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The Answer is Vitamin D! From Pediatrics to Geriatrics in Orthopaedics

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Abstract

Vitamin D is necessary for the regulation of calcium and phosphate in the human body. Decreased vitamin D levels can alter the bone mineralization process. The prevalence of vitamin D deficiency in the general population is high, and low vitamin D levels are associated with disorders such as rickets and osteoporosis. As knowledge about vitamin D metabolism increases, physicians of all specialties are becoming more attentive to the vitamin D status of their patients. Similarly, orthopaedic surgeons, through various initiatives such as "Own the Bone," are making greater efforts to medically manage skeletal disorders. Unfortunately, universal guidelines for the optimization of vitamin D levels have not been adopted by orthopaedic surgeons, and, despite substantial efforts, vitamin D is not an integral part of most orthopaedic residency training programs. Although this may be partially attributed to attitudes among orthopaedic surgeons, the large number of vitamin D recommendations in the literature may be confusing and require substantial effort to synthesize into a viable approach for a given patient. Despite this confusion, orthopaedic surgeons should understand how to diagnose and manage disorders related to vitamin D and calcium deficiency.

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Video 41.1: The Answer is Vitamin D! From Pediatrics to Geriatrics in Orthopaedics. Barbara Minkowitz, MD (13 min)

Background

Vitamin D deficiency was first described in 1822 by Jędrzej Śniadecki, who reported that a lack of sun exposure in Polish children was associated with bone deformity. In 1918, Kurt Huldschinsky reported that ultraviolet radiation could be used to manage rickets. Soon thereafter, the irradiation of food was reported to be sufficient for the prevention of rickets, and rickets was largely eliminated in the United

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States by 1945. Despite large successes in the treatment of children with vitamin D disorders, a global subclinical vitamin D deficiency crisis exists in all age groups.[1] Although various methods are available to evaluate for and manage vitamin D deficiency, this chapter will focus on 25-hydroxyvitamin D (25[OH]D) levels and vitamin D_3 supplementation. Other vitamins and minerals, such as vitamin K, boron, silicon, and magnesium, also are important for bone health but are not discussed in this chapter.

Humans obtain vitamin D through sun exposure and diet. Therefore, an individual's vitamin D level is influenced by diet, geographic latitude, season, skin tone, and body habitus. With regard to sun exposure, vitamin D_3 is produced by the skin as a result of exposure to ultraviolet radiation. Although sufficient vitamin D may be able to be obtained via exposure to sunlight, this method to manage decreased vitamin D levels has fallen out of favor because it is not feasible in the industrialized world and because of the carcinogenic effects of ultraviolet radiation on the skin. Thus, the prevalence of vitamin D deficiency has increased as a result of avoidance of sun exposure and the extensive use of sunscreen as part of a western lifestyle. Therefore, dietary supplementation is the preferred method to manage decreased vitamin D levels.

In children, the goal is to optimize 25(OH)D levels to minimize fracture, maximize the mineralization of growing bones, attain optimal peak bone mass (PBM), obviate secondary hyperparathyroidism, and assist in fracture healing. Clinical hypovitaminosis D in the form of rickets has almost been eliminated in the United States as a result of the widespread adoption of vitamin D–fortified milk. However, the effects of subclinical vitamin D deficiency are less clear. Unfortunately, the American Academy of Pediatrics does not recommend the routine evaluation of 25(OH)D levels in children who are not on an at-risk list, which includes children with disorders that predispose them to poor nutrition or bone health. However, studies have revealed subclinically low 25(OH)D levels in many healthy children.[2,3] The exact effect of vitamin D insufficiency in pediatric patients is unclear. Contreras et al[4] reported no relationship between vitamin D deficiency and fracture risk. Minkowitz et al[5] reported similar results in a study of 1,031 children. In the study by Minkowitz et al,[5] a significant difference in 25(OH)D levels existed between the patients with fractures that required surgical management and the patients with fractures that required nonsurgical management.[5] The odds ratio for a fracture that required surgical management based on 25(OH)D level was significant. Patients with a 25(OH)D level between 20 and 30 ng/mL were two times more likely to sustain a fracture that required surgical management compared with patients with a 25(OH)D level greater than 40 ng/mL. Patients with a 25(OH)D level less than 20 ng/mL were six times more likely to sustain a fracture that required surgical management, and patients with a 25(OH)D level less than 12 ng/mL were 55 times more likely to sustain a fracture that required surgery.[5] Therefore, the authors concluded that the likelihood of a fracture that required surgical management was increased in patients with a 25(OH)D level less than 40 ng/mL, but the overall risk for fracture did not appear dependent on a patient's 25(OH)D level.

In skeletally mature adults, vitamin D deficiency is associated with skeletal muscle dysfunction. In a systematic review of six controlled trials, five of which were randomized and blinded, that compared muscle strength 4 weeks to 6 months after the initiation of vitamin D supplementation, Chiang et al[6] reported improvements in muscle strength in healthy athletes aged 18 to 45 years who underwent vitamin D supplementation. The sample sizes of the controlled trials ranged from 10 to 30 patients, and the controlled trials tended to consist of cohorts of patients who were active (eg, ballet dancers, professional athletes, active adult males). Pretreatment vitamin D levels ranged from 14.4 to 38.8 ng/mL, and the controlled trials that measured posttreatment vitamin D levels reported significant improvements in the patients in the treatment groups. Two of the controlled trials examined vitamin D_2 supplementation and reported that it was ineffective at improving muscle strength at the doