

Vitamin-D supplementation among children with epilepsy

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Epilepsy is a very common neurological disease in childhood, with a high prevalence of vitamin D deficiency. In pediatric epileptic population, treatment with antiepileptic drugs influence bone metabolism, reducing bone mass and levels of serum vitamin D. Vitamin D deficiency may cause rickets and osteomalacia, resulting in a higher fracture risk and an increased incidence of osteoporosis in adult life. Vitamin D monitoring and

supplementation is important in the management of epileptic children on long-term antiepileptic drugs. There are a few studies in literature related to the effects of vitamin D supplementation in epileptic children, concluding that the effects in these children differ from that in healthy population. Most studies recommend the prescription of vitamin D supplementation; however there is still a debate regarding the optimal level of vitamin D supplementation and its exact impact on bone mineralization.

Key Words: *Children, Epilepsy, Anti-epileptic drugs, Vitamin D, Supplementation*

Childhood is one of the most important ages of bone mineralization. Apart from genetic factors, bone growth is affected by the mode of life, hormones, exercise, age body characteristics and nourishment (1). Epilepsy is the most frequent illness of the childhood, characterized by repeated seizures and influencing the physical and mental state of many children (2). As a treatment, epileptic children receive antiepileptic drugs [AEDs], which trigger off a lot of side effects. In particular, AEDs influence bone turnover leading to several bone manifestations such as rickets and osteomalacia (3,4).

Vitamin D metabolism and actions

Vitamin D is a member of a group of fat-soluble secosteroids which are mainly important for the homeostasis of calcium, phosphate and magnesium. In this group, the most important compounds are vitamin D₂ [ergocalciferol] and vitamin D₃ [cholecalciferol]. Vitamin D major source is by cutaneous synthesis, where exposure to ultraviolet spectra from sunlight results in the conversion of 7-dehydro-cholesterol to vitamin D₃ (5). Biologically inert, vitamin D₃ needs a first hydroxylation to form 25-OH-vitamin D in the liver, and then a second hydroxylation to form its active type 1,25-[OH]₂-vitamin D in the kidneys [calcitriol], circulating as a hormone in the blood (5).

Calcitriol mediates most of the physiological actions of vitamin D through binding to the vitamin D receptor [VDR], which can be found almost in every tissue and cell in the body. It is a nuclear receptor and with a dual role, maintaining gene transcription and provoking direct rapid responses. VDR can communicate with signal pathways, resulting in opening of calcium and chloride channels (6). Calcitriol stimulates the differentiation, dissuades angiogenesis, excites insulin generation, prevents rennin generation and excites macrophage cathelicidin generation (7). Vitamin D and its receptor have vital roles in the brain, such as organization of cell growth and cellular differentiation in addition to neuroprotection (8). However, the importance of vitamin D is mostly essential in bone metabolism through the intestinal absorption of calcium and phosphate, increase of osteoclast number and promotion of normal functioning of parathyroid hormone [PTH] to maintain serum calcium levels. Insufficient serum levels of calcium and vitamin D may lead to rickets and osteomalacia due to disturbance of bone mineralization (9).

Epilepsy and bone metabolism

Epilepsy and bone metabolism

Reduction of bone mass density [BMD] has been observed in most epileptic patients and also 25% of patients with epilepsy suffer from osteoporosis (10). Moreover, BMD of epileptic children is remarkably lower compared with healthy children; as a result, the diagnosis and management of this pathogenetic procedure is of vital importance. Serum levels of calcium and vitamin D are playing an important role in the pathophysiology of epilepsy-induced osteoporosis.

AEDs and bone turnover

AEDs are separated in two groups: AEDs inducing the cytochrome p450 enzyme in the liver [carbamazepine, phenytoin, phenobarbitale, primidone] and non-inducing AEDs [valproate acid, lamotrigine, gabapentin, clonazepam, topiramate]. Epilepsy daily treatment with AEDs, used for seizures interception, is an identified factor effecting in bone turnover. Polytherapy, as well as treatment with AEDs for a long time, is shown to be related with low levels of vitamin D, having a negative effect in bone health (11). Non cytochrome p450 inducing AEDs affect bone turnover via different pathways [direct effects on osteoblasts, resistance to PTH, inhibition of calcitonin production and decreased calcium absorption] (12). Administration of AEDs in epileptic children has been associated with a reduction of BMD, while BMD in children with epilepsy has been noted to be decreased by 9% (13,14). 20% of Malaysian children with epilepsy on long-term AEDs have low BMD (15). Monotherapy with carbamazepine and valproate in 11 studies has shown a small reduction in BMD, where in one study involving phenytoin, topiramate and phenobarbitale, none fluctuation in BMD was found (16). Nevertheless, a recent study concluded that both types of AEDs resulted in a decrease of BMD, even though no decrease was observed in epileptic children that received no treatment (17). Bone physiology in children is different from that of the adults because of the existence of growth plates which are important for bone development. AEDs, such as valproate acid, can have a direct negative impact on bone growth plates (18). AEDs influence bone mineral status in children receiving AEDs for more than 6 months, altering both biochemical and radiologic markers. Administration for more than 2 years have severe side effects on BMD (19).

