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REVIEW

Vitamin D and adolescent health

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Abstract: Vitamin D is a hormone sequentially produced at different body sites, and which plays a significant role in human health, particularly bone health. However, other roles are emerging. When the serum concentration of vitamin D is very low, the risk of rickets, osteomalacia and osteoporosis is increased. In children and adolescents there is a high prevalence of low vitamin D status, especially in females and during the winter–the prevalence being lower than during the summer. Although there is no unanimous agreement over the minimum values necessary for good health, serum 25-hydroxyvitamin D [25(OH)D] levels below 20 ng/mL may be regarded as a vitamin D-deficient condition, and levels between 20–30 ng/mL may be the range of vitamin D insufficiency. Mild low levels have been associated with bone mass accrual alterations in children and adolescents, diminished muscle strength, negative cardiovascular outcomes, insulin resistance and obesity, and neurological disorders. Effective preventive strategies are needed to guarantee adequate vitamin D levels throughout childhood and adolescence, taking into account the geographical setting, season of the year, the level of environmental pollution, skin characteristics, eating habits and body weight, with a view to securing optimum health during these phases, and the prevention of complications in adulthood. There needs to be a renewed appreciation of the beneficial effect of moderate sunlight for providing all humans with the vitamin D needed for ensuring good health. Prolonged sun exposure is not advised, however, due to the risk of skin cancer. In addition, a balanced diet is indicated, since vitamin D-rich foods are better assimilated than supplements. When such conditions cannot be met, then the supplementation of 400 IU/day of vitamin D is advised in children and adolescents–though correcting vitamin D insufficiency or deficiency may require 1000 IU/day or more. High-dose calcifediol depots are an alternative for guaranteeing treatment adherence and in patients with liver disease.

Keywords: Vitamin D, rickets, osteomalacia, osteoporosis supplements, balanced diet

Introduction

Vitamin D deficiency has been associated with rickets in children as well as osteomalacia in adults, and contributes to the risk of osteoporosis. Mild insufficient vitamin D status prior to the development of rickets may be associated to hypocalcemic seizures, slow growth, lethargy, irritability and respiratory infections.[1–5] All these conditions would be preventable with an adequate nutritional intake of vitamin D and slight sun exposure.[6–10] Despite this knowledge, inadequate vitamin D levels or clear deficiency is prevalent the world over, particularly among consumers of fast food, people with darkly pigmented skin, obese individuals, subjects with low sunlight exposure, sunscreen users, and those living far from the equator.

Although vitamin D has been considered as simply a bone builder–along with other biological factors–the emerging research suggests that vitamin D may be far

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more versatile, offering an array of health benefits. Vitamin D may support a healthy immune system, cardiological health, normal blood pressure, cognitive performance, lessened total mortality, and healthy aging.[10–18] Ongoing research continues to explore the potential connection between vitamin D and certain diseases, including some cancers. Many of these actions have to do with vitamin D as an endocrine, autocrine and paracrine biochemical signal which acts on almost any given tissue and cell. Children and adolescents are particularly vulnerable to vitamin D deficit, due to bone growth and bone mass acquisition that characterize these phases. In addition, new data show negative consequences of deficient or insufficient serum vitamin D levels in relation to other morbid conditions far beyond bone and mineral metabolism.

Vitamin D acquisition

There are two natural forms of vitamin D: ergocalciferol (vitamin D_2) synthesized by plants, and cholecalciferol (vitamin D_3) synthesized by the mammalian skin. Humans obtain most of their vitamin D from the action of sunlight on the skin. Thus, ultraviolet (UV) B radiation and the heat effect of the skin convert 7-dehydrocholesterol into cholecalciferol. During winter, those people living at latitudes $>35°$ are exposed to little UVB since at the sun's zenith the atmosphere absorbs most UVB radiation before it reaches the surface of the earth. The intensity of UVB rays is also reduced by clouds, pollution and the fact that it does not travel through glass; as a result, sitting next to a window will not provide enough UVB to stimulate the production of vitamin D.[19] These different factors determine a high prevalence of vitamin D insufficiency among adolescents, including populations in regions close to the equator, such as Sao Paulo (Brazil), at latitude 23° South.[20] However, season seems to be more important than latitude although both account for less than one-fifth of the observed variation in serum 25-hydroxyvitamin D [25(OH)D].[21,22]

Vitamin D is a significant natural ingredient in fatty fish (salmon, tuna, mackerel, sardines) and certain fish oils, liver and fat from aquatic mammals, eggs, and mushrooms. Meat also contains small amounts of vitamin D.[23] In some countries (eg, the United States, Canada, Finland), some foods are fortified with vitamin D, including milk, orange juices, breakfast cereals and margarines.[24] Vitamin D_3 is absorbed much more efficiently than vitamin D_2 by the human intestine.[25]

Vitamin D acquired from both photosynthesis and digestive intake is transported to the liver and hydroxylated to 25(OH)D or calcifediol. Additional hydroxylation of 25(OH)D occurs in the kidney, and yields a wide variety of vitamin D metabolites, including 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] or 1,25-dihydroxycholecalciferol (Figure 1).[10,26] The 25(OH)D serum concentration is used to assess endogenous vitamin D status, instead of 1,25(OH)$_2$D measurement, which may be normal or elevated in the presence of vitamin D deficit.[27,28] Serum 25(OH)D is expressed as ng/mL, 1 ng/mL being equivalent to 2.5 nmol/L. 1,25(OH)$_2$D is the most potent vitamin D metabolite, and exerts its effects through the vitamin D receptor leading to gene expression, or through a nongenomic plasma membrane mechanism mediated by second messengers such as cyclic adenosine nanophospate (AMP).[10,13,16,17,26]

Prevalence of low serum vitamin D levels

The definition of the normal serum 25(OH)D range for adults is a controversial issue, with additional difficulties for children and adolescents. Thus, there are various definitions of vitamin D deficiency, insufficiency and sufficiency in the literature,[2,9,10,17,29] and as a result differences between studies due to the cut-off values employed. There is a high frequency of insufficient serum vitamin D in the general population, especially in the elderly and in people with osteoporosis.[9,10,22,30] Serum 25(OH)D > 32 ng/mL levels would plateau parathyroid hormone (PTH) secretion.[9,10,31] Vitamin D deficiency leads to secondary hyperparathyroidism, which has a negative effect upon bone metabolism. PTH is secreted by the parathyroid glands as an 84 amino acid polypeptide that increases the concentration of calcium (Ca^{2+}) in the blood; in contrast, calcitonin, produced by the thyroid parafollicular cells, decreases blood calcium concentration.[32–34] PTH increases the concentration of calcium in the blood by acting upon body PTH receptors.

Healthy children, adolescents and young adults also show a high prevalence of vitamin D insufficiency and deficiency, especially during the winter.[35–40] Low vitamin D status affects PTH concentrations in female adolescents; thus, decreasing 25(OH)D has been inversely correlated to PTH,[41,42] and serum 25(OH)D levels above 20 ng/mL are needed to keep PTH low.[29,43] In adolescents, serum 25(OH) below 20 ng/mL may be considered the cutoff point for vitamin D deficiency, and between 20–30 ng/mL may be considered the range for vitamin D insufficiency.[44,45] However, these values are not unanimously accepted by all researchers. Furthermore, optimal vitamin D function in a determined organ or tissue may need a different vitamin D setpoint. The prevalence of low vitamin D status affects adolescents more than children.[46,47] although a recent meta-regression analysis reports that 25(OH)D levels are higher in subjects aged >15 years than in younger subjects.[22] Adolescent males seem to have both

Digestive intake   *Skin photosynthesis*
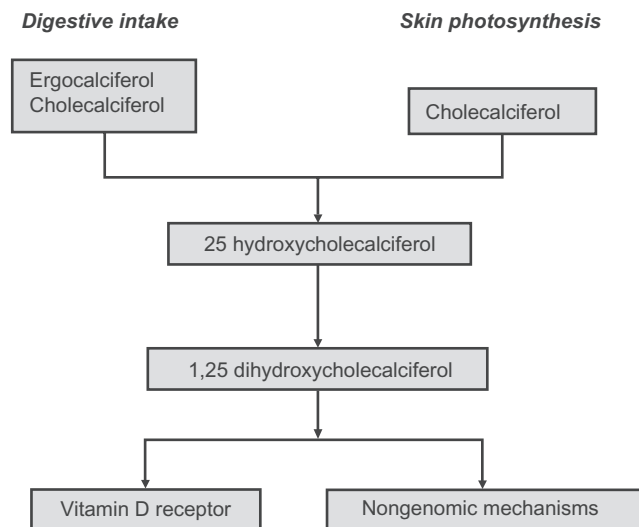
Figure 1 Vitamin D acquisition, metabolism and mechanisms of action in humans.

higher vitamin D intake and higher 25(OH)D levels than female adolescents.[46,48]

