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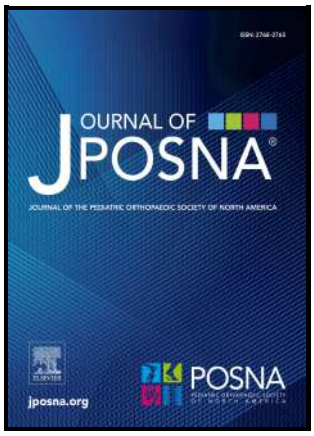

Fatima Bouftas, Clarabelle DeVries

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Vitamin D and Pediatric Bone Health – Important Information and Considerations for the Pediatric Orthopaedic Surgeon

Fatima Bouftas, BS[1]; Clarabelle DeVries, MD[2]

[1]University of Chicago Pritzker School of Medicine, Chicago, Illinois

[2]Department of Orthopaedic Surgery, University of Chicago Medicine, Chicago, Illinois

Corresponding Author:

Clarabelle DeVries, MD

Assistant Professor, Department of Orthopaedic Surgery

The University of Chicago

5841 S. Maryland Avenue

Room S-256A

Chicago, Illinois 60637

Phone: 773-702-6983

Fax: 773-702-5434

Email: cdevries@bsd.uchicago.edu

Abstract

Vitamin D is an essential fat-soluble vitamin produced in the skin during sun exposure. It plays a considerable role in musculoskeletal health and is largely responsible for the regulation of calcium and phosphate metabolism to maintain a healthy, mineralized skeleton. Optimizing bone mineral density in childhood and adolescence is essential to the foundation of skeletal health; however, the literature lacks consensus on values for normal, deficient, and insufficient serum 25-hydroxyvitamin D levels making supplementation and treatment somewhat challenging.

The pediatric orthopaedic surgeon is important to optimizing bone health, particular in the context of bony pathology/injury. Up to 60% of boys and 40% of girls sustain a fracture in childhood. On top of this baseline incidence, children with low vitamin D levels have been noted to be subject to a higher incidence of fractures from normal activities. While the prevalence of vitamin D deficiency in children in the general population has been determined to be 9%, the

prevalence of vitamin D deficiency in the pediatric fracture population can be as high as 75% and 61% of the pediatric population has been determined to have vitamin D insufficiency. The pediatric orthopaedist also often is the first to diagnose nutritional rickets as these patients can present solely for complaints of limb deformity. Knowledge of appropriate evaluation, vitamin D supplementation, and indications for pediatric endocrinology referral is vital for treatment of these patients.

In the pediatric population, there is a lack of consensus regarding risk factors that warrant screening for vitamin D deficit, determining insufficient thresholds, and identifying optimal supplementation recommendations and treatment dosages. More research is needed to clarify ideal amounts of vitamin D necessary through critical growth periods to prevent rickets and to mitigate fracture risk. Regardless, pediatric orthopaedic surgeons should promote supplementation to all children and treat diagnosed vitamin D deficiency.

Keywords: vitamin D; bone health; pediatric fractures; fracture risk

Key Concepts:

- Vitamin D plays a vital role in musculoskeletal health and optimizing vitamin D levels in childhood and adolescence is crucial to proper bone development.
- Vitamin D deficiency and insufficiency in the general population is common; 9% of the pediatric population, representing 7.6 million US children and adolescents, are vitamin D deficient and 61%, representing 50.8 million US children and adolescents, are vitamin D insufficient. The prevalence of vitamin D deficiency in the pediatric fracture population can be as high as 75%.
- Vitamin D deficiency can lead to nutritional rickets which is the most frequent cause of pediatric bone disease in the world, is entirely preventable, and is characterized by deficient mineralization and subsequent architectural disruption of the physis.
- Vitamin D supplementation is widely recommended and believed to be beneficial, but there are inconsistent guidelines regarding target levels for optimal vitamin D status.

INTRODUCTION

Vitamin D deficiency is relatively common in the pediatric population and is a relevant condition to the pediatric orthopaedic surgeon as it relates to bone health. Children with underlying vitamin

D deficiency may often present to the pediatric orthopaedic surgeon in the form of rickets and limb deformity. There is also a collection of evidence that demonstrates higher rates of vitamin D deficiency in the pediatric fracture population than controls. Fractures are common in childhood and account for 25% of injuries, with about a third of boys and girls sustaining at least one fracture before the age of 17.[1] There is evidence that about 66% of all pediatric fractures occur in children who fracture on more than one occasion, suggesting that there may be some intrinsic predisposition to fracture in this population, perhaps indicating an alteration in bone health.[2]

The purpose of this article is to review the rates of vitamin D deficiency in the pediatric population as well as rates of rickets and vitamin D deficiency in the pediatric fracture population, discuss vitamin D deficiency diagnosis and treatment, and offer guidance to the pediatric orthopaedic surgeon on vitamin D supplementation and treatment in the pediatric population.

