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Original Article

Vitamin D levels in epileptic children on long-term anticonvulsant therapy

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Abstract

Background Long-term anticonvulsant therapy, especially with enzyme inducers, has been associated with low 25-hydroxyvitamin D [25(OH)D] levels and high prevalence of vitamin D deficiency. However, there have been inconsistent results in studies on the effect of long-term, non-enzyme inducer anticonvulsant use on vitamin D levels.

Objective To compare 25(OH)D levels in epileptic children on long-term anticonvulsant therapy and non-epileptic children. We also assessed for factors potentially associated with vitamin D deficiency/insufficiency in epileptic children.

Methods This cross-sectional study was conducted at two pediatric neurology outpatient clinics in Jakarta, from March to June 2013. Subjects in the case group were epileptic children, aged 6-11 years who had used valproic acid, carbamazepine, phenobarbital, phenytoin, or oxcarbazepine, as a single or combination therapy, for at least 1 year. Control subjects were non-epileptic, had not consumed anticonvulsants, and were matched for age and gender to the case group. All subjects' 25(OH)D levels were measured by enzyme immunoassay.

Results There were 31 epileptic children and 31 non-epileptic control children. Their mean age was 9.1 (SD 1.8) years. Most subjects in the case group were treated with valproic acid (25/31), administered as a monotherapy (21/31). The mean duration of anticonvulsant consumption was 41.9 (SD 20) months. The mean 25(OH)D level of the epileptic group was 41.1 (SD 16) ng/mL, lower than the control group with a mean difference of 9.7 (95%CI 1.6 to 17.9) ng/mL. No vitamin D deficiency was found in this study. The prevalence of vitamin D insufficiency in the epileptic group was higher than in the control group (12/31 vs. 4/31; P=0.020). No identified risk factors were associated with low 25(OH)D levels in epileptic children.

Conclusion Vitamin D levels in epileptic children with long-term anticonvulsant therapy are lower than that of non-epileptic children, but none had vitamin D deficiency. **[Paediatr Indones. 2015;55:164-70.]**

Keywords: *epileptic children, vitamin D, 25(OH) D, anticonvulsant*

Vitamin D is an important prohormone which has roles in calcium and bone metabolism, as well as other metabolic processes.[1-6] Vitamin D inadequacy is an epidemic condition but it is not realized. An estimated one billion people in the world have vitamin D deficiency or insufficency (<30 ng/mL).[7] Studies conducted in several countries reported that the prevalence of vitamin D deficiency (<20ng/mL) in children ranged from 14 to 60%.[8-12]

One potential cause of vitamin D deficiency is long-term use of anticonvulsants in epileptic children.[2,5,7] Epileptic children need long-term anticonvulsant therapy, therefore, they have a

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higher risk of adverse effects.[13] The long-term use of anticonvulsants has been associated with increased incidence of rickets or osteomalacia, increased risk of fracture, and reduced bone mineral density.[13-20] All these conditions are associated with vitamin D deficiency.[13,15] The effects of anticonvulsants on vitamin D levels have been studied for 40 or more years.[21-24] Phenobarbital, phenytoin, carbamazepine, valproic acid, and oxcarbazepine were frequently studied for their impact on 25(OH)D levels. Most enzyme-inducing anticonvulsants (phenytoin, phenobarbital, primidone, and carbamazepine) were associated with low levels of vitamin D.[16,25-32] Other studies showed insignificant effects,[24,33-35] especially with valproic acid and newer anticonvulsants.[17,19,32,36] The prevalence of vitamin D deficiency has varied between 23 to 76%, depending on the definition of vitamin D deficiency, anticonvulsant type, number and duration of use, as well as the location of the study.[25,27-30]

Studies to assess for an association between anticonvulsants and vitamin D deficiency have had inconsistent results, especially for non-enzyme-inducing anticonvulsants such as valproic acid. Therefore, further studies are still needed. We conducted this study to investigate 25(OH)D levels and the prevalence of vitamin D deficiency/insufficiency in epileptic children who used long-term anticonvulsants, and to describe factors potentially associated with low 25(OH)D.