There have been several reports detailing the prevalence and risk factors for vitamin D deficiency across European countries.[39,43,49–52] In the OPTIFORD study, 25(OH)D levels were measured between February and March in adolescent girls from four European countries between the latitudes of 51° and 60° North. The prevalence of vitamin D deficiency ($<$10 ng/mL) ranged from 26% to 51%, while over 90% of the adolescents had suboptimal 25(OH)D levels ($<$19 ng/mL).[52] In the United States over the last 20 years the prevalence of low vitamin D levels has increased among adolescents included in the American National Health and Nutrition Examination Survey (NHANES).[48,53] American NHANES data showed that individuals with serum 25(OH)D below 11 ng/mL increased from 2.6% in 1988–1994 to 9.2% between 2005 and 2006. Using the less conservative cutoff point of 20 ng/mL, the prevalence of vitamin D deficiency is adjusted to 28% to 40% during the period of 2001 to 2006, and when using a cutoff point of 30 ng/mL to define vitamin D insufficiency, there were 70% to 80% of cases below the limit for the same time period.[48]

Racial/ethnic differences in serum 25(OH)D levels may have important implications for health disparities.[54] Among participants aged 12 to 19 years included in the American NHANES cohort, there was a disproportionate number of serum 25(OH)D deficient levels in the non-Hispanic black adolescent population, females and overweight adolescents being at increased risk.[48] Obese adolescents have serum 25(OH)D deficiency without elevated PTH concentrations, the fat distribution being dependent on metabolic factors.[55]

The main reasons for such almost epidemic deficient or insufficient vitamin D levels seem to be both a poor dietary intake of vitamin D and low sun exposure. Some variability in 25(OH)D levels across studies are due to differences in study design, variability in assays, geographic latitude of the individuals, outdoor leisure activities, gastronomic habits, ethnicity, winter season and body weight. People with lighter pigmentation generate between 10,000 and 20,000 IU of vitamin D_3 within 24 hours after 10 to 15 minutes of full body exposure to UV-B light. Subjects with darker skin require prolonged exposure to synthesize similar amounts of the vitamin.[56,57] Climatic and environmental factors also affect vitamin D synthesis, including the degree of latitude, season, the amount of cloud cover and the extent of air pollution, as well as the amount of skin exposed and the degree of UV protection–including clothing and sunscreens.[58,59] In addition changes in social and modern-day lifestyle have occurred in the last decades, including the time dedicated to indoor activities and negative messages concerning exposure to sunlight.[48]

Low vitamin D levels and adolescent health disorders
Bone mass accrual

During childhood and adolescence both bone mass and density increase and reach the maximal bone mass content (BMC) by the end of the third decade of life. There are ethnic differences in bone mass accrual in adolescents due to genetic as well as the stages of puberty and lifestyle factors–including physical activity, body size, weight, lean mass and diet.[61–65] A longitudinal study has annually assessed bone mass for up to four years at different sites in Asian, black, Hispanic and Caucasian individuals (aged between 9 to 25 years), using dual-energy X-ray absorptiometry. Among females, blacks had greater mean levels of area bone mineral density (BMD) and volumetric BMD at all assessed skeletal sites. Femoral neck volumetric BMD was lower among Asian and Caucasian females than in Hispanics.[66] There are limited data available on the relationship between 25(OH)D levels and bone turnover markers in adolescents.[64]

During female puberty, girls acquire 40% of peak bone mass (PBM) and accumulate 99% of BMC around 26 years of age.[67,68] However, bone mass acquisition is not homogeneous. Hence, neck femoral PBM may be reached by age 16, while spinal BMC may still increase up to age 30.[69–71] Bone turnover during adolescence shows gender differences that persist up to Tanner stage V.[72] In addition, BMD is higher in boys than in girls, the differences being higher for Tanner stages IV

and V.[72,73] The gender differences are related to sex steroid hormone peculiarities.[75–76]

Adolescent vitamin D serum level is an independent factor for bone mass gain. Sustained very low serum 25(OH)D levels are associated with rickets, although insufficient levels (<50 nmol/L) alter calcium absorption and bone mineralization.[77,78] Serum calcium and vitamin D are associated with total body and hip BMD, although associations are reduced when adjusted for age, ethnicity and swimming.[77] Using a serum 25(OH)D concentration cut-off value of 40 nmol/L in female adolescents, Outila and colleagues[43] reported a significantly higher radial BMD. Cheng and colleagues[79] showed a progressive increase in cortical BMD at both the distal radius and the tibial shaft using peripheral quantitative computed tomography, although there were no differences based on 25(OH)D levels in the total femur, the lumbar spine, or whole body as evaluated by dual-energy X-ray absorptiometry. In a prospective study, a relationship was found between 25(OH)D levels and BMD at the femoral neck and spine when time prior to the onset of menarche was considered.[80] These results are not comparable, due to the different bone assessment methods used and the variable duration of ovarian function, which has a significant effect on bone mass accrual.[81]

In postpubertal girls aged between 16 and 22 years, 59% of the subjects were 25(OH)D insufficient (≤29 ng/mL), and strong negative relationships were present between serum 25(OH)D and visceral and subcutaneous fat. In addition, there was no relationship between 25(OH)D levels and measures of BMD at any site.[40] There are complex metabolic links between fat mass and vitamin D, due to possible effects of fat hormones (leptin, resistin and adiponectin) on bone metabolism, and because vitamin D is taken up by adipose tissue.

Vitamin D and the muscle system

Vitamin D insufficiency affects muscle strength in adults.[9] Muscle strength declines with age in ambulatory elderly people and shows a positive correlation to $1,25(OH)_2D$ vitamin D in both sexes, and to 25(OH)D in male subjects. Children with serum 25(OH)D levels < 25 ng/mL show either rickets or symptoms of hypocalcemia without radiological evidence of rickets caused by vitamin D deficiency. Therefore, vitamin D deficiency appears to contribute to the age-related loss of muscle strength.[82]

In postmenarche girls the effects of low vitamin D on muscle function is also evident after weight adjustment.[83] It seems that vitamin D affects muscle function in several

ways before bone mass alterations become detectable. Girls with adequate vitamin D status had higher handgrip muscle strength compared with those with poor vitamin D status.[84] In a recent publication, Ward and colleagues[85] assessed serum 25(OH)D in girls aged 12 to 14 years, and measured muscle power with a novel outcome which is sensitive for muscles most often affected by vitamin D deficiency. In this study, vitamin D levels were significantly associated with muscle power and force in adolescent girls. Thus, vitamin D myopathy is associated with fatigue induction and low physical activity, thus reducing motivation for exercise, which in turn may alter psychophysical development and health during these years of life, contributing to low mechanical bone stimulus for bone mass gain and elevated body weight.

Low vitamin D and cardiovascular risk

In adults, different degrees of hypovitaminosis D have been associated to a variety of cardiovascular-related outcomes.[11,86,87] Recent data from the long-term NHANES findings, which included 3577 adolescents aged 12 to 19 years, show low serum vitamin D to be associated with an increased risk of high blood pressure, high blood sugar and metabolic syndrome. The average serum level of 25(OH)D was 28.0 ng/mL in Caucasians, 15.5 ng/mL in blacks, and 21.5 ng/mL in Mexican Americans. After adjusting for age, sex, race, body mass index, socioeconomic status and physical activity, adolescents with 25(OH)D levels in the lowest quartile (<15 ng/mL) were 2.36 times more likely to have high blood pressure, 2.54 times more likely to have high blood sugar, and 3.99 times more likely to have metabolic syndrome than those with vitamin D levels in the highest quartile (>26 ng/mL).[53] To confirm the biological plausibility of this study, prospective clinical trials should be designed to determine the preventive effects of adequate food choices, vitamin D supplementation, or enough sun exposure, on cardiovascular risk.

Vitamin D, obesity and diabetes

Dietary vitamin D is associated with fat percentage and visceral fat in healthy adolescents. Hypovitaminosis D and vitamin D deficiency are very frequent among obese children and adolescents, and are associated with higher PTH concentrations as compared with nonobese subjects.[88,89] In addition, 25(OH)D levels are positively correlated with insulin sensitivity, but negatively correlated to hemoglobin A(1c), which suggests that obese children and adolescents with low vitamin D levels are at increased risk of developing glucose metabolic alterations. It has been calculated that

a 25(OH)D concentration of 15 ng/mL or less may be the threshold at which vitamin D deficiency confers negative effects on insulin sensitivity.[90]

Negative correlations have been reported between 25(OH)D and visceral and subcutaneous fat and dual-energy X-ray absorptiometry values for body fat.[40] Reduction of elevated body weight is associated with a decrease in PTH concentrations and an increase in 25(OH)D levels.[88] Studies are currently underway to determine the influence of vitamin D on insulin secretion and sensitivity in obese adolescent girls.[91]

Type 1 diabetes mellitus is the second most common chronic disease in childhood. It is more frequent in regions that are distant from the equator as compared to those more closer to the equator.[92] Experimental evidence supports that autoimmune destruction of mouse β-cells may be prevented by $1,25(OH)_2D$ treatment. In addition, mice raised with a vitamin D deficient status develop diabetes at a much earlier age than animals without vitamin D deficit.[93–95] Significantly deficient vitamin D levels have been reported in children with type 1 diabetes.[96] Case-control studies showed that infants receiving vitamin D supplements may reduce the risk of type 1 diabetes.[97]

Vitamin D and neurological function

Neurological function and brain development seem to be influenced by vitamin D. In particular, this vitamin could play an immunomodulatory role in the central nervous system. Tetany caused by hypocalcemia may be associated with vitamin D deficiency in children and adults. This status may lead to symptoms such as loss of feeling in the lip or tongue regions and in the fingers, with facial spasms, and sometimes seizures. However, there are no specific clinical studies in children and adolescents concerning specific neurological impairment and vitamin D levels.