What is Vitamin D?

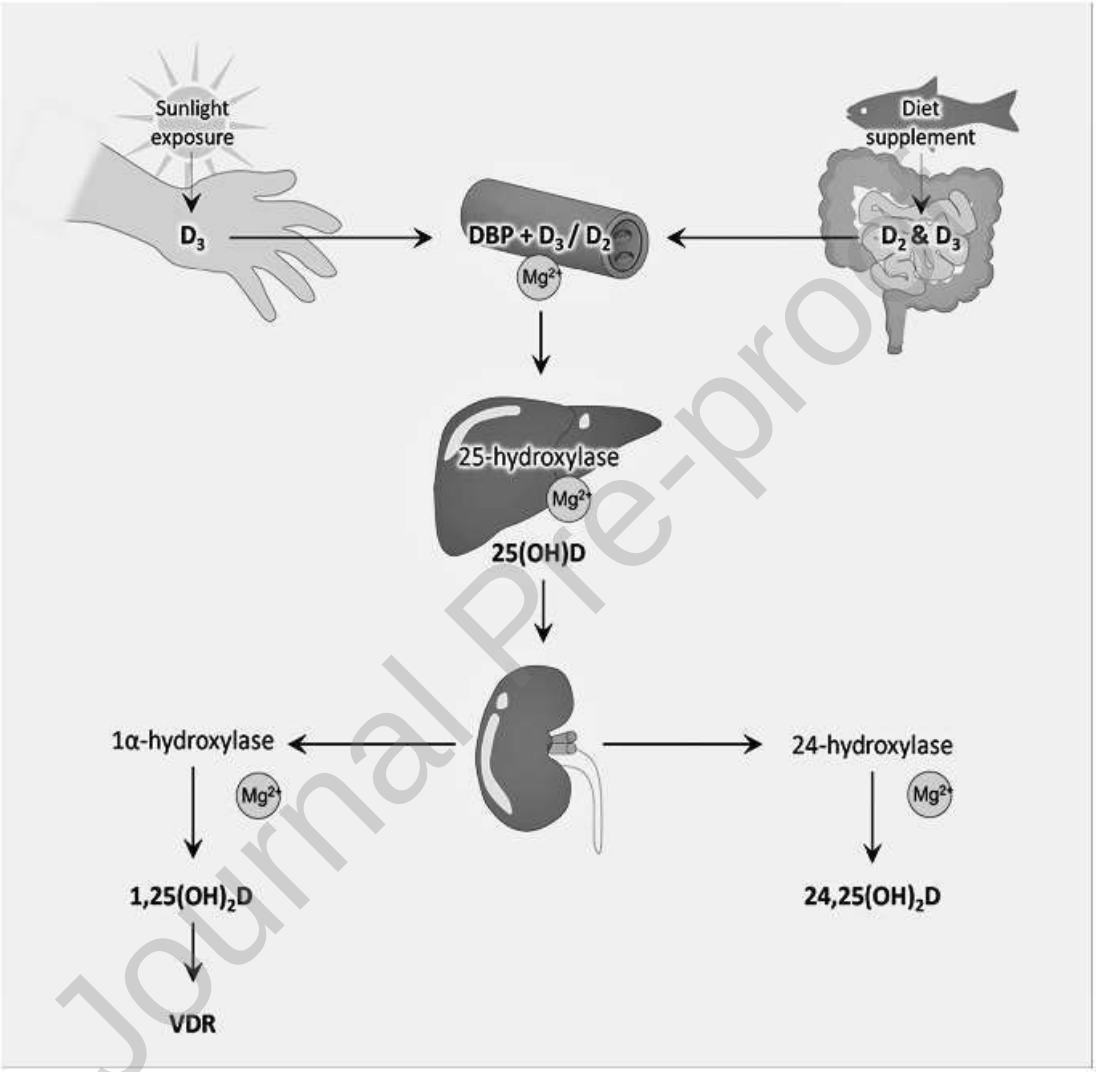
Vitamin D, known as the "sunshine vitamin," is a fat-soluble vitamin produced in the skin during sun exposure.[3] It is known to play a considerable role in musculoskeletal health and contributes to multiple functions in bone biology, cell growth, inflammation, neuromuscular, and immune functions.[4] It is largely responsible for the regulation of calcium and phosphate metabolism and maintaining a healthy mineralized skeleton.[5] Vitamin D also plays an essential role in