Epilepsy and vitamin D deficiency

In spite of few cross-sectional data among children with epilepsy, it is believed that this population is in danger of vitamin D hypovitaminosis (20,21). Additionally, in large surveys of epileptic patients, a high incidence of hypocalcaemia augmentation of alkaline phosphatase [ALP], and radiological rickets has been remarked (22). Levels of serum vitamin D have been found to be significantly decreased in children with newly diagnosed epilepsy in comparison to healthy children and about half of epileptic children have decreased vitamin D levels (23). Obesity is a risk factor for vitamin D deficiency in epileptic children, as the fat-soluble vitamin D can be extensively stored in the adipose tissue (24).

Many studies support the relation between low vitamin D and seizures and there are various studies trying to find the consequences of vitamin D deficiency in the epilepsy onset (25). A possible etiology includes a direct effect of vitamin D in the brain, resulting in a reduction of neuronal hyperexcitability and incidence of seizures. Vitamin D may influence seizures by maintaining the expression of neuromediator genes which participate in neurotransmission. Furthermore, vitamin D, as a neurosteroid, can directly

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interact with GABA-A receptors in the brain (26). Nevertheless, vitamin D deficiency has been associated with several disorders of nervous system such as Alzheimer's and Parkinson's disease, multiple sclerosis, depression, autism and schizophrenia (27).

Anticonvulsant treatment in epileptic children has been correlated with reduced levels of serum vitamin D and vitamin D deficiency (18,26,28-33). Most of AEDs raise the hepatic metabolism of vitamin D, through cytochrome P450 enzyme generation, leading to decreased levels of 25-OH-Vitamin D (11). Valproate acid has a negative effect over the nuclear pregnane X receptor which enhances the expression of vitamin D genes (34). The duration of AED administration is an important factor for the evolution of vitamin D deficiency (31).

Vitamin D supplementation in epileptic children

Sufficient sun exposure is very important, particularly in places where the sunlight is apparent many hours per day. Typical dietary recommendations suppose that all amount of vitamin D is received per os, as sun exposure in each population is variable and recommendations about the amount of safe sun exposure are uncertain in relation to risk of skin cancer. However, it seems that the issue of vitamin D deficiency among epileptic children is underestimated, as few of them are routinely monitored for 25-OH-vitamin D levels (35). The Guidelines of Endocrine Society suggest assessment of vitamin D status by serum 25- OH -Vitamin D levels in individuals on AEDs (5). Despite the few data recommending global screening and interposing in patients with low vitamin D levels, there are adequate data in the literature to support the significance of vitamin D supplementation, especially in epileptic children (36).

During childhood, serum levels of calcium, phosphate, and vitamin D are important for proper development of bone tissue. Concentration of these nutrient factors should be evaluated before the initiation of early vitamin D supplementation. Routine measurement of vitamin D levels is widely proposed and low dose vitamin D supplements, 400 IU, is usually subscribed (26,37). Enrichment of milk with vitamin D can increase serum concentrations of these nutrients. Moreover, it has been proposed that every epileptic child under AEDs administration for 2 years or more, should receive supplementation of vitamin D and calcium (38,39). Measurement of bone alkaline phosphatase isoenzyme can be helpful to determine the cases that demand further evaluation of the bone physiology (16). Measurement of body mass index [BMI] is important for sufficient evaluation of bone metabolism of every epileptic child. In addition, as epileptic children are often undernourished, a routine evaluation of the nutritional status can be useful in terms of adjusting the levels of every essential nutrient (40).

Normal levels of vitamin D

There is still controversy in scientific literature about normal levels of vitamin D, partly because of the differences in serum levels between ethnic groups (41). A recent review suggested that optimal levels of vitamin D for all outcomes are approximately 30 ng/ml [75 nmol/l] (42). The latest guidelines supported by Royal College of Pediatrics and Child Health [RCPCM] indicates that deficiency exists when blood levels of 25-OH-vitamin D is below 25 nmol/L, insufficiency when blood levels of 25-OH-vitamin D ranges between 25 to 50 nmol/L, and sufficiency when blood levels of 25-OH-vitamin D is more than 50 nmol/L. The World Health Organization defines vitamin D deficiency when 25-OH-vitamin D level is under 20 ng/ml and insufficiency when 25-OH-vitamin D levels is 21 - 29 ng/ml (7).

Necessity of supplementation

There is a lack of experimental data to support global screening and specific interventions for epileptic children with vitamin D hypovitaminosis. Most studies to date are inconsistent and of limited quality. Larger studies are needed, using clinically significant outcomes such as fractures, including populations at risk such as symptomatic generalised epilepsy, impaired mobility and anticonvulsant polytherapy. However, there are adequate data to suggest that low vitamin D levels may be important for epileptic children. In the absence of good evidence to the contrary, it seems that vitamin D supplementation may be beneficial for epileptic children (3). Two randomized trials have concluded that high-dose vitamin D therapy in children on AEDs, resulted in BMD increase (43). A study by Fischer et al. has suggested that vitamin D supplementation improve bone status in children on anticonvulsant therapy (44). A recent review has suggested that the neurologists should ensure that low-dose vitamin D supplementation are prescribed in children with epilepsy (37). Nevertheless, vitamin D supplementation is a safe and low cost procedure. In February 2015, the Eastern Paediatric Epilepsy Network [EPEN] published clinical guidelines

where vitamin D supplementation was suggested in all epileptic children who receive treatment with AEDs (36).