Methods

This cross-sectional study was conducted in two neurology outpatient clinics in Jakarta: the Neurology Clinic, Child Health Department, Cipto Mangunkusumo Hospital (CMH) and the Klinik Anakku Pondok Pinang Center, South Jakarta, from March to July 2013. The study was approved by the Research Ethics Committee of the University of Indonesia Faculty of Medicine. Subjects (case group) were epileptic children, aged 6 – 11 years who had used anticonvulsants for at least 1 year. The anticonvulsants used were phenobarbital, phenytoin, carbamazepine, valproic acid, and oxcarbazepine, either as monotherapy or polytherapy. We excluded children with neurological deficits which might impair physical activity, special diet/dietary regimen, obesity, skin grafting, fat malabsorption, cholestasis or impaired liver function, renal failure or nephrotic syndrome, cerebral palsy, and those who consumed vitamin D supplements (400 IU/day or more), systemic corticosteroids, rifampicin, or antiretroviral drugs. The control subjects were patients from the Pediatric Clinic of CMH who were non-epileptic patients, did not consume anticonvulsants and did not fulfill any exclusion criteria. Control subjects were matched for age and gender to the case subjects.

We measured 25(OH)D level by *EUROIMMUNE 25-OH Vitamin D ELISA*. Blood specimen were taken from all subjects after obtaining parental consents. Vitamin D deficiency was defined as 25(OH)D level less than 20 ng/mL, whereas vitamin D insufficiency was defined as 25(OH)D level of 20-<30 ng/mL.[7] Daily intake of vitamin D was calculated using *Nutrisurvey for Windows* (Indonesian food modification). Data were analyzed using SPSS version 17.0. Paired T-test was performed to compare the mean 25(OH)D levels between the epileptic and control groups, followed by subgroup analysis of the epileptic children. Chi-square test was performed to compare the proportion of vitamin D deficiency/insufficiency between the two groups.

Results

We recruited 31 epileptic and 31 non-epileptic children for this study. Twenty-five epileptic children were recruited from the Neurology Clinic at the Child Health Department of CMH, and six epileptic children were recruited from Klinik Anakku Pondok Pinang Center. Control subjects were non-epileptic patients from the General Pediatric Clinic, Pediatric Cardiology Clinic, Pediatric Gastroenterology Clinic, and Hematology Clinic at the Child Health Department of CMH. Most control subjects were elective surgery patients.

The mean age of subjects was 9.1 (SD 1.8) years and the proportion of boys was 16/31. Most of the subjects (19/31) had partial epilepsy and consumed valproic acid (25/31). The mean duration of anticonvulsant use was 41.9 (SD 20) months, most often administered as a monotherapy (21/31). Based

Table 1. Subjects' characteristics

Characteristics	Epilepsy group (n=31)	Control group (n=31)
Gender		
Male	16	16
Female	15	15
Mean age (SD), years	9.1 (1.8)	9.1 (1.8)
Nutritional status		
Overweight	15	2
Well-nourished	13	21
Undernourished	3	8
Type of epilepsy		
Generalized	12	
Partial	19	
Type of anticonvulsant*		
Valproic acid	25	
Carbamazepine	14	
Phenobarbital	4	
Oxcarbazepine	1	
Number of anticonvulsants		
Polytherapy	10	
Monotherapy	21	
Mean duration of anticonvulsant use, months (SD)	41.9 (20)	
Mean vitamin D intake (SD), IU/day	255 (194)	216 (130)
Mean 25(OH)D level (SD), ng/mL	41.1 (16)	52.8 (15)

*some subjects consumed >1 anticonvulsant type

on dietary analysis, the mean daily intake of vitamin D was 255 (SD 194) IU in the epilepsy group and 216 (SD 130) IU in the control group (**Table 1**). Only a small proportion of subjects (7/31 in the epilepsy group and 3/31 in the control group) fulfilled the recommended vitamin D intake of ≥400 IU/day.

Table 2. Comparison of 25(OH)D level between the epilepsy and control groups

	Epilpsy group n=31	Control group n=31
Mean 25(OH)D level (SD), ng/mL	41.1 (16)	52.8 (15)
Mean difference, ng/mL	9.7	
95% CI	1.6 to 17.9	
P value	0.014*	

* paired T-test

Table 3. Comparison of vitamin D status between the epilepsy and control groups

Vitamin D status	Insuficiency N	Normal N	P value
Epilepsy group	12	19	0,020*
Control group	4	27	