extraskeletal functions including skeletal muscle growth, cardiopulmonary functions, and inflammatory modulation. Finally, through an interaction with the immune system, Vitamin D can modulate injury recovery and influence the risk of infection.[6]

The foundation for skeletal health is established early in life by optimizing gains in bone mineral density throughout childhood and adolescence; peak bone mass (PBM) is achieved by early adulthood and is a key determinant of the lifetime risk of osteoporosis.[7 8 9] Optimizing vitamin D levels in adolescence provides a window of opportunity to ensure that a sufficient foundation of bone health is established.[10 11]

25-hydroxyvitamin D [also known as 25(OH)D] is the only vitamin D metabolite used to determine whether a patient is vitamin D deficient, sufficient, or intoxicated.[12] 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] is the biologically active form of vitamin D. It has a shorter half-life of 4 to 6 hours, and circulating levels of 1,25(OH)D are a thousand-fold less than 25(OH)D.[12 13] 25(OH)D is a summation of both dietary vitamin D intake and intrinsic vitamin D production and has a half-life of about 2 to 3 weeks.[12 14 15 16]

Figure 1. Simplified diagram of the different stages of vitamin D synthesis. (DBP: vitamin D binding protein, VDR: vitamin D receptor)



Note. This diagram was published in an article by Mark Eskander and Mohammed S. Razzaque in 2022.[17]

Assessing "normal" 25(OH)D levels is challenging - there are a variety of assays used to measure circulating serum 25(OH)D, but these assays are fraught with technical difficulties.[18] Furthermore, there is no absolute consensus as to what a normal range for 25(OH)D should be.[12]

[19] [20] Historically, a “normal” nutritional vitamin D status was defined any circulating level of 25(OH)D in asymptomatic subjects.[21]

Oral supplementary vitamin D, also known as calciferol, is produced in 2 forms: D_2 (ergocalciferol) and D_3 (cholecalciferol). Vitamin D_2 is largely human-made and added to foods, while vitamin D_3 is synthesized in the skin of humans and is also consumed in the diet via the intake of animal-based foods.[22] Vitamin D_2 has a shorter plasma half-life and a lower affinity for the vitamin D binding protein, the hepatic vitamin D hydroxylase, and the vitamin D receptor.[23] Most existing studies have shown vitamin D_3 to be significantly more efficacious at increasing serum levels of 25(OH)D than vitamin D_2, thus making it the preferred choice for supplementation.[24] [25] However, there are various flaws in these study designs and thus there is still a need for a large, robust, randomized-controlled trial to provide conclusive evidence about whether vitamin D_3 actually is more efficacious than vitamin D_2.[26]

What Defines Deficiency?

In patients suspected to have vitamin D deficiency, a 25-hydroxyvitamin D serum level is obtained. However, there is not a consensus regarding what levels constitute vitamin D deficiency, insufficiency, or optimal levels. Multiple published values are discordant across different academic societies with threshold for deficiency ranging from 15 to 30 nanograms/milliliter (ng/mL). (Table 1).

Table 1. Definitions of vitamin D deficiency, insufficiency, and optimal range as published by various medical societies and/or institutions. Vitamin D levels listed in ng/mL.

	American Academy of Pediatrics[27]	American Association of Clinical Endocrinologists[28]	Institute of Medicine (Health and Medicine Division of the National Academies)[22]	The Endocrine Society[29]	The Mayo Clinic[30]	American Academy of Family Physicians[31]
Severe Deficiency	≤ 5				< 10	
Deficiency	≤ 15	< 30	< 12	≤ 20		< 20
Insufficiency/ Mild-Moderate Deficiency	15-20		12-20	21-29	10-24	20-30
Optimal/Sufficiency	20-100	30-50	≥ 20	≥ 30	25-80	

