, Cheng G, Wang H, Chen B. The associations between serum 25-hydroxyvitamin D level and the risk of total fracture and hip fracture. Osteoporos Int. 2017; 28(5): 1641-52. doi:10.1007/s00198-017-3955-x

11. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014; 55(4): 475-82. doi:10.1111/epi.12550

12. Tabachnick BG, Fidell LS. Experimental Designs Using ANOVA. Vol 724. Thomson/Brooks/Cole Belmont, CA; 2007.

13. Lips P, Cashman KD, Lamberg-Allardt C, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. Eur J Endocrinol. 2019; 180(4): P23-P54. doi:10.1530/EJE-18-0736

14. Cunha IA, Saraiva AM, Lopes P, et al. Vitamin D deficiency in a Portuguese epilepsy cohort: who is at risk and how to treat. Epileptic Disord. 2021; 23(2): 291-8. doi:10.1684/epd.2021.1268

15. Siniscalchi A, Murphy S, Cione E, Piro L, Sarro GD, Gallelli L. Antiepileptic Drugs and Bone Health: Current Concepts. Psychopharmacol Bull. 2020; 50(2): 36-44. Accessed November 19, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7255839/

16. Suljic EM, Mehicevic A, Mahmutbegovic N. Effect of Long-term Carbamazepine Therapy on Bone Health. Med Arch. 2018; 72(4): 262-6. doi:10.5455/medarh.2018.72.262-6,

17. Sreedharan M, Devadathan K, Mohammed Kunju PA, et al. Vitamin D Deficiency in Ambulant Children on Carbamazepine or Sodium Valproate Monotherapy. Indian Pediatr. 2018; 55(4): 307-10.

18. Menninga N, Koukounas Y, Margolis A, Breslow R, Gidal B. Effects of enzyme-inducing antiseizure medication on vitamin D dosing in adult veterans

with epilepsy. Epilepsy Res. 2020; 161: 106287. doi:10.1016/j.eplepsyres.2020.106287

19. Aksoy D, Güveli BT, Ak PD, et al. Effects of Oxcarbazepine and Levetiracetam on Calcium, Ionized Calcium, and 25-OH Vitamin-D3 Levels in Patients with Epilepsy. Clin Psychopharmacol Neurosci. 2016; 14(1): 74-8. doi:10.9758/cpn.2016.14.1.74

20. Wang W, Gao Y, Zheng W, Li M, Zheng X. Phenobarbital inhibits osteoclast differentiation and function through NF-κB and MAPKs signaling pathway. Int Immunopharmacol. 2019; 69: 118-25. doi:10.1016/j.intimp.2019.01.033

21. Koo DL, Joo EY, Kim D, Hong SB. Effects of levetiracetam as a monotherapy on bone mineral density and biochemical markers of bone metabolism in patients with epilepsy. Epilepsy Res. 2013; 104(1-2): 134-9. doi:10.1016/j.eplepsyres.2012.09.002

22. Artemiadis AK, Lambrinoudaki I, Voskou P, et al. Preliminary evidence for gender effects of levetiracetam monotherapy duration on bone health of patients with epilepsy. Epilepsy Behav. 2016; 55: 84-6. doi:10.1016/j.yebeh.2015.12.025

23. Albaghdadi O, Alhalabi MS, Alourfi Z, Youssef LA. Bone health and vitamin D status in young epilepsy patients on valproate monotherapy. Clin Neurol Neurosurg. 2016; 146: 52-6. doi:10.1016/j.clineuro.2016.04.019

24. Rahimdel A, Dehghan A, Moghadam MA, Ardekani AM. Relationship between Bone Density and Biochemical Markers of Bone among Two Groups Taking Carbamazepine and Sodium Valproate for Epilepsy in Comparison with Healthy Individuals in Yazd. Electron Physician. 2016; 8(11): 3257-65. doi:10.19082/3257

25. Yildiz EP, Poyrazoglu Ş, Bektas G, Kardelen AD, Aydinli N. Potential risk factors for vitamin D levels in medium- and long-term use of antiepileptic drugs in childhood. Acta Neurol Belg. 2017; 117(2): 447-53. doi:10.1007/s13760-017-0775-x

26. Osteoproz ve metabolik kemik hastalıkları tanı ve tedavi klavuzu. tjem. Published online 2016. doi:10.4274/tjem.omkhttk

27. Snoeijen-Schouwenaars FM, van Deursen KC, Tan IY, Verschuure P, Majoie MH. Vitamin D supplementation in children with epilepsy and intellectual disability. Pediatr Neurol. 2015; 52(2): 160-4. doi:10.1016/j.pediatrneurol.2014.10.001