*chi-square

The mean 25(OH)D level in the epilepsy group was significantly lower than in the control group, with a mean difference 9.7 ng/mL (95%CI 1.6 to 17.9; P=0.014) (**Table 2**). None of the subjects had vitamin D deficiency, however, 12/31 subjects had vitamin D insufficiency in the epilepsy group compared to only 4/31 subjects in the control group. The prevalence of vitamin D insufficiency was significantly higher in the epilepsy group than in the control group (P=0.020). Of the 12 epileptic subjects with vitamin

Table 4. Analysis of potential associations between 25(OH)D level and vitamin D intake, gender, anticonvulsant type, number, and duration of use

	n	Mean 25(OH)D level (SD), ng/mL	Mean difference, ng/mL (95%CI)	P value
Vitamin D intake				
<400 IU/day	24	41.3 (18)	0.7 (-13.9 to 15.3)	0.842*
≥400 IU/day	7	40.6 (11)		
Gender				
Male	16	43.7 (17)	5.3 (-6.7 to 17.4)	0.348*
Female	15	38.4 (16)		
Type of anticonvulsant				
Enzyme inducer	15	39.8 (14)	-2.6 (-14.8 to 9.6)	0.818*
Non-enzyme inducer	16	42.4 (19)		
Number of anticonvulsants				
Polytherapy	10	36.2 (11)	-7.2 (-20.0 to 5.6)	0.362*
Monotherapy	21	43.5 (18)		
Duration of anticonvulsant use				
>2 years	23	38.6 (16)	-9.7 (-23.1 to 3.8)	0.095#
1-2 years	8	48.3 (17)		

* Unpaired T-test; #Mann-Whitney

D insufficiency, 11 had taken anticonvulsants for more than 2 years (**Table 3**).

In the subgroup analysis, there were no significant differences in mean 25(OH)D levels between: (i) epileptic children who consumed <400 IU/day vitamin D compared to those who consumed ≥400 IU/day; (ii) males compared to females; (iii) enzyme-inducing anticonvulsants compared to non-enzyme-inducing anticonvulsants; (iv) polytherapy compared to monotherapy; and (v) epileptic children who consumed anticonvulsants for more than 2 years compared to 1-2 years (**Table 4**).

Discussion

In this cross-sectional study, we found an association between long-term anticonvulsant use (one year or more), decreased 25(OH)D level, and vitamin D status. Epileptic children who used anticonvulsants for at least 1 year had an 18.4% reduction in mean 25(OH)D level compared to that of the control group, and they had a higher prevalence of vitamin D insufficiency.

This study had several limitations. First, we were unable to determine a causal relationship since the study had a cross-sectional design. Second, quantity and quality of sun exposure, and other potential confounders, were not measured. However, we attempted to reduce those effects by recruiting subjects without sun exposure limitations and relatively equal sun exposure. We also used age- and gender-matched controls. Furthermore, there was no standard or valid questionnaire that could be routinely used to measure sun exposure, and the questionnaire had weak to moderate correlation (r=0.34–0.49) with ultraviolet dosimetry.[37] Third, we did not assess bone metabolism or bone mineral density, therefore, we could not evaluate the burden effect of vitamin D level reduction. On the other hand, this study was the first to be conducted in Indonesia, a tropical country, on a population of epileptic children. We applied strict exclusion criteria with regards to ambulatory patients without sun exposure limitations, so we believe the study results, i.e., vitamin D levels, were the exclusive effect of anticonvulsant therapy.

Several studies showed a reduction in 25(OH)D level in epileptic children who had used anticonvulsants for 6 months or more,[19,28-30,32] while others did not.[17,34,36,38,39] These latter studies found this to be the case for non-enzyme-inducing anticonvulsants (valproic acid) use[36,38] or new anticonvulsants (lamotrigine, topiramate, oxcarbazepine, sulthiamine).[17,39]

In this study, none of the subjects had vitamin D deficiency, but we found higher prevalence of vitamin D insufficiency in epileptic children (39%) compared to control subjects (13%). Other studies showed a variety of results on the prevalence of vitamin D deficiency in epileptic children using long-term anticonvulsants. A cross-sectional study conducted in Germany on epileptic children aged 5-12 years showed the prevalence of vitamin D deficiency to be as high as 75% (23% in control group). The subjects consumed valproic acid or carbamazepine as a monotherapy, or in combination with a new anticonvulsant.[29] A cohort study in Greece showed vitamin D deficiency in 49% of subjects.[30] However, that study used a lower definition of vitamin D deficiency (≤10 ng/mL), therefore, higher prevalence of vitamin D deficiency was found if a higher definition of vitamin D deficiency (<20 ng/mL) was used, as we did in our study. Another cross-sectional study in Lebanon showed that 35% of subjects had vitamin D deficiency and 27% of subjects had vitamin D insufficiency.[25] The study also used a lower definition of vitamin D deficiency (<10 ng/mL) than our study, and recruited cerebral palsy patients, which could be a potential confounder. The high prevalence of vitamin D deficiency in these three studies may have been associated with subtropical locations.