It is estimated that over 1 billion people globally have vitamin D deficiency, while 50% of the population worldwide has vitamin D insufficiency.[32] Vitamin D deficiency is found more commonly in populations with higher melanin content as well as those who tend to cover up more of their skin. In the United States, vitamin D deficiency is found in 47% of African American infants and 56% of Caucasian infants, 35% of adults, and 61% of the elderly population.[33]

Common pediatric risk factors for vitamin D deficiency are listed below: [31] [34]

- Breastfed exclusively without vitamin D supplementation
- Dark skin
- Insufficient sunlight exposure
- Medication use that alters vitamin D metabolism (e.g., anticonvulsants, glucocorticoids)
- Obesity (body mass index greater than 30 kg per m^2)
- Sedentary lifestyle

Of note, approximately a third of individuals with known deficiency have no identifiable risk factors; a 1999 study of 142 healthy individuals who consumed milk and supplements found that participants ages 18-29 had the lowest levels of vitamin D even though they had no risk factors for deficiency.[35]

The economic burden of vitamin D deficiency is estimated to be between $40 to $53 billion in the United States per year; this includes the burden of disease from rickets and osteomalacia, associated deformities, fractures, muscle weakness, and pneumonia, as well as multiple sclerosis and common cancers associated epidemiologically with vitamin D deficiency such as prostate, colon, and breast cancers.[27]

Beyond bone health, children with a higher vitamin D status have a decreased pediatric risk for autoimmune, infectious, and allergic diseases.[36] Other studies have revealed the neurohormonal effects of vitamin D on brain development and behavior, linking it to mental health disorders such as depression, seasonal affective disorder, and schizophrenia.[37]