It has been postulated that the increase in the prevalence of autism over the last decades could be due to the recommendations to avoid sunlight exposure and to low vitamin D levels.[98] Although children with autism have several markers that may be controlled with high vitamin D doses, autism is a heterogeneous condition. In addition, children with autism are selective with food intake and have behavioral difficulties, the low serum vitamin levels being the consequence rather than the cause of the disorder.[99] The etiology of autism is complex, and in most cases the underlying pathological mechanisms are unknown.

Genetic and environment factors–including vitamin D status–have been associated to multiple sclerosis. In animal studies, vitamin D both prevents and improves experimental autoimmune encephalomyelitis. Epidemiological and clinical studies have shown the influence of latitude, sun exposure and serum vitamin D levels.[100] Accordingly, high circulating levels of vitamin D are associated with a lower risk of multiple sclerosis in the general population.[101,102] This disease prevalence increases up to one case in 300 individuals in people with a single copy of the DRB1 gene variation, and to one case in 100 among those with two copies of the variant. It seems that proteins activated by vitamin D bind to a particular DNA sequence lying next to the DRB 1501 variant.[103]

Gaucher's disease type 1–a lysosomal storage disorder–is frequently associated to vitamin D deficiency,[104] although there are no studies concerning vitamin D supplements and clinical course.

Reduced 25(OH)D serum levels in women have also been associated with cognitive impairment and low mood.[105–107] However, there is no specific information in this respect in adolescents.

Final remarks

Low vitamin D may have negative consequences, or interfere with, bone mass gain, muscle function, the cardiovascular system, glucose metabolism and insulin sensitivity in children and adolescents.

Exposure to sunlight is the natural way for acquiring adequate vitamin D levels, while food intake provides some 10% of the daily needs. There is a need to encourage short (15 minute) sun exposure, outdoor sport and leisure activities, and a vitamin D-rich diet including foods with natural vitamin D. The risk of harmful UVB effects is small as long as time exposure is not excessive. However, there is growing concern over the irradiation doses accumulated in the skin as a causal factor in skin cancer. The American Academy of Dermatology released a statement confirming its recommendation that people obtain their vitamin D from food and dietary supplements and not from unprotected sun exposure.[108] Adherence to these recommendations does not guarantee that vitamin insufficiency or deficiency can be corrected without sun exposure. There needs to be a renewed appreciation of the beneficial effect of moderate sunlight in providing all humans with the vitamin D needed for good health.

Fortified products are alternatives, but are not substitutes for a healthy lifestyle and nutrition in children and adolescents. Few foods contain vitamin D naturally, and not in amounts sufficient to meet the daily vitamin D requirements, although vitamin D supplementation may reverse rickets and all conditions associated with vitamin D deficiency.[1] In otherwise

healthy children and adolescents, the recommended dietary allowance (RDA) is 400 IU of vitamin D per day,[109] although in vitamin D insufficient and deficient individuals this RDA is not enough.[10,65] The dose is especially low for dark-skinned, obese and covered or sunscreen-using adolescents. Many children and adolescents would need at least 1000 to 2000 IU/day.[110] Cholecalciferol supplements are absorbed much better than ergocalciferol. When very low vitamin D levels are present, high dose vitamin D supplementation may be useful and without significant pathological risk.[111] In order to ensure adherence to treatment, and in patients with severe liver disease, a high-dose supplementation with 25(OH)D (calcifediol) may improve the clinical results in a more convenient way and ensure greater treatment compliance–though this form of vitamin D is not available in many countries. Other vitamin D derived compounds are more expensive and are reserved for cases of intolerance of the previously mentioned compounds, severe hypocalcemia, or clinical situations characterized by hyperparathyroidism.

Children and adolescents deserve the best vitamin D metabolic conditions for their optimal growth and development, and to prevent the described prevalent morbid conditions. Prospective studies are needed to define the optimum doses of vitamin D according to the environmental factors that have been discussed in this study, with a view to maintaining sufficient vitamin levels from intrauterine life, and during childhood and adolescence, in order to start adult life under in the best possible heallth.

Disclosures

The authors report no conflicts of interest in this work.

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