Three possibilities may explain the lack of vitamin D deficiency in our epileptic subjects. First, this study was conducted in Jakarta, a tropical region, on subjects without limitation of sun exposure. Considering that more than 90% of the source of vitamin D comes from its synthesis in skin, which is facilitated by ultraviolet B,[4,6] sun exposure has a high influence. Second, the mean duration of anticonvulsant use was shorter than the previous three studies mentioned above. Although prospective studies in children and adults showed that the reduction of 25(OH)D level occurred after anticonvulsant usage for more than 3 months,[30,40] other studies in children and adults which showed high prevalence of vitamin D deficiency had longer mean durations (5 years or more) of anticonvulsant therapy than our study.[25,29,31,41] Third, most

of our subjects consumed valproic acid which has less impact on reducing vitamin D levels than enzyme-inducing anticonvulsants.[25,32,38] Several studies have shown that valproic acid was not associated with vitamin D deficiency.[36,38]

Mean daily intake of vitamin D in our study was lower than that recommended by the Institute of Medicine (IOM). This might be due to subjects consuming only small amounts of milk and fish (sources of vitamin D), or sub-optimal vitamin D supplementation. Although most subjects had a vitamin D daily intake less than the IOM recommendation, they had normal 25(OH)D levels, and no vitamin D deficiency. This finding may suggest that the main source of vitamin D is not from diet, but from its synthesis in skin, facilitated by ultraviolet B. Indonesia is a tropical country and subjects in this study had no limitation in sun exposure, therefore, vitamin D from the diet may have had little impact on 25(OH)D levels. However, regions with higher latitudes (subtropical) have limitations in vitamin D synthesis from skin, especially during winter. Hence, dietary vitamin D source is important and IOM recommends a vitamin D intake of 400 IU/day for healthy babies, children, and adolescents to maintain a 25(OH)D level >20 ng/mL and to prevent rickets.[6,42,43]

We performed a bivariate analysis on potential associations between 25(OH)D level and the following: type of anticonvulsant used (enzyme inducer vs. non-enzyme inducer), number of anticonvulsants used (polytherapy vs. monotherapy), or duration of anticonvulsant use (>2 years vs. 1-2 years). We found no significant differences in mean 25(OH)D levels for these three variables. Nevertheless, we observed a tendency of decreased 25(OH)D levels in subjects who consumed enzyme-inducing anticonvulsants, had polytherapy, or consumed anticonvulsants for more than 2 years (statistically insignificant). These results were likely not deemed significant due to the small number of subjects in our study.

Most studies which showed an association between anticonvulsant use and vitamin D levels were conducted on subjects who used enzyme-inducing anticonvulsants.[19,27-30,32] One Lebanese study that showed a high prevalence of vitamin D deficiency had subjects who mostly consumed enzyme-inducing anticonvulsants and administered as polytherapy, with a mean duration of 5±4 years.[25] A cross-sectional study in Germany showed a lower level of 25(OH)D in subjects using carbamazepine (enzyme inducer) compared to those who used valproic acid (non-enzyme inducer).[32] Another study in Germany showed lower level of 25(OH)D in subjects using anticonvulsants administered as polytherapy than those who received monotherapy.[29]

Our study showed that girls tended to have lower 25(OH)D levels than boys. A prospective study in India showed that reduced 25(OH)D level after consumption of carbamazepine was more evident in girls.[28] Other studies on a population of healthy children also showed lower 25(OH)D level and higher prevalence of vitamin D deficiency in girls compared to boys.[8-10] There was no further explanation for the findings in these studies. Unfortunately, our study also does not explain this finding. One possibility is the difference in the quantity of sun exposure, which may be associated with shorter time duration of outdoor activities in girls compared to boys.

In conclusion, epileptic children who took long-term anticonvulsant therapy have lower mean 25(OH)D level and higher prevalence of vitamin D insufficiency than the non-epileptic control group. Daily intake of vitamin D, gender, type and number of anticonvulsants, as well as duration of anticonvulsant therapy for more than 2 years are not associated with reduced 25(OH)D levels in epileptic children who used anticonvulsants for at least 1 year.

Conflict of inetrest

None declared.

References

1. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab. 2009;94:26-34.
2. Fitzpatrick LA. Pathophysiology of bone loss in patients receiving anticonvulsant therapy. Epilepsy Behav. 2004;5:S3-15.
3. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc. 2006;81:353-73.
4. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics.

2008;122:398-417.
5. Valsamis HA, Arora SK, Labban B, McFarlane SI. Antiepileptic drugs and bone metabolism. Nutr Metab. 2006;3:36-46.
6. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics. 2008;122:1142-52.
7. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357: 266-81.
8. Zhu Z, Zhan J, Shao J, Chen W, Chen L, Li W, *et al*. High prevalence of vitamin D deficiency among children aged 1 month to 16 years in Hangzhou, China. BMC Public Health. 2012;12:126.
9. Saintonge S, Bang H, Gerber LM. Implications of a new definition of vitamin D deficiency in a multiracial US adolescent population: the National Health and Nutrition Examination Survey III. Pediatrics. 2009;123:797-803.
10. Andiran N, Celik N, Akca H, Dogan G. Vitamin D deficiency in children and adolescents. J Clin Res Pediatr Endocrinol. 2012;4:25-9.
11. Khor GL, Chee WS, Shariff ZM, Poh BK, Arumugam M, Rahman JA, *et al*. High prevalence of vitamin D insufficiency and its association with BMI-for-age among primary school children in Kuala Lumpur, Malaysia. BMC Public Health. 2011;11:95.
12. Binkley N, Novotny R, Krueger D, Kawahara T, Daida YG, Lensmeyer G, *et al*. Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab. 2007;92:2130-5.
13. Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health. Osteoporos Int. 2007;18:129-42.
14. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. Epilepsia. 2004;45:1330-7.
15. Sheth RD. Metabolic concerns associated with antiepileptic medications. Neurology. 2004;63:S24-9.
16. Morijiri Y, Sato T. Factors causing rickets in institutionalised handicapped children on anticonvulsant therapy. Arch Dis Child. 1981;56:446-9.
17. Guo CY, Ronen GM, Atkinson SA. Longterm valproate and lamotrigine treatment may be a marker for reduced growth and bone mass in children with epilepsy. Epilepsia. 2001;42:1141-7.
18. Crosley CJ, Chee C, Berman PH. Rickets associated with long-term anticonvulsant therapy in a pediatric outpatient population. Pediatrics. 1975;56:52-7.
19. Cansu A, Yesilkaya E, Serdaroglu A, Hirfanoglu T, Camurdan O, Gulbahar O, *et al*. Evaluation of bone turnover in epileptic children using oxcarbazepine. Pediatr Neurol. 2008;39:266-71.
20. Drezner MK. Treatment of anticonvulsant drug-induced bone disease. Epilepsy Behav. 2004;5:S41-7.
21. Dent CE, Richens A, Rowe DJF, Stamp TCB. Osteomalacia with long-term anticonvulsant therapy in epilepsy. Br Med J. 1970;4:69-72.
22. Hunter J, Maxwell JD, Stewart DA, Parsons V, Williams R. Altered calcium metabolism in epileptic children on anticonvulsants. Br Med J. 1971;4:202-4.
23. Silver J, Davies TJ, Kupersmitt E, Orme M, Petrie A, Vajda F. Prevalence and treatment of vitamin D deficiency in children on anticonvulsant drugs. Arch Dis Child. 1974;49:344-50.
24. Weisman Y, Fattal A, Eisenberg Z, Harel S, Spirer Z, Harell A. Decreased serum 24,25-dihydroxy vitamin D concentrations in children receiving chronic anticonvulsant therapy. Br Med J. 1979;2:521-3.
25. Farhat G, Yamout B, Mikati AM. Effect of antiepileptic drugs on bone density in ambulatory patients. Neurology. 2002;58:1348-53.
26. Gough H, Bissesar A, Goggin T, Higgins D, Baker M, Crowley M, *et al*. Factors associated with the biochemical changes in vitamin D and calcium metabolism in institutionalized patients with epilepsy. Ir J Med Sci. 1986;155:181-9.
27. Menon B, Harinarayan CV. The effect of anti epileptic drug therapy on serum 25-hydroxyvitamin D and parameters of calcium and bone metabolism--a longitudinal study. Seizure. 2010;19:153-8.
28. Misra A, Aggarwal A, Singh O, Sharma S. Effect of carbamazepine therapy on vitamin D and parathormone in epileptic children. Pediatr Neurol. 2010;43:320-4.
29. Nettekoven S, Ströhle A, Trunz B, Wolters M, Hoffmann S, Horn R, *et al*. Effects of antiepileptic drug therapy on vitamin D status and biochemical markers of bone turnover in children with epilepsy. Eur J Pediatr. 2008;167:1369-77.
30. Nicolaidou P, Georgouli H, Kotsalis H, Matsinos Y, Papadoupoulou A, Fretzayas A, *et al*. Effects of anticonvulsant therapy on vitamin D status in children: prospective monitoring study. J Child Neurol. 2006;21:205-9.
31. Pedrera JD, Canal ML, Carvajal J, Postigo S, Villa LF, Hernandez ER, et al. Influence of vitamin D administration on bone ultrasound measurements in patients on anticonvulsant therapy. Eur J Clin Invest. 2000;30:895-9.
32. Rieger-Wettengl G, Tutlewski B, Stabrey A, Rauch F, Herkenrath P, *et al*. Analysis of the musculoskeletal system in children and adolescents receiving anticonvulsant monotherapy with valproic acid or carbamazepine. Pediatrics. 2001;108:e107-11.
33. Baer MT, Kozlowski BW, Blyler EM, Trahms CM, Taylor ML,

Hogan MP. Vitamin D, calcium, and bone status in children with developmental delay in relation to anticonvulsant use and ambulatory status. Am J Clin Nutr. 1997;65:1042-51.
34. Verrotti A, Greco R, Latini G, Morgese G, Chiarelli F. Increased bone turnover in prepubertal, pubertal, and postpubertal patients receiving carbamazepine. Epilepsia. 2002;43:1488-92.
35. Williams C, Netzloff M, Folkerts L, Vargas A, Garnica A, Frias J. Vitamin D metabolism and anticonvulsant therapy: effect of sunshine on incidence of osteomalacia. South Med J. 1984;77:834-42.
36. Rauchenzauner M, Griesmacher A, Tatarczyk T, Haberlandt E, Strasak A, Zimmerhackl LB, *et al*. Chronic antiepileptic monotherapy, bone metabolism, and body composition in non-institutionalized children. Dev Med Child Neurol. 2010;52:283-8.
37. McCarty CA. Sunlight exposure assessment: can we accurately assess vitamin D exposure from sunlight questionnaires? Am J Clin Nutr. 2008;87:1097S-101S.
38. Borusiak P, Langer T, Heruth M, Karenfort M, Bettendorf U, Jenke AC. Antiepileptic drugs and bone metabolism in children: data from 128 patients. J Child Neurol. 2013;28:176-83.
39. Cetinkaya T, Kurtulmus YS, Tutkavul K, Tireli H. The effect of oxcarbazepine on bone metabolism. Acta Neurol Scand. 2009;120:170-5.
40. Krishnamoorthy G, Nair R, Sundar U, Kini, Shrivastava M. Early predisposition to osteomalacia in Indian adults on phenytoin or valproate monotherapy and effective prophylaxis by simultaneous supplementation with calcium and 25-hydroxy vitamin D at recommended daily allowance dosage: a prospective study. Neurol India. 2010;58:213-9.
41. Kulak CA, Borba VZ, Bilezikian JP, Silvado CE, Paola L, Boguszewski CL. Bone mineral density and serum levels of 25 OH vitamin D in chronic users of antiepileptic drugs. Arq Neuropsiquiatr. 2004;62:940-8.
42. Institute of Medicine of the National Academies. Dietary reference intakes for calcium and vitamin D. Report Brief 2010; 1-4 [cited 2013 August 2]. Available from http://www.iom.edu/~/media/Files/Report%20 Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf.
43. Rajakumar K, Thomas SB. Reemerging nutritional rickets: a historical perspective. Arch Pediatr Adolesc Med. 2005;159:335-41.