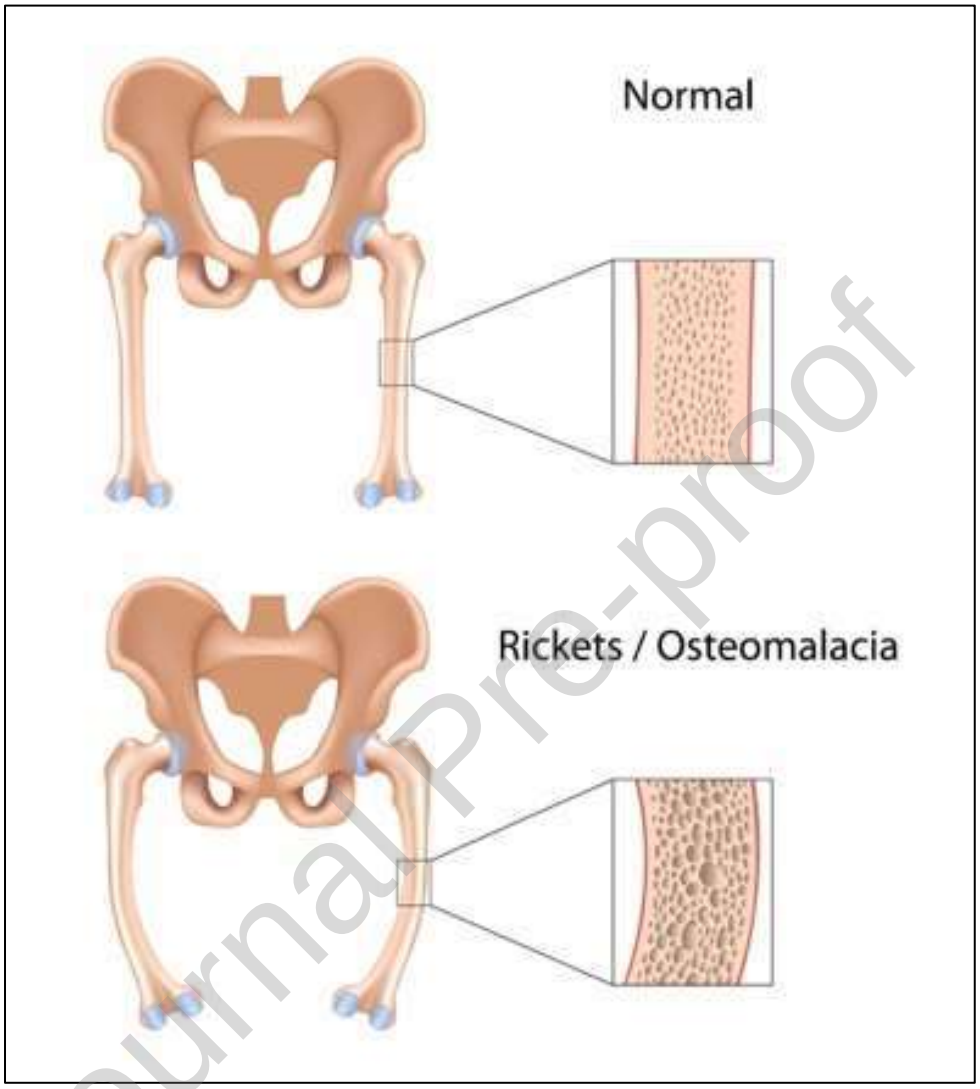
Rickets

In children, vitamin D deficiency can lead to nutritional rickets which is characterized by deficient mineralization and subsequent architectural disruption of the physis. Geometry of the physis and metaphysis become progressively altered, bony stability is compromised, and structural deformity of the bone can develop. Nutritional rickets is the most frequent cause of pediatric bone disease in the world and is, theoretically, entirely preventable.[38] [39] [40] A population-based incidence study over 40 years in Olmsted County, Minnesota has illustrated the incidence and temporal trends of nutritional rickets. It found that the incidence of nutritional rickets in children younger than 3 years was relatively stable from 1970 to 2000 (0-3.7 per 100,000), but dramatically increased after 2000 (24.1-220 per 100,000).[41] This was potentially due to a number of factors: an increase in nonwhite immigrants – with the frequency of rickets mirroring immigration trends, the temporal trend of declining vitamin D status in infants and toddlers – which could be explained by either a downward trend in maternal 25(OH)D values leading to reduced infant stores at birth, or due to trends in infant vitamin D and dietary calcium intake. Today, case rate of rickets estimates of 2.9-27 per 100,000 individuals have been reported in the United States and Europe.[40]

Rickets is frequently diagnosed in children between the ages of 6 months to 2 years and the diagnosis is usually established by medical history, physical examination, biochemical tests, and radiography.[42] The clinical presentation of rickets may vary based on underlying duration, severity, and etiology of the disease.[43] Most children present with osseous manifestations, especially at the sites of rapid bone proliferation.[44]

