

Review Article

Vitamin D deficiency in adolescents

Ashraf T. Soliman, Vincenzo De Sanctis¹, Rania Elalaily², Said Bedair³, Islam Kassem⁴

Departments of Pediatrics and ⁴Faciomaxillary Surgery, University of Alexandria, Alexandria, Egypt, ¹Pediatric and Adolescent Outpatients Clinic, Quisisana Hospital, Ferrara, Italy, ²Department of Primary Health Care, AbuNakhla Hospital, Doha, ³Department of Radiology, AlKhor Hospital, Hamad Medical Center, Doha, Qatar

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 decreased 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]

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 osteomalacia) is almost eradicated in western populations, its prevalence remains unacceptably high in Asia, Africa and the Middle-east.^[3,4] In a review conducted

Access this article online

Quick Response Code:



Website:
www.ijem.in

DOI:
10.4103/2230-8210.145043

Corresponding Author: Dr. Ashraf T. Soliman, Professor of Pediatrics and Endocrinology, Alexandria University Children's Hospital, Alexandria, Cairo, Egypt. E-mail: ATSOLIMAN@yahoo.com

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 osteomalacia 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 decreased 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-collagen α 1 (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 valgus 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 osteomalacia can 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 coxapofunda 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)

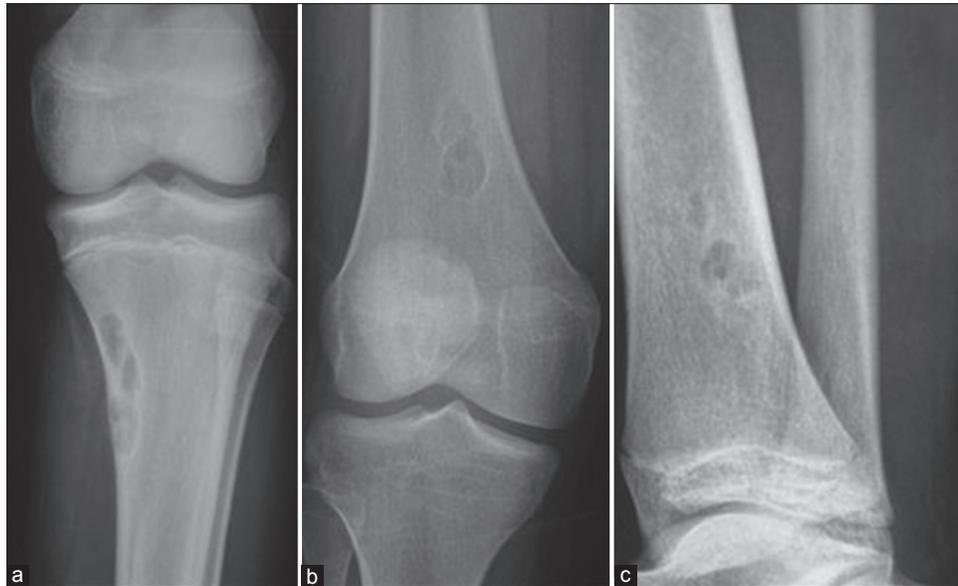


Figure 2: Pattern (I) Adolescent VDD rickets. The lesions appear as: (a). Multilocular bone cystic lesion with sclerotic margins, exocentric subcortical location (it simulates brown tumor secondary to hyperparathyroidism), (b). No other metaphyseal manifestations of VDD, (c). No cortical erosions, no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

REFERENCES

1. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al.* Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96:1911-30.
2. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, *et al.* The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53-8.
3. Prentice A. Vitamin D deficiency: A global perspective. *Nutr Rev* 2008;66 Suppl 2:S153-64.
4. Prentice A. Nutritional rickets around the world. *J Steroid Biochem Mol Biol* 2013;136:201-6.
5. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, *et al.* IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* 2009;20:1807-20.
6. Marwaha RK, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC, *et al.* Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr* 2005;82:477-82.
7. Bassil D, Rahme M, Hoteit M, El-Hajj Fuleihan G. Hypovitaminosis D in the Middle East and North Africa Prevalence, risk factors and impact on outcomes. *Dermatoendocrinol* 2013;5:274-98.
8. Hintzpete B, Scheidt-Nave C, Müller MJ, Schenk L, Mensink GB. Higher prevalence of vitamin D deficiency is associated with immigrant background among children and adolescents in Germany. *J Nutr* 2008;138:1482-90.
9. Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States: A review of the current evidence. *Arch Pediatr Adolesc Med* 2008;162:513-9.
10. Van der Meer IM, Middelkoop BJ, Boeke AJ, Lips P. Prevalence of vitamin D deficiency among Turkish, Moroccan, Indian and sub-Saharan African populations in Europe and their countries of origin: An overview. *Osteoporos Int* 2011;22:1009-21.
11. Soliman A, Kalra S. Adaptation to vitamin D deficiency: Age specific clinical presentations. *Indian J Endocrinol Metab* 2013;17:775-9.
12. Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. *Altern Med Rev* 2008;13:6-20.
13. Soliman AT, Al Khalaf F, Alhemaidi N, Al Ali M, Al Zyoud M, Yakoot K. Linear growth in relation to the circulating concentrations of insulin-like growth factor I, parathyroid hormone and 25-hydroxy vitamin D in children with nutritional rickets before and after treatment: Endocrine adaptation to vitamin D deficiency. *Metabolism* 2008;57:95-102.
14. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006;116:2062-72.
15. Holick MF, Garabedian M. Vitamin D: Photobiology, metabolism, mechanism of action, and clinical applications. In: Favus MJ, editor. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. Vol. 87. 6th ed. Washington, DC: American Society for Bone and Mineral Research; 2006. p. 129- 37.
16. Bouillon R. Vitamin D: From photosynthesis, metabolism, and action to clinical applications. In: DeGroot LJ, Jameson JL, editors. *Endocrinology*. Vol. 114. Philadelphia, PA: WB Saunders; 1995. p. 2224-33.
17. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004;80 Suppl:1689-96S.
18. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* 2003;22:142-6.

19. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006;84:1253.
20. Pettifor JM. Rickets and vitamin D deficiency in children and adolescents. *Endocrinol Metab Clin North Am* 2005;34:537-53.
21. Boonen S, Bischoff-Ferrari HA, Cooper C, Lips P, Ljunggren O, Meunier PJ, *et al.* Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: A review of the evidence. *Calcif Tissue Int* 2006;78:257-70.
22. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. *Am J Med* 1992;93:69-77.
23. Bianda T, Glatz Y, Bouillon R, Froesch ER, Schmid C. Effects of shortterm insulin-like growth factor-I (IGF-I) or growth hormone (GH) treatment on bone metabolism and on production of 1,25-dihydroxycholecalciferol in GH-deficient adults. *J Clin Endocrinol Metab* 1998;83:81-7.
24. Schmid C, Ernst M, Binz K, Zapf J, Froesch ER. The endocrine/paracrine actions of IGFs on bone. In: Spencer EM, editor. Proceedings of the second international symposium of insulin-like growth factors. New York: Elsevier; 1991. p. 16-22.
25. Tanaka H, Quarto R, Williams S, Barnes J, Liang CT. *In vivo* and *in vitro* effects of insulin-like growth factor-I on femoral mRNA expression in old rats. *Bone* 1994;15:647-53.
26. Krohn K, Haffner D, Hugel U, Himmele R, Klaus G, Mehls O, *et al.* 1,25(OH) 2D3 and dihydrotestosterone interact to regulate proliferation and differentiation of epiphyseal chondrocytes. *Calcif Tissue Int* 2003;73:400-10.
27. Robson H, Siebler T, Shalet SM, Williams GR. Interactions between GH, IGF-I, glucocorticoids, and thyroid hormones during skeletal growth. *Pediatr Res* 2002;52:137-47.
28. Yonemura K, Fujimoto T, Fujigaki Y, Hishida A. Vitamin D deficiency is implicated in reduced serum albumin concentrations in patients with end-stage renal disease. *Am J Kidney Dis* 2000;36:337-44.
29. Klaus G, Weber L, Rodriguez J, Fernandez P, Klein T, Grulich-Henn J, *et al.* Interaction of IGF-I and 1 alpha, 25(OH) 2D3 on receptor expression and growth stimulation in rat growth plate chondrocytes. *Kidney Int* 1998;53:1152-61.
30. Lund B, Charles P, Egsmose C, Lund B, Melsen F, Mosekilde L, *et al.* Changes in vitamin D metabolites and bone histology in rats during recovery from rickets. *Calcif Tissue Int* 1985;37:478-83.
31. Winzenberg T, Powell S, Shaw KA, Jones G. Effects of vitamin D supplementation on bone density in healthy children: Systematic review and meta-analysis. *BMJ* 2011;342:c7254.
32. El-Hajj Fuleihan G, Nabulsi M, Tamim H, Maalouf J, Salamoun M, Khalife H, *et al.* Effect of vitamin D replacement on musculoskeletal parameters in school children: A randomized controlled trial. *J Clin Endocrinol Metab* 2006;91:405-12.
33. El-Hajj Fuleihan G, Rahme M, Bassil D. Do Desirable Vitamin D Levels Vary Globally? In: Burckhardt P, Dawson-Hughes B, Weaver C, editors. *Nutritional Influences on Bone Health – 6th International Symposium*. Springer Science publisher; 2012. Available from: <http://www.inkling.com/read/endocrinology-jameson-de-groot-6th/chapter-58/vitamin-d-from-photosynthesis>. [Last accessed date 2014 Apr 15].
34. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 2003;78:1463-70.
35. Holick MF. Vitamin D deficiency: What a pain it is. *Mayo Clin Proc* 2003;78:1457-9.
36. Priemel M, Von Demarus C, Klatt TO, Kessler S, Schlie J, Meier S, *et al.* Bone mineralization defects and vitamin D deficiency: Histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *J Bone Miner Res* 2010;25:305-12.
37. Ballane GT, Sfeir JG, Dakik HA, Brown EM, El-Hajj Fuleihan G. Use of recombinant human parathyroid hormone in hypocalcemic cardiomyopathy. *Eur J Endocrinol* 2012;166:1113-20.
38. Ukinc K. Severe osteomalacia presenting with multiple vertebral fractures: A case report and review of the literature. *Endocrine* 2009;36:30-6.
39. Lips P. Vitamin D physiology. *Prog Biophys Mol Biol* 2006;92:4-8.
40. Eriksen EF, Glerup H. Vitamin D deficiency and aging: Implications for general health and osteoporosis. *Biogerontology* 2002;3:73-7.
41. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266-81.
42. Soliman A, De Sanctis V, Adel A, El Awwa A, Bedair S. Clinical, biochemical and radiological manifestations of severe vitamin D deficiency in adolescents versus children: Response to therapy. *Georgia Med News* 2012;210:58-64.
43. Sahay M, Sahay R. Rickets-vitamin D deficiency and dependency. *Indian J Endocrinol Metab* 2012;16:164-76.
44. Steinbach HL, Kolb FO, Gilfillan R. A mechanism of the production of pseudofractures in osteomalacia (Milkman's syndrome). *Radiology* 1954;62:388-95.
45. Bhambri R, Naik V, Malhotra N, Taneja S, Rastogi S, Ravishanker U, *et al.* Changes in bone mineral density following treatment of osteomalacia. *J Clin Densitom* 2006;9:120-7.
46. Chakravorty NK. Triradiate deformity of the pelvis in Paget's disease of bone. *Postgrad Med J* 1980;56:213-5.
47. Eisman JA. Osteomalacia. *Baillière's Clin Endocrinol Metab* 1988;2:125-55.
48. Oestreich AE. The acrophysis: A unifying concept for understanding enchondral bone growth and its disorders. II. Abnormal growth. *Skeletal Radiol* 2004;33:119-28.
49. Çakur B, Sümbüllü MA, Dağistan S, Durna D. The importance of cone beam CT in the radiological detection of osteomalacia. *Dentomaxillofac Radiol* 2012;41:84-8.
50. Jackson WP, Dowdle E, Linder GC. Vitamin D-resistant osteomalacia. *Br Med J* 1958;31:1269-74.
51. LeMay M, Blunt JW Jr. A factor determining the location of pseudofractures in osteomalacia. *J Clin Invest* 1949;28:521-5.
52. Ghazi AA, Hosseinpanah F, M Ardakani E, Ghazi S, Hedayati M, Azizi F. Effects of different doses of oral cholecalciferol on serum 25(OH) D, PTH, calcium and bone markers during fall and winter in schoolchildren. *Eur J Clin Nutr* 2010;64:1415-22.
53. Shakinba M, Tefagh S, Nafei Z. The optimal dose of vitamin D in growing girls during academic years: A randomized trial. *Turk J Med Sci* 2011;41:33-7.
54. Soliman AT, Adel A, Wagdy M, Alali M, Aziz Bedair EM. Manifestations of severe vitamin D deficiency in adolescents: Effects of intramuscular injection of a megadose of cholecalciferol. *J Trop Pediatr* 2011;57:303-6.
55. Goswami R, Gupta N, Ray D, Singh N, Tomar N. Pattern of 25-hydroxy vitamin D response at short (2 month) and long (1 year) interval after 8 weeks of oral supplementation with cholecalciferol in Asian Indians with chronic hypovitaminosis D. *Br J Nutr* 2008;100:526-9.
56. Vieth R. Why the optimal requirement for Vitamin D3 is probably much higher than what is officially recommended for adults. *J Steroid Biochem Mol Biol* 2004;89-90:575-9.
57. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001;73:288-94.
58. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations and safety. *Am J Clin Nutr* 1999;69:842-56.
59. Weaver CM, Fleet JC. Vitamin D requirements: Current and future.

Soliman, *et al.*: VDD in adolescents

- Am J Clin Nutr 2004;80:1735-59S.
60. Working Group of the Australian and New Zealand Bone and Mineral Society; Endocrine Society of Australia; Osteoporosis Australia. Vitamin D and adult bone health in Australia and New Zealand: A position statement. Med J Aust 2005;182:281-5.
 61. Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management. National Osteoporosis Society. April 2013. Available from: <http://www.nos.org.uk/document.doc?id = 1352> [Last accessed on 2014 Jan 03].
 62. Holick MF The vitamin D deficiency pandemic: A forgotten hormone important for health. Public Health Rev 2010;32:267-83.
 63. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Drug and therapeutics committee of the lawson wilkins pediatric endocrine society. Review Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. Pediatrics 2008;122:398-417.
 64. Wharton B, Bishop N. Review Rickets. Lancet 2003;362:1389-400.

Cite this article as: Soliman AT, De Sanctis V, Elalaily R, Bedair S, Kassem I. Vitamin D deficiency in adolescents. Indian J Endocr Metab 2014;18:9-16.
Source of Support: Nil, **Conflict of Interest:** None declared.

