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REVIEW

Vitamin D deficiency/insufficiency from childhood to adulthood: Insights from a sunny country

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Abstract

Vitamin D is known to be a key regulator of bone metabolism and is associated with muscle strength. Vitamin D deficiency is widely prevalent worldwide. In adults, vitamin D deficiency has been implicated in numerous health conditions including osteoporosis, cancer, diabetes, and autoimmune diseases. Considerable changes have occurred in lifestyles and childhood activities in the past years. Studies have shown that the children population is at high risks of vitamin D deficiency. The objective of this study was to learn about the extent of vitamin D deficiency in children worldwide and especially in sunny country like Israel. In this article we reviewed the extent and severity of vitamin D deficiency worldwide and especially in Israel, through a very comprehensive review of previous reports and research studies done during the last years. We found reports on vitamin D deficiency in children, which was associated with metabolic syndromes and obesity. It was more prevalent in children who spend less time on outdoor activities, in obese children, and in cases when there was imbalance between nutritional intakes and requirements. Vitamin D deficiency is common even in children living in sunny places like Israel. Health professionals should be aware of the fact that although vitamin D deficiency is prevalent in the elderly population, it is also common in children, and can be associated with different illnesses. We encourage supplementation of vitamin D to special populations (pregnant and lactating women, infants, and high risk groups). We also encourage implementation of international food fortification programs.

Key words: Vitamin D; Deficiency; Children; Obesity; Bone metabolism; Muscle strength; Osteoporosis; Non-skeletal diseases

Core tip: Vitamin D is known to be a key regulator of bone metabolism and muscle strength. Vitamin D deficiency is widely prevalent worldwide. In this article we emphasize that vitamin D status may be also related to a number of non-skeletal diseases, including cardiovascular events, cancer, diabetes, and autoimmune diseases. Obesity has also been recently associated with vitamin D insufficiency. We demonstrate that the pediatric population is also at high risks of vitamin D deficiency. Studies that investigated the status of vitamin D deficiency in Israel, which is a known multi-cultural sunny country, revealed a high prevalence of vitamin D deficiency.

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INTRODUCTION

Vitamin D deficiency is widely prevalent worldwide. Low levels of 25-hydroxy vitamin D [25(OH)D], the primary circulating storage form of vitamin D, are present in 30%-50% of otherwise healthy middle-aged to elderly adults. Many studies have shown that the pediatric population is also at high risk of vitamin D deficiency[1,2].

DEFINITIONS

Vitamin D deficiency is currently defined as serum 25(OH)D level less than 10 ng/mL (25 nmol/L) below which osteomalacia and rickets are commonly observed. In the osteoporotic/osteopenic adult population a general consensus is that 25(OH)D levels should be maintained above 30 ng/mL (75 nmol/L)[3]. There is some controversy in the definition of vitamin D insufficiency and what target levels should be achieved in the general population. Blood levels below 30 ng/mL are considered by many as insufficient but the Institute of Medicine has set the cutoff at 20 ng/mL (50 nmol/L)[4].

VITAMIN D AND BONE HEALTH

Vitamin D plays an important role in the regulation of bone metabolism and has great impact on muscle strength[5,6].

Vitamin D has a positive effect on bone density and bone quality[7]. Several studies indicate that vitamin D increases bone mineral density (BMD)[8] and prevents fractures related to osteoporosis[9,10]. Furthermore, having enough vitamin D reduces the risk of falling in the elderly[11] by increasing muscle strength and improving muscle performance, whether these individuals are community-dwelling or institutionalized[6,12]. Thus, vitamin D lowers the risk of fracture in this population by improving both bone and muscle strength[13].

On the other hand, several studies in adolescents and young adults described a direct link between vitamin D and bone mass[14-17] while others have not[18,19].

The association between vitamin D and bone strength may also be dependent on the genetic background of the population under study. For example, a recent study in adults found a positive correlation between circulating levels of 25(OH)D and BMD in Caucasian subjects, but not in African-American or Hispanic populations[20].

VITAMIN D AND NON-SKELETAL DISEASES

In addition to the well-known effects on musculoskeletal system, vitamin D status is also related to a number of non-skeletal health problems[7,13].

While there is strong and clear evidence for a beneficial effect of vitamin D on musculoskeletal health based on randomized controlled trials (RCTs)[21] and large epidemiological studies[22], studies on other health issues in humans are more controversial. A meta-analysis of 18 RCTs that included over 57000 individuals concluded that supplements of vitamin D were associated with decreased mortality[23]. The mechanisms underlying this apparent beneficial effect on overall mortality may be multifactorial, affecting the cardiovascular system, the immune system and tumor progression, among others[24-28].

Cardiovascular risks

Low levels of 25(OH)D appear to be an independent risk factor for cardiovascular events[24]. However, the association between vitamin D deficiency and myocardial diseases is still inconclusive[29].

For instance, in large studies, cardiovascular risk factors were not significantly improved by vitamin D[27,28,30].

Although an adequate vitamin D status seemed to be associated with the prevention of arterial hypertension[31,32], a recent meta-analysis didn't show any beneficial effect on either systolic or diastolic blood pressure.

From the mechanistic standpoint, it is noteworthy that both the vitamin D receptor (VDR) and the 1-alpha hydroxylase enzyme responsible for the activation of vitamin D are expressed in cardiomyocytes as well as in other cardiovascular system's cells[33], suggesting a local influence of vitamin D on heart function. This is further supported by the adverse cardiovascular effects observed in VDR- and 1alpha hydroxylase-null mice[34].

Likewise, other studies have shown that the active form of vitamin D 1α,25 dihydroxy-vitamin D [1α,25(OH)2D] reduces inflammation[35], controls some metalloproteinases involved in vascular calcification[36], and improves endothelial function[37], therefore directly affecting the cardiovascular system. Indirectly, 1α,25 (OH)2D may also improve cardiovascular outcomes by modulating the secretion of insulin and improving insulin sensitivity[38,39], and decreasing parathyroid hormone (PTH) secretion[40]. A recent meta-analysis seems to support the adverse role of PTH in cardiovascular outcomes[41].

Autoimmune diseases

The role of vitamin D in autoimmune diseases has been investigated in animal models as well as in humans. Studies using animal models of several autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and inflammatory bowel diseases, have identified vitamin D as a potential key modulator of significant processes in the autoimmune reaction[42-44]. However, the benefits of taking vitamin D supplements need additional supporting data.

Cancer

The role of vitamin D in cancer has been the subject of many studies in animal and human models. *In-vitro* data on a variety of cancer cells have clearly demonstrated that calcitriol [1,25(OH)2D_3] directly stimulates apoptosis and inhibits proliferation of tumor cells[45]. Calcitriol also inhibits angiogenesis, invasion and tumor progression[46]. Animal models of cancer, particularly of breast cancer, have shown that vitamin D has a strong beneficial effect on tumor-initiation, tumor-progression and metastasis[47].

Numerous studies suggest that circulating 25(OH)D levels are inversely associated with the risk of developing several types of cancer[48]. Furthermore, some studies have reported an association between low 25(OH)D levels and cancer progression and recurrence[49,50].

However, large human RCTs are lacking and the bulk of evidence comes from epidemiological data in breast, colon and prostate cancer[51]. Small human trials have shown a beneficial effect or no effect at all, and recent meta-analyses have been inconclusive[25,26]. An international effort is now underway to determine the effect of vitamin D on both cancer and cardiovascular outcomes[52].

Obesity and fat distribution

Obesity has become an epidemic[53]. For example, in the United States the combined percentage of overweight and obese children and adolescents is 32%, and for young adults is 66%[54]. Vitamin D deficiency and vitamin D insufficiency are prevalent in these populations, especially in populations of low socioeconomic background[54,55]. Several studies have shown an inverse correlation between obesity in adults and 25(OH)D levels[56-62], and it has been argued that 1α,25(OH)2D may be involved in the inhibition of adipogenesis[63].

Interestingly, it has been noted that the 25(OH)D levels were substantially lower in obese adults who consumed supplemental vitamin D_2 and were exposed to UV light as compared to non-obese matched controls[60].

Several studies in adults demonstrate that obesity is associated with vitamin D insufficiency[56-60,62,64], and that low intake of vitamin D is an independent predictor of obesity[61]. Another study in postmenopausal women who consumed vitamin D reported a small but significant effect on weight gain prevention compared to placebo controls[65].

The underlying mechanisms are still elusive but 1α,25(OH)2D has been shown to lower leptin levels and may thus influence the body mass maintenance[66].

In addition, vitamin D could also be trapped in fat tissues, thus body fat itself may be a factor which lowers the circulating 25(OH)D levels[50,60]. Thus, obesity maybe a direct outcome of vitamin D insufficiency and/or may be a cause of vitamin D insufficiency[7].

Kremer *et al*[7] found a strong inverse correlation between body mass, weight and circulating vitamin D. A stronger association was found with visceral fat suggesting that fat distribution was affected by vitamin D. They also demonstrated that 25(OH)D was inversely correlated not only with total body fat, but also with specific features of visceral fat and sub cutaneous (SC) fat. This study showed a stronger association with visceral fat, suggesting that vitamin D targets more specifically a fat compartment related to cardiovascular complications.

Vitamin D and height

In their research population, Kremer *et al*[7] described a positive correlation between circulating 25(OH)D and height. Although vitamin D is considered as an important factor in skeletal development and rickets may be associated with vitamin D deficiency[17], none of the subjects in the study had any evidence of rickets (clinical or radiological).

Decreased height was also significant in adolescent girls, who had vitamin D deficiency without any clinical manifestation of rickets[18]. The mechanism(s) underlying these unique observations remain(s) to be elucidated, and whether vitamin D has a direct or indirect effect on bone size and growth remains to be determined.

Overall, vitamin D insufficiency/deficiency has been associated with numerous health problems, such as osteoporosis, diabetes, rheumatoid arthritis, and even cancer[67-69]. It has also been associated with increased body fat, which by itself carries a greater risk of diabetes and cancer[70]. Consequently, vitamin D insufficiency/deficiency may play a significant role in the development of various and important clinical conditions through multiple mechanisms.

DEFICIENCY OF VITAMIN D IN CHILDREN

Breastfed infants are at higher risk of vitamin D deficiency because the content of vitamin D in the mother's milk is totally dependent of her vitamin D intake. The regular content of vitamin D in breast milk is normally insufficient to provide the baby with his daily requirements[4,71].

The high prevalence of vitamin D insufficiency in the pediatric age group is surprising and likely to be multifactorial.

The rapid growth in childhood requires sufficient nutrients, including vitamin D. Consequently, the children population has indeed a high risk of developing vitamin D deficiency, which was demonstrated by many studies[1,2].

Considerable changes have occurred in lifestyles and childhood activities in the past 20 years. Children are now more sedentary and no longer routinely play outside for long periods. Voortman *et al*[72] reported that children who spend less time on outdoor activities actually had lower serum levels of vitamin D.

In addition, children with obesity are more likely to have low vitamin D levels[73]. This is partly attributable to lifestyle factors but also it is thought that vitamin D and its metabolic product, 25(OH)D, are sequestered in body fat, thereby making them unavailable when required[60].

It has also been reported that in children, vitamin D deficiency is associated with metabolic syndromes[73,74].

Weng *et al*[55] reported that insufficiency of vitamin D was frequent in children living in the northeastern area of the United States. It was associated with the season of the year, ethnicity (black race), age, and level of vitamin D intake.

A study from Southeastern China[75] evaluated the vitamin D status of 5571 young children aged 1-3 years living in Wuxi. Although there was a low prevalence of vitamin D deficiency in this population, the risk of vitamin D deficiency was increased as the children grew older, implying development of an imbalance between the nutritional intakes and requirements.

The observation that children and adolescents demonstrate an increased prevalence of both vitamin D insufficiency and obesity, implies that vitamin D may be an independent predictor of weight gain[60,73]. As previously mentioned, several studies in the adult population have also demonstrated that insufficient levels of vitamin D are associated with obesity[56-60,62,64], and that low intake of vitamin D may serve as an independent predictor of obesity[61].

VITAMIN D DEFICIENCY IN ISRAEL

The status of vitamin D deficiency in Israel was investigated in about ten studies over the last decade, and demonstrated a considerably high prevalence of vitamin D deficiency and insufficiency. Several studies were carried out in the elderly population[76], Ethiopians[77,78] and Bedouins[79].

One study compared vitamin D levels in orthodox and non-religious women and showed increased prevalence of low 25(OH)D levels in both populations, even in the summer, but orthodox women had significantly lower 25(OH)D levels[80]. Vitamin D deficiency/insufficiency was also observed in soldiers[81], in hospitalized patients[82] and teenagers[83]. In a study of Orthodox Yeshiva male students, severe vitamin-D deficiency was prevalent in ultra-Orthodox males[84].

Additional research[85] included 204 children in 2 clinics in Jerusalem. The vitamin D levels declined gradually with age, with the lowest levels observed mostly in the 10-19 years old age category.

In an ecological study made on a representative sample of the population of Israel in 2010[86], it was found that 78% had vitamin D insufficiency (< 30 ng/mL). Vitamin D levels were higher in infants as compared to older age groups. As may be explained by the level of skin darkness, Israelis of Ashkenazi origin had higher vitamin D mean levels than those of Sephardic origin who, in turn, had higher vitamin D levels than Arab subjects (Table 1).

A large study[87] among 198834 members (mostly adults) assessed vitamin D status among demographic subgroups in Israel. Vitamin D deficiency (vitamin D levels below 25 nmol/L), was detected in 14.4% of the subjects tested.

RECOMMENDATIONS

Historically, humans were designed to synthesize vitamin D naturally obtained through the action of the sun. However, this source of endogenous production of vitamin D proved to be inadequate due to the migration of populations to the Northern hemisphere and to the changes in cultural habits. Although vitamin D is present to various degrees in food products (oily fish, egg yolk, fortified cereals and spreads, Shitake mushrooms, *etc.*), these food products are not usually preferred by children. Thus, in children it would be difficult to implement recommendations based on nutrition alone in order to obtain the recommended daily amounts.

Furthermore, the natural vitamin D production through exposure of the skin to sunlight is prevented in several high risk populations. People with darker pigmented skin need considerably more exposure to the sun to generate the same vitamin D amounts due to the presence of melanin, which acts as a natural sunscreen. Increased prevalence of deficiency/insufficiency was identified in certain populations who wear clothing to cover the body for religious or cultural reasons[88,89].

Finally, health promotion campaigns promoting safe sun exposure to lower the risk of skin malignancies may be contributing to reduced levels of vitamin D. Sunscreen with a factor of 8 or above blocks enough UVB rays to reduce the skin's ability to synthesize vitamin D by approximately 95%[88].

In addition, fat malabsorption seen in individuals with Crohn's disease, certain liver conditions and gastric bypass surgery is associated with low vitamin D absorption by the small intestine and a higher risk of vitamin D deficiency[44]. It is therefore important to identify those populations at increased risk and offer appropriate advice and supplementation (NICE 2014)[90].

Simple and effective preventive measures could be implemented by providing vitamin D as oral preparations of vitamin D3 (cholecalciferol) derived from animal sources, or vitamin D2 (ergocalciferol) derived from vegetable sources.

Although Armas *et al*[91] found that ergocalciferol is less easily absorbed, both forms can be prescribed. In

Table 1 Main reports on vitamin D deficiency in children

Prevalence	Age group	Place	Year	Ref.
In infants 0.4% - deficient (< 25 nmol/L) 33.6% - insufficient (< 75 nmol/L) 2-5 yr stage (preschool) 1.1% - deficient 68.6% - insufficient 6-11 yr (school age) 2.0% - deficient 88.3% - insufficient Adolescents 3.3% - deficient 89.6% - insufficient	1 mo-16 yr	Hangzhou, China	2012	[1]
86% - deficient (< 37 nmol/L) 38.3% - severely deficient (< 12.5 nmol/L) 91.7% - insufficient (< 50 nmol/L)	9-12 yr	Tehran, Iran	2007-2008	[2]
66.7% - insufficient (< 75 nmol/L), 23.6% - deficient 6.2% - severely deficient (< 25 nmol/L)	6 yr (school age)	The Netherlands	2015	[72]
Obese subjects 12.7% - deficient (< 30 nmol/L) 92% - insufficient (< 75 nmol/L) Non-obese subjects 3.4% - deficient 68% - insufficient	6-16 yr	North Texas, United States	2012	[73]
34% - insufficient 62.2% - deficient	8-16 yr	Izmir, Turkey	2012	[74]
31.0% - deficient 65.0% - insufficient	7-11 yr	Zanjan, Iran	2015	[71]
55% - insufficient (< 75 nmol/L) 5% - deficient (< 25 nmol/L)	6-21 yr	Northeastern United States	2007	[55]
55% - insufficient (< 75 nmol/L) 0.8% - deficient (< 30 nmol/L)	1-3 yr	Wuxi, China	2014-2015	[75]
Age < 5 yr 52.4% - insufficiency 19% - deficiency Age > 5 and < 20 yr 79.4% - insufficiency 26.5% - deficiency	1-50 yr	Israel	2008	[86]

Worldwide prevalence of vitamin D deficiency/insufficiency in infants, children and adolescents. Vitamin D deficiency was defined as 25(OH)D levels of ≤ 25 nmol/L and vitamin D insufficiency as 25(OH)D levels of ≤ 75 nmol/L.

subjects with decreased capacity of intestinal absorption or to improve compliance, cholecalciferol can be administered by intramuscular injection, using various regimens ranging from monthly to yearly injections[92].

Recommendations from the Institute of Medicine of the National academies[4] are as follows: 400 IU in newborn and infants from 0-13 mo, 600 IU from 1 to 70 years of age and 800 IU over 70 years of age.

The recommended doses for supplementation listed in the British National Formulary for Children are 400 IU daily for neonates and 400-600 IU daily for children aged one month to 18 years[93].

However, implementation of these recommendations has been less successful than anticipated due to healthcare professionals' lack of knowledge and confusion over dosage and available products[94-96]. There are preparations that contain also 100% of the recommended daily amount of vitamin A. Therefore, if the amount of vitamin D required is greater than 400 IU - alternative products should be considered in order to avoid vitamin A toxicity.

Another possible complication can be caused in cases of prescribed products that not only provide vitamin D but are combined with calcium, especially in children over 12 years of age. In addition to the fact that calcium increases the unpalatability of the preparation, additional calcium supplements are not required for the great majority of children who obtain it in sufficient amounts from their diet. There may also be additional risks of calcium supplementation such as those reported on cardiovascular outcomes in adults[97]. The risks appear to be moderate, but the long-term effects have not been investigated. Although the risk of hypercalcemia occurring during treatment with cholecalciferol is rare, and those incidents have occurred in infants or in children/adults receiving much higher doses than are normally prescribed[98,99], the risk of hypercalciuria and kidney stones has not been thoroughly investigated even at lower doses[100]. Consequently, in the absence of strong evidence for the added benefit of calcium and its inherent risks, calcium supplementation should be avoided.

A consensus statement from a group of leading experts on vitamin D and osteomalacia[96] recommended the global adoption of the following: (1) Vitamin D supplements for all pregnant and lactating women; (2) Vitamin D supplements for all infants (as given in Israel for many years); (3) Vitamin D supplements for individuals in high-risk groups; and (4) Worldwide implementation of programs for food fortification to ensure nutritional sufficient amounts of vitamin D and calcium for the entire population.

The recommended amounts of preventive supplements of vitamin D currently advised according to the consensus statement are: (1) For all infants from birth to 12 mo of age - recommended dose of 400 IU/d (10 μg), which is adequate to prevent rickets, independently of their mode of feeding; (2) Beyond 12 mo of age, the nutritional requirement for vitamin D is at least 600 IU/d (15 μg), through diet and/or supplementation. The candidates for preventative vitamin D supplementation in this age group, in the absence of food fortification: Children with a history of symptomatic vitamin D deficiency who required treatment; and children and adults at high risk of vitamin D deficiency, with factors or conditions that reduce synthesis or intake of vitamin D; and (3) In healthy children, routine screening for 25(OH)D is not recommended, and therefore, no specific 25(OH)D threshold for vitamin D supplementation is targeted in this population.

SUMMARY

Vitamin D is known to play a significant role in bone metabolism, muscle strength, musculoskeletal health, and is also related to a number of non-skeletal diseases. Its deficiency has been related to many health conditions including osteoporosis, diabetes, rheumatoid arthritis and cancer.

Vitamin D deficiency is prevalent in the elderly population, but it can also appear in the pediatric population. This is mainly due to changes of lifestyles and childhood activities in the past decades. Children are now more sedentary and no longer routinely play outside for long periods.

We strongly support the recommendations published recently that encourage supplementation of vitamin D to special populations (pregnant and lactating women, infants, and high risk groups). We also recommend that international food fortification programs be implemented to ensure nutritional sufficiency of vitamin D and calcium for the entire population.

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