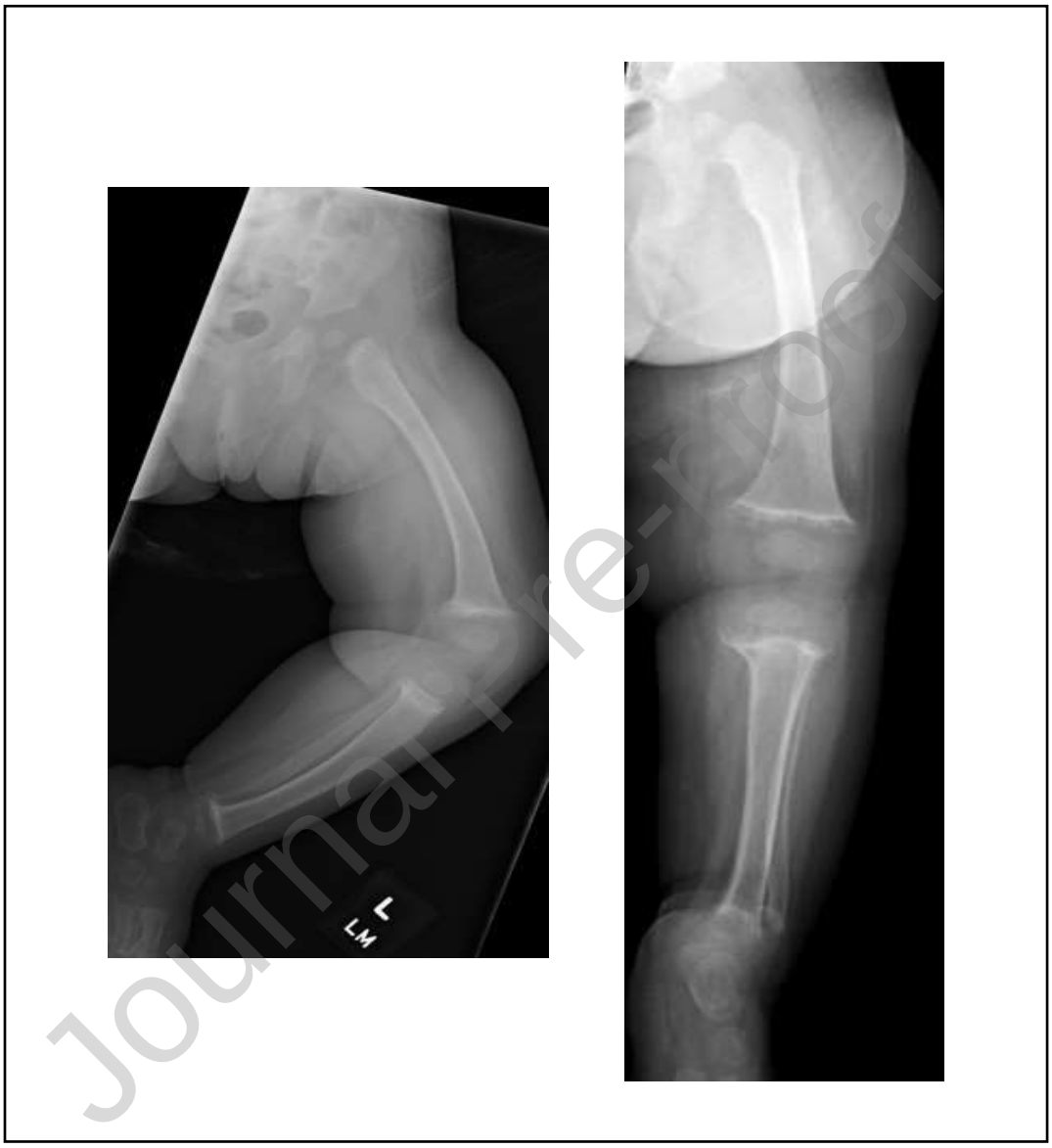
Infants with rickets have softer skull bones, known as craniotabes, as well as delayed closing of the fontanels and frontal bossing.[43 45] Other skeletal symptoms include abnormal ribcage development, with flattening of the rib cage and projecting breast bones – these deformities can lead to an increased risk of acute lower respiratory infections.[46] Some children also develop rachitic rosary which are bumps at the ends of their ribs.[47] Extremity deformity usually depends on the weight-bearing patterns of the child.[40] Upper limb deformities, especially in crawling infants, include wrist widening and thickening.[44 47] Lower limb deformities are often noticed once a child starts walking. These include genu varum and genu valgus potentially accompanied by knee/ankle joint swelling.[44]

Figure 2. Illustration of the architecture of normal bone versus rachitic bone.



MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); [updated 2020 Jun 24]. Vitamin D-dependent rickets; [updated 2017 Dec 1; cited 2023 Sept 5]. Available from: https://medlineplus.gov/genetics/condition/vitamin-d-dependent-rickets/.

Figure 3. Radiographic findings in rickets. Findings can include widening of the physis, fraying and cupping of the metaphysis, and angular deformity of the long bones.



Growth retardation, delayed tooth eruption, muscle weakness, bone pain, and hypocalcemic seizures have also been reported along with an increased susceptibility to fractures.[40 45] It is also important to note that an absence of clinical symptoms does not exclude a diagnosis of rickets, especially in the early stages.[48]

Risk of Fracture in the Pediatric Population

While up to 60% of boys and 40% of girls sustain a fracture in childhood,[49] children with low vitamin D levels have been noted to be subject to a higher incidence of fractures from normal activities.[50]

Numerous recent studies have shown that children who present with fractures often have vitamin D deficiencies. A 2016 study by Rodda et al found 80% of children in Southern Australia presenting with fractures were found to have vitamin D deficiency.[51] Herdea et al. found 75.1% of 688 pediatric patients presenting with a fracture to have below normal vitamin D serum levels (31.4 insufficient and 43.8% deficient) compared to an unfractured control group with only 55.6% having below normal vitamin D serum levels. The study concluded that children with a less than normal vitamin D level had a 2.127 times higher chance of having a fracture than children with normal levels.[52]

A population-based case-control study of 37 MENA (Middle East North African) children with low-energy fractures compared to 70 controls found that children with fractures had lower levels of vitamin D (21.87 ± 8.40 ng/ml vs. 25.89 ± 7.62 ng/ml; P = 0.01). It also found that males had 3 times greater fracture risk than females (OR, 3.00; 95% CI, 1.12-8.07; P = 0.03), and that overall, vitamin D deficiency correlated with almost five times increased risk of pediatric low-energy fractures (OR, 4.63; 95% CI, 1.92-11.18; P = 0.001).[53]

