Review Article

Vitamin D deficiency in adolescents

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ABSTRACT

The prevalence of severe vitamin D deficiency (VDD) in adolescents is variable but considerably high in many countries, especially in Middle-east and Southeast Asia. Different factors attribute to this deficiency including lack of sunlight exposure due to cultural dress codes and veiling or due to pigmented skin, and less time spent outdoors, because of hot weather, and lower vitamin D intake. A potent adaptation process significantly modifies the clinical presentation and therefore clinical presentations may be subtle and go unnoticed, thus making true prevalence studies difficult. Adolescents with severe VDD may present with vague manifestations including pain in weight-bearing joints, back, thighs and/or calves, difficulty in walking and/or climbing stairs, or running and muscle cramps. Adaptation includes increased parathormone (PTH) and deceased insulin-like growth factor-I (IGF-I) secretion. PTH enhances the tubular reabsorption of Ca and stimulates the kidneys to produce 1, 25-(OH) 2D3 that increases intestinal calcium absorption and dissolves the mineralized collagen matrix in bone, causing osteopenia and osteoporosis to provide enough Ca to prevent hypocalcaemia. Decreased insulin like growth factor-I (IGF-I) delays bone growth to economize calcium consumption. Radiological changes are not uncommon and include osteoporosis/osteopenia affecting long bones as well as vertebrae and ribs, bone cysts, decalcification of the metaphysis of the long bones and pseudo fractures. In severe cases pathological fractures and deformities may occur. Vitamin D treatment of adolescents with VDD differs considerably in different studies and proved to be effective in treating all clinical, biochemical, and radiological manifestations. Different treatment regiments for VDD have been discussed and presented in this mini-review for practical use. Adequate vitamin D replacement after treating VDD, improving calcium intake (milk and dairy products), encouraging adequate exposure to the sun and possible enrichment of the stable food with vitamin D in areas with high prevalence of VDD are important measures to prevent the harmful consequences of VDD.

Key words: Adaptation, adolescents, biochemical, calcium, clinical, phosphorus, radiology, Vitamin D deficiency, Vitamin D therapy

Vitamin D Deficiency: The Definitions

In general, a serum 25(OH) D at concentration less than 25 nmol/L (10 ng/mL) is a useful marker of the risk of clinical deficiency, but the terminology and cut-offs used to define less than desirable vitamin D status is controversial. It includes terms such as insufficiency, inadequate level, deficiency (VDD) and hypovitaminosis D and may result in subclinical conditions with chronic latent manifestations, the most recognized of which is osteoporosis. The 25(OH) D cut-offs to define this condition vary and have recently been defined as desirable level at 20 ng/ml (50 nmol/L), and the Endocrine Society Guidelines set at 30 ng/ml (75 nmol/L).[1,2]

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Prevalence of VDD in Adolescents Worldwide

Adequate vitamin D status is essential for active calcium absorption in the gut and for bone development and remodeling. While bone disease secondary to VDD (rickets and osteomalcia) is almost eradicated in western populations, its prevalence remains unacceptably high in Asia, Africa and the Middle-east.[3,4] In a review conducted

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by the nutrition working group of the International Osteoporosis Foundation (IOF), hypovitaminosis defined as 25(OH) D level below 30 ng/ml (75 nmol/L) was prevalent in all regions of the world, whereas levels below 10 ng/ml (25 nmol/L) were most common in South Asia and the Middle-east.[5] In India, Marwaha *et al.* reported high prevalence of severe VDD (<22.5 nmol/L) in adolescent males (27%) and females (42%).[6] In the Middle-east and North Africa (MENA) VDD prevails with rates varying 30-90%, considering a desirable serum 25 hydroxy-vitamin D [25(OH) D] of 20 ng/ml.[6,7]

Recently, a high prevalence of VDD among children and adolescents has been reported in countries even with moderate climates. Few randomized vitamin D trials revealed that the majority of mothers or children failed to achieve a desirable 25(OH) D level, even with doses by far exceeding current recommendations. In western countries and USA, milder deficient states are more common. Consistent predictors across these studies for lower vitamin D values were female gender, winter season, lack of sunlight exposure due to cultural dress codes and veiling, pigmented skin, and lower vitamin D intake.[8-10]

Vitamin D, Calcium Metabolism, and Skeletal Mineralization and Adapatation

Vitamin D is an essential hormone for growth and development of bones in children and adolescents and critical for calcium homeostasis and mineralization of the skeleton.[1] In VDD, only 10-15% of calcium of normal diet is absorbed. This amount increases to 40% in the presence of adequate vitamin D. VDD leads to rickets (a mineralization defect at the epiphyseal growth plates and bone tissue) and osteomalacia (a mineralization defect of bone tissue). Both rickets (before closure of the growth plate) and osteomalacia (after closure of the growth plate) are still reported in adolescents with VDD.[11] The development of clinical manifestations of VDD rickets depends on many factors including the severity and duration of the VDD (circulating concentrations of 25-hydroxy vitamin D [25-OH-D], calcium demand (speed of growth), calcium intake and absorption. The balance between osteoblastic and osteoclastic activities and the interaction between kidneys, gut, bone, is well controlled by the endocrine system.[11,12]

A potent adaptation process, mediated by PTH and IGF-I, modifies the clinical and radiological manifestations of VDD in adolescents. Therefore, overt cases of rickets and osteomalcia represent only the tip of the iceberg of patients with severe VDD and malfunction of adaptation.[13-19]

Without VD, only 10-15% of dietary Ca and about 60% of phosphorus is absorbed. The active form, 1,25-dihydroxy vitamin D (1,25-(OH) 2D3) markedly increases the efficiency of intestinal Ca and phosphorus absorption.[13-17] Serum levels below 30 ng/ml are associated with a significant decrease in intestinal Ca absorption. In children, adolescents VDD is associated with increased PTH and deceased IGF-I secretion.[13-20]

PTH enhances the tubular reabsorption of Ca and stimulates the kidneys to produce 1,25-(OH) 2D3. It also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts.[14-17] Osteoclasts dissolve the mineralized collagen matrix in bone, causing osteopenia and osteoporosis[21-24] and provide enough Ca to prevent hypocalcemia.

Systemically, IGF-I stimulates the production of 1, 25-(OH) 2D3 by kidney cells and stimulates bone formation, through an intrinsic action on osteoblasts. It supports proliferation, differentiation and matrix synthesis in cultures of osteoblast-like cells and bone organ cultures. It stimulates the production of type I collagen (the main structural protein of bone) and increases pro-collagenα1 (I) mRNA expression both in osteoblasts *in vitro* and in bone *in vivo*.[23-27] Lack of IGF-I, therefore, may impact skeletal health adversely. Locally in the growth plate, 1,25-(OH) 2D3 potentiates local IGF-I synthesis in chondrocytes and stimulates cell proliferation and differentiation as judged by increased alkaline phosphatase (ALP) activity, collagen X mRNA, and matrix calcification in long-term experiments. 1,25-(OH) 2D3 stimulates chondrocytes proliferation and cell differentiation.[28-30]

Skeletal Health in Children and Adolescents in Relation to Vitamin D Status

Serum levels of 25-OH-D are directly related to bone mineral density with a maximum density achieved when the 25-OH-D level reached 40 ng/ml or more.[13-20] The Institute of Medicine (IOM) report states that the Recommended Dietary Allowance (RDA) is the dose of vitamin D that would result in desirable 25(OH) D levels, above 20 ng/ml, in 97.5% of the population. In children, the RDA is 600 IU/d. However, the administration of doses of vitamin D, several folds above 600 IU, fail to bring most subjects above the 20 ng/ml cut-off, presuming the same desirable level is needed across ethnic groups.[2]

A recent meta-analysis of 6 randomized placebo controlled trials with planned subgroup analyses by baseline 25(OH) D level suggest that vitamin D supplementation of

deficient adolescents produces significant improvements of 25(OH) D level. In a randomized placebo-controlled trial in 179 adolescent Lebanese girls, vitamin D administered weekly, at the equivalent daily doses of 200 IU and 2000 IU/day produced significant effect on musculoskeletal parameters, including bone mineral content, density, area, and lean mass.[31-33]

Clinical Presentation of Vdd in Adolescents

In adolescents, presentation of severe and/or prolonged VDD markedly differs from young children. VDD in adolescents may be asymptomatic and go undetected. They may present with vague manifestations including pain in weight-bearing joints, back, thighs, and/or calves, difficulty in walking and/or climbing stairs, getting up from a squatting position and/or running and muscle cramps. The pain is symmetrical, non-radiating and is accompanied by sensitivity in the involved bones. Facial twitches and carpo-pedal spasms are less frequent symptoms. Due to the demineralization of bones become occurrence of deformities may occur, like triradiate pelvis, lordosis, and/or genu valug or varus. These manifestations may go unnoticed for long periods and in severe and prolonged deficiency vertebral compression fractures and fractures of the long bones may occur. Convulsions and hypocalcemic cardiomyopathy are rare manifestation of severe hypocalcemia secondary to VDD. Moreover, VDD can be misdiagnosed as fibromyalgia, chronic fatigue syndrome, or simply depression in adolescents.[34-41]

The diagnosis is usually made on basis of the classic clinical profile of bone pain, fractures and proximal myopathy, combined with confirmatory laboratory tests including a low 25(OH) D (usually below 5 and 10 ng/ml (25-50 nmol/L), low serum phosphate, and a high alkaline level with normal or borderline low serum calcium concentrations.

Compared to children with VDD, adolescents have relatively higher serum Ca, PO4 and IGF-I concentration and lower PTH and ALP concentrations. This is due to their better adaptation due to higher bone mass density (Ca and PO4 stores) and area as well as higher sex steroid and IGF-I levels.[42]

Radiological Manifestations of Severe Vdd in Adolescents

In adolescents with VDD radiological changes are less frequent and less significant compared to children with rickets.[43] However, in severe VDD the shafts of the long bones appears osteopenic and the cortices become thin. The trabecular pattern is fuzzy, coarse, and has a ground-glass appearance. Deformities of the shafts of the long bones may occur, looser zones and bone cysts may be noted. In severe cases, pathological fractures may occur[43] [Figure 1].

Osteopenia may be the only finding and osteomalaciacan be confused with osteoporosis. Looser zones are pseudo-fractures that present as narrow radiolucent lines (2-5-mm wide), with sclerotic borders and considered a characteristic radiologic finding in osteomalacia. They are bilateral and symmetric and lie perpendicular to the cortical margins of bones. The femoral neck, on the medial part of the femoral shaft, immediately under the lesser trochanter, and the pubic and ischial rami are the mostly affected sites. They also may occur in the ulna, scapula, clavicle, rib, and metatarsal bones. Pseudo-fractures represent either stress fractures that have been repaired by the laying down of inadequately mineralized osteoid or erosion of bone by arterial pulsations, since they often lie in apposition to arteries. The term "Milkman syndrome" refers to the combination of multiple, bilateral, and symmetric pseudofractures in a patient with osteomalacia.[36,44,45]

In long bones, two different radiological patterns of severe VDD in adolescents have been detected. Pattern (I), with localized metaphyseal multilocular cystic lesions, occur in overweight adolescents with good intake of milk/milk products. [Figure 2] Adolescents with pattern (I) appear to have better adaptation to VDD because of maintaining near-normal bone architecture of the cortex of long bones (better bone mass) and having higher serum PO4 concentrations and absence of hypocalcemia episodes. Adolescents with pattern (II) [Figure 3] with relatively low BMI < 18, low calcium and phosphate intake and lower IGF-I level) have generalized reduction of bone density versus those with pattern (I). Severe osteomalacia can lead to shortening and bowing of the tibia, pathologic fractures, and coxaprofunda hip deformity. There may be biconcave vertebral bodies (cod fish vertebrae).[42]

Several studies have demonstrated markedly reduced spine, hip, and forearm bone density [as measured by dual-energy