Forms of supplementation

Vitamin D supplementation can be found as ergocalciferol, cholecalciferol and calcitriol (10). Ergocalciferol and cholecalciferol can increase vitamin D repositories in different rates (45). Cholecalciferol can raise calcitriol concentrations two to three times more than ergocalciferol (46). Vitamin D₂, commercially can be found as oral solution, capsule or tablet while vitamin D₃ is available in oral drops, capsule, tablet, oral solution and in chewable or dispersible tablets. The formulations of 1,25-[OH]₂-vitamin D is available as solution for injection, capsule and oral solution (45). Although there are dynamic differences comparing cholecalciferol to ergocalciferol [without having any direct comparison], most of the guidelines do not have a choice between these two formulas. Moreover vitamin D stores cannot be filled by calcitriol (45).

Optimal doses of supplementation

Generally, in children and adolescents, vitamin D levels must be above 30 ng/ml, which is achieved by receiving about 600 IU vitamin D (18). The American Academy of Pediatrics has recommended that all healthy children should receive 400 IU of vitamin D supplements as infants and continue through adolescence. British Department of Health recommends a dose of approximately 300 IU for all healthy children from 6 months to 5 years of age.

According to the EPEN guidelines, in epileptic children, the treatment of vitamin D hypovitaminosis is the same as in symptomatic deficiency: Children of age up to 6 months should receive a vitamin D dose of 1.000 units - 3.000 units per day for 4 - 8 weeks. Children of age between 6 months and 12 years should receive a vitamin D dose of 6.000 units per day for 4 - 8 weeks and children of age between 12 and 18 years old should receive a dose of 10.000 units per day for 4 - 8 weeks (36). In a recent Malaysian study, authors recommended that all children on anticonvulsant therapy should receive 2 or 3 times more vitamin D supplementation [1200 - 3000 units/day] in relation to healthy children (33).

The vitamin D supplementation may be tablets or capsules of 400, 1.000, 10.000, 20.000 units. Tablets with the combination of calcium and vitamin D very often contain low units of vitamin D up to 400 units. If calcium levels are adequate, isolated vitamin D product can be prescribed. An alternative way to treat vitamin D deficiency is to administer once per week the daily dose multiplied by seven (36). Individuals with a secondary osteoporosis because of cause AED treatment is possible in need of higher dose of vitamin D supplementation than others patients on AEDs for the correction of PTH, calcium, and phosphorus. In epileptic population where daily adherence is necessary, an alternative treatment known as "stoss therapy" can be used in patients of at least two months of age. Stoss therapy regimens with large doses of vitamin D₃ has been shown to provoke increased and sustained higher levels of vitamin D. Stoss therapy is safe and can lead to hypercalcemia only at very high doses (4).

Adverse effects of supplementation

Even though, vitamin D hypervitaminosis is rare in children, prolonged administration of vitamin D supplements, optimization of vitamin D levels, and administration of higher doses may potentially increase vitamin D toxicity. In epileptic children, vitamin D overdose is usually rare and asymptomatic. Vitamin D hypervitaminosis may be attributed in defective manufacturing, formulation, or prescription. It involves high total intake between 240,000 to 4,500,000 IU and is accompanied by severe hypercalcemia, hypercalciuria, or nephrocalcinosis. Mild hypercalcemia due to usual doses has been observed in infants with rickets. Furthermore, there is a potential need for recording vitamin D levels when doses at upper limit are used. Serum 25- OH -vitamin D levels should be obtained in infants and children who receive prolonged vitamin D supplementation (47). Taking into consideration the widespread use of vitamin D in larger dosages in adults, vitamin D supplements in small children must be used with caution. Dosage recommendations may need to be reevaluated, particularly, where follow-up and monitoring may be compromised (48). Multivitamin supplements should be used with caution as vitamin A toxicity is a concern. Multivitamin supplements often contain a surprisingly low dose of vitamin D.

CONCLUSION

Vitamin D insufficiency is common to all pediatric epileptic population, leading to rickets and osteomalacia. It carries not only with the risk of suboptimal skeleton health but also provokes several extraskeletal

consequences, especially in a long-term treatment on AEDs. There are enough data in medical literature for vitamin D routine supplementation without important risk, but there is still a lack of consensus regarding optimal doses, assessment and monitoring of vitamin D levels. More controlled trials examining the effect of vitamin D supplementation on bone status in epileptic children is needed, in order to fully elucidate the role of vitamin D supplementation in bone mass, osteoporosis and fracture incidence and optimal doses of treatment.

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