Obesity likely represents an additional risk factor for fracture in the setting of low vitamin D. A prospective case-control study comparing 76 children with fractures with 50 controls found that fractures were substantially more frequent in children with vitamin D deficiency (<20 ng/mL, $\chi 2$: 7.781, P = 0.005) and in a multivariate logistic model, that BMI percentile and vitamin D levels remained significantly associated with increased odds of fracture [1.02 (1.01-1.04), P < 0.001 and 0.93 (0.89-0.98), P = 0.01][54]

Results from a systematic review and meta-analysis of observational studies that compared serum vitamin D levels between fracture and non-fracture pediatric cases (including 2929 fracture cases and 5000 controls) indicated that serum vitamin D was lower in pediatric patients with fractures and levels ≤ 50 nmol/L were associated with increased fracture risk (P = 0.002, pooled OR = 1.29).[55]

Some studies, however, argue against a relationship between vitamin D level and fracture risk. A 2021 systematic analysis of 13 studies and 3943 subjects, concluded there to be no relationship between vitamin D level and risk of bone fractures in children and adolescents.[56] Similarly, a case-control study comparing 100 children with fractures and 100 without fractures, found no relationship between vitamin D deficiency and fracture risk (OR, 0.94; 95% CI, 0.51-1.77; Wald P = 0.859).[57] Such incongruities in the literature may be due to the inconsistencies in definitions regarding levels of vitamin D deficiency and/or insufficiency and at what serum vitamin D level there may be potential for a detrimental bone health effect.

Risk of Fracture in the Adult Population

Vitamin D deficiency has been identified as a common metabolic/endocrine abnormality and is considered a major public health concern in adults, especially for the elderly.[58] Osteoporosis-related fractures and associated injuries are a worldwide burden, making their prevention a priority and major public health goal.[59] Even if regularly exposed to sunlight, elderly people produce 75% less cutaneous D_3 than young adults.[30] There has been an increasing amount of research aimed at answering questions regarding the most convenient tests that can assess vitamin D status, the indications for screening, and the utility of treatments for vitamin D deficiency.[60] And while vitamin D supplements are often recommended for the general population, data on whether or not they actually prevent fractures has been found to be inconsistent. Ultimately, this underscores the importance of appropriate vitamin D status in childhood and adolescence to optimize peak bone mass and likely mitigate fracture risk and/or osteoporosis in adulthood.[10, 11]

Supplementation and Treatment of Deficiency

Vitamin D supplementation is a common practice used to prevent deficiency in individuals with suboptimal sun exposure and to maintain optimal vitamin D levels for bone health in all members of a healthy population. The Institute of Medicine recommends daily amounts, known as adequate intake (AI), as follows: 200 international units (IU) for infants, children, and adults younger than 51 years, 400 IU for adults 51 to 70 years of age, and 600 IU for adults older than 70 years.[31] The American Academy of Pediatrics has recently recommended doubling this

minimum intake amount for children and adolescents to 400 IU.[61] However, there is considerable variation in incremental circulating 25-hydroxyvitamin D levels when administering vitamin D supplements, even when similar age groups and identical vitamin D doses are compared.[62] Thus, it is also important to note that baseline 25-hydroxyvitamin D, body mass index, ethnicity, type of vitamin D (D_2 or D_3), and genetics affect the response of serum 25-hydroxyvitamin D to vitamin D supplementation.[63] Further complicating supplementation is the lack of consensus on the definition of 'normal' vitamin D concentration in healthy children and inconsistent guidelines regarding target levels for optimal vitamin D status.[45]

Wolff et al. concluded that based on the results of three recent meta-analyses, fracture protection is optimal when patient adherence exceeds 80% and vitamin D doses exceed 700 IU/day.[64] A recent study demonstrated the importance of obtaining vitamin D levels – patients were more likely to be compliant with supplementation after fracture . The proportion of patients who had their 25(OH)D levels recorded and were compliant (61%) was higher than the proportion of patients who did not have their 25(OH)D levels recorded and were compliant (21.8%, $P<0.001$).[65] This data should encourage clinicians to order serum vitamin D levels when supplementing.