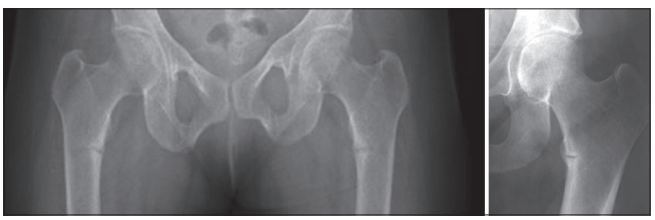

Figure 1: Looser's Zone (Pseudofractures)

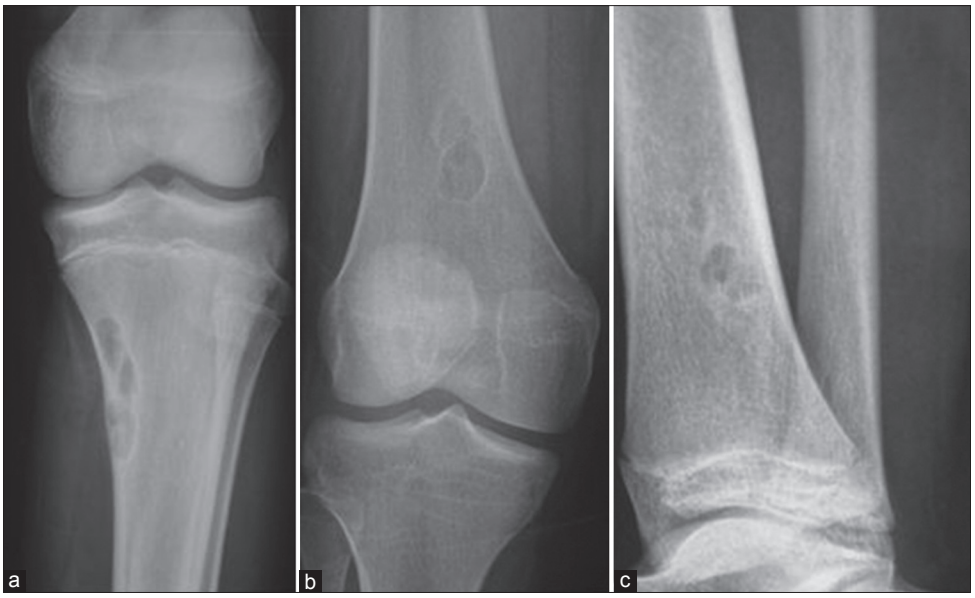

Figure 2: Pattern (I) Adolescent VDD rickets. The lesions appear as: (a). Multilocular bone cystic lesion with sclerotic margins, exocentric subcortical location (it simulates brown tumor secondary to hyperparathyroidism), (b). No other metaphyseal manifestations of VDD, (c). No cortical erosions, no periosteal reaction, no osteoporosis

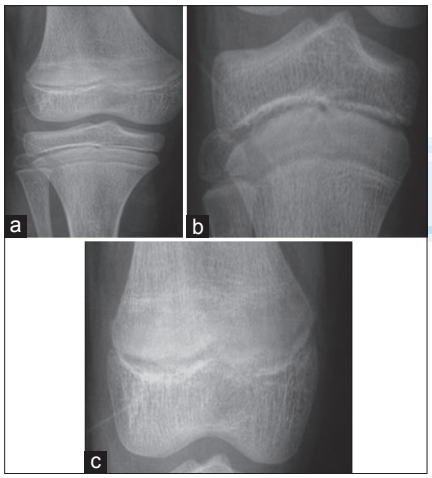

Figure 3: Pattern (II) adolescent VDD rickets: (a) Generalized diminished bone density with prominent primary and 2-yr bone trabeculation (b). Wide metaphysealzone with loss of bone trabiculation representing wide metaphyseal zone of poor ossification of bone matrix, (c). No cupping or fraying of metaphyses

X-ray absorptiometry (DXA)] in patients with osteomalacia related to VDD. However, bone mineral density (BMD) is not required for the diagnosis of osteomalacia, and reduced BMD does not distinguish osteoporosis from osteomalacia.

Bone mineral density is significantly low in adolescents with severe VDD and their T-scores may reach -4 to -5, with normalization after aggressive vitamin D therapy.[11,32,36,43,46-48]

In adolescents, teeth osteomalacia may occur and can be detected easily with axial cone beam CT image. Several recent reports demonstrate a significant association between periodontal health and the intake of vitamin D. Osteomalacia may be observed in the jaw near the angle, cysts and decreased alveolar bone density, osteoporosis and periodontal disease may occur. On panoramic projections, there may be an overall radiolucent appearance with the coarse trabeculae of bone. The lamina dura may be especially thin in individuals with long-standing or severe osteomalacia. The teeth are not altered in this condition in as much as they are fully developed before the onset of osteomalacia[49-51] [Figure 4].

The Histopathology of Osteomalacia in Relation to 25OH D Concentration

The histomorphometric characteristics of osteomalacia include: Prolonged mineralization lag time, widened osteoid seams, and increased osteoid volume per bone volume. All of these features are necessary for the diagnosis because other disorders may show one of

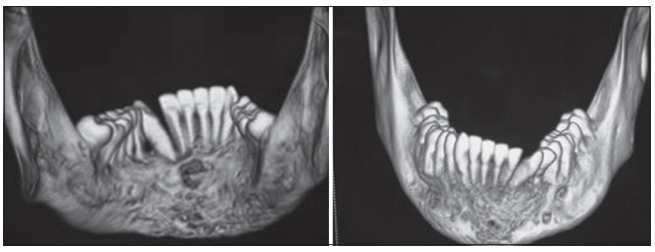

Figure 4: Bone density and cone beam CT Scan (CBCT) showing severe mandibular radiolucency and alveolar bone resorption associated with severe vitamin D deficiency in an 18-year-old adolescent

these findings. Priemel *et al.* did not find pathologic accumulation of osteoid in any patient with circulating 25(OH) D above 75 nmol/L and demonstrated that pathologic mineralization defects of bone occur in patients with a serum 25(OH) D below 75 nmol/L. They strongly argued that in conjunction with a sufficient calcium intake, the dose of vitamin D supplementation should ensure that circulating levels of 25(OH) D reach this minimum threshold (75 nmol/L or 30 ng/mL) to maintain skeletal health.[36]

Treatment of Vitamin D Deficiency in Adolescents

In a randomized double-blind, placebo-controlled trial, 210 adolescents (14-20 years) with VDD, Ghazi *et al.*, assigned three groups; group A ($n = 70$) received 50 000 U oral cholecalciferol monthly (equal to 1600 U per day), group B ($n = 70$), 50 000 U bimonthly (equal to 800 U/day) and group C ($n = 70$), placebo for 6 months. Monthly administration of 50 000 U vitamin D increased serum 25(OH) D significantly without any hypercalcuria but was apparently not enough to correct VDD, especially in girls.[52]

In support, Shakinba *et al.*, showed that that in an area with high prevalence of VDD (more than 50%), the recommended dose of neither 400 IU/day nor 800 IU/day was sufficient to maintain optimal level in all. However, after treatment with 300,000 IU of vitamin D, both doses of 1000 or 2000 IU/day would maintain serum 25(OH) D concentrations >20 ng/mL in all of the adolescents during the year. If level more than 30 ng/mL is the target, higher doses of vitamin D should be recommend.[53]

In another double-blind, placebo-controlled for a year, El-Hajj Fuleihan *et al.*, studied 179 adolescent girls and randomly assigned them to receive weekly oral vitamin D doses of 1,400 IU (equivalent to 200 IU/d) or 14,000 IU (equivalent to 2,000 IU/d). The bone area and total hip Bone mineral content (BMC) increased significantly in the high-dose group.[32]

Soliman *et al.* showed that treatment of 40 adolescents with severe VDD using a mega dose of vitamin D (300,000 IU/IM) every 3 months, results in mineralization of osteoid, disappearance of osteopenia and correction of epiphyseal, metaphyseal, and diaphyseal radiological changes.[54]

When cholecalciferol (56,000 IU) was given every week for 8 weeks in 23 Asian Indians with chronic hypovitaminosis D, 13/23 became vitamin D-sufficient with serum 25(OH) D levels >79.8 nmol/l, 9/23 had serum 25(OH) in the insufficient range and only one subject remained vitamin D-deficient at the end of the 8 weeks. In addition, such quick supplementation could not maintain their 25(OH) D levels in the sufficient range for longer period (1 year).[55]

To maintain a healthy blood level of 25-OH-D, most healthy adolescents require at least 1000 IU of vitamin D2 each day if they do not get exposure to the sun and there is evidence that doses up to 2000 IU per day can be considered safely. In areas with high prevalence of VDD the recommended daily dietary intake for vitamin D as suggested by various authors has varied from 1000 to 10,000 IU. The assembled data from many vitamin D supplementation studies reveal a curve for vitamin D dose versus serum 25(OH) D response that is surprisingly flat up to 250 μg (10000 IU) vitamin D/day.[56-58]

One or two annual intramuscular doses of 300 000 IU of cholecalciferol has been shown to reverse vitamin D deficiency states. The authors' simple dosing regimen (a mega dose of vitamin D 10,000 IU/kg (max 300 000 IU) every 3 months) has proven to be convenient and safe and improved patient compliance as suggested by others.[42,54,58-61] Although symptoms of VDD deficiency disappear early after initiating adequate vitamin D therapy (2-4 weeks) skeletal changes may take 6-12 months to heal completely.[54]

Possible regimens for treating VDD in Adolescents.[61,62]

1. Loading regimes for the treatment of deficiency
   - A. A total of 300,000 IU given either as weekly or daily split doses. The exact regimen will depend on the local availability of vitamin D preparations but will include:
     - 50,000 IU capsules, one given weekly for 6 weeks (300,000 IU) or
     - 20,000 IU capsules, two given weekly for 7 weeks (280,000 IU) or
     - 800 IU capsules, five a day given for 10 weeks (280,000 IU).
   - B. Another recommendation with proven safety and efficacy has been based on oral use of 50 000 IU vitamin D2 or D3 once weekly for 8 weeks and then to continue daily dose of 1500-2000 IU
   - C. A mega dose (300, 000 IU every 3-4 months) is another convenient and safe option and improve patient compliance.
2. Maintenance regimens
   - May be considered 1 month after loading with doses equivalent to 1000 to 2000 IU daily (occasionally up

to 4,000 IU daily), given either daily or intermittently at a higher equivalent dose.

The following should be borne in mind:

- Supplements should be taken with food to aid absorption
- Calcium/vitamin D combinations should not be used as sources of vitamin D for the above regimens, given the resulting high dosing of calcium.

Both oral continuous low-dose (150 000 IU vitamin D orally during 3 months) on a daily manner and short-term high-dose vitamin D (500 000 IU oral vitamin D during 10 days) have been proved to be effective in increasing serum 25(OH) D to within normal range in treating vitamin D- deficient Australian patients.[1]

However, there is a need for consensus to undertake corrective measures for hypovitaminosis D in countries with high prevalence of VDD especially in children and adolescents.

Screening Adolescents for Vitamin D Deficiency

It is not necessary to perform universal screening of serum 25(OH) D levels in the general population, however patients who present with nonspecific musculoskeletal pain and those with elevated levels of serum alkaline phosphatase (ALP) (e.g. 500-1000 IU/L in children and adolescents should be screened.[63,64] In addition, screening for VDD is recommended in some high-risk groups of patients including those with malabsorption, gastric bypass, liver disease, nephrotic syndrome, renal impairment, and patients on drugs affecting vitamin D metabolism. It is advisable to measure serum 25(OH) D to assess the amount necessary to reach the target 25(OH) D level, and then to measure again 3-4 months later to verify that the target has been achieved.

Conclusions

High prevalence of nutritional rickets and osteomalacia in adolescents still occurs in parts of the World including the Middle-east and North Africa and India despite its plentiful sunshine. Clinical presentation of severe VDD markedly differs during the different stages of growth. Adolescents with VDD may be asymptomatic or present with pain in the weight-bearing joints and back with myopathy. Biochemical changes may show hypophosphatemia and elevated alkaline phosphatse levels. Radiological changes may reveal significant abnormalities in long bones and vertebrae as well as the mandible. Pediatricians and endocrinologists should properly diagnose and manage VDD in the adolescent age group when bone accretion is at its maximum.

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