Beyond fracture care, an RCT published by The Journal of Clinical Endocrinology & Metabolism in 2006 demonstrated the positive effects of vitamin D replacement on musculoskeletal parameters in school-aged girls, especially during the premenarchal period. It

found that lean mass increased significantly in both low- and high-dose treatment groups ($P \leq 0.05$), while bone area and total hip bone mineral content increased in the high-dose group ($P < 0.02$). Additionally, in the premenarchal group, there were consistent trends for increments in bone mineral density and/or bone mineral content at several skeletal sites, however, there were no significant changes in lean mass, bone mineral density (BMD), or bone mineral content (BMC) in postmenarchal girls.[66]

Beyond oral supplementation, other sources of vitamin D include select nutritional sources and exposure to sunlight. However, according to the American Association of Orthopaedic Surgeons, there are few foods that contain a significant dose of vitamin D, diet alone may not be sufficient to treat vitamin insufficiency/deficiency.[67] Additionally, the UV action spectra for DNA damage (and thus risk of skin cancer) and vitamin D_3 photosynthesis are identical[68] and as such, there is hesitation and concern in advocating for increased sun exposure as a public health approach for increasing vitamin D status.[69,70,71,72]

In vitamin D deficient patients, it's recommended that age- and weight-dependent therapeutic dosages should be administered based on the respective regional or national guidelines, for a duration of 1-3 months.[73] As expected, there is a lack of international consensus on optimal treatment schemes.[74] In the United States, The Endocrine Society suggests using vitamin D_2 or D_3 for the treatment and prevention of vitamin D deficiency and recommends the following dosage amounts as described in Table 2.[29]

Table 2. Dosage amounts of vitamin D recommended by The Endocrine Society.

	0-1 years	**1-18 years**	**Adults (> 18 years)**
Treatment*	2000 IU/day or 50,000 IU/week for 6 weeks	2000 IU/day or 50,000 IU/week for at least 6 weeks	6000 IU/day or 50,000 IU/week for 8 weeks
Maintenance	400-1000 IU/day	600-1000 IU/day	1500-2000 IU/day

*Treatment is defined as supplementing vitamin D to achieve a blood level of 25(OH)D above 30 ng/ml.

Based on data provided by the Institute of Medicine, Food and Nutrition Board, the National Institutes of Health (NIH) fact sheet recommends the following dietary allowances for vitamin D seen in Table 3.[22]

Table 3. Dietary allowances for vitamin D recommended by the National Institutes of Health (NIH) fact sheet. Please note that 1 mcg vitamin D is equal to 40 IU.

Age	Male	Female	Pregnancy	Lactation
0-12 months	10 mcg (400 IU)	10 mcg (400 IU)		
1-13 years	15 mcg (600 IU)	15 mcg (600 IU)		
14-18 years	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
19-50 years	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
51-70 years	15 mcg (600 IU)	15 mcg (600 IU)		
> 70 years	20 mcg (800 IU)	20 mcg (800 IU)		

Hypervitaminosis D is associated with cancer, cardiovascular risks, autoimmune diseases, and obesity,[75] however, the prevalence of vitamin D toxicity is rare. In the past decade, both the Institute of Medicine and The Endocrine Society have determined vitamin D toxicity to be

extremely uncommon in the literature and related to misuse of over-the-counter supplements, erroneous prescriptions, or fortification of foods or supplements with higher than intended amounts as was the case in the 2015 FDA recall of Glades Drugs multivitamins due to excessive amounts of vitamin D.[76, 77]

SUMMARY

Vitamin D is a central component of musculoskeletal health with beneficial effects on both bone stability and muscle function.[78] Childhood is a crucial time for bone development and attaining peak bone mineral density. Vitamin D deficiency can be present in the pediatric fracture population up to 75%[52] and while retrospective cohorts carry an inherent risk of bias and do not determine causation, it does appear there is a strong association and treating vitamin D deficiency in this population is likely warranted with low risk of harm.[49, 79] Additionally, it is well established that vitamin D deficiency can lead to nutritional rickets and subsequent deformity. The pediatric orthopaedic surgeon may be the first to diagnose and initiate treatment for this population. Serum testing with a 25-hydroxyvitamin D level in at-risk patients may best guide vitamin D repletion. The pediatric orthopaedic surgeon can and should play a vital role in optimizing bone health during the evaluation and treatment of patients with rickets and fractures.

Additional Links

https://www.posnacademy.org/media/D-Mystifying+Bone+Health+in+Pediatrics/0_kfbpx4zw/19139682

https://pubmed.ncbi.nlm.nih.gov/30998583/

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Conflict of Interest

No conflicts of interest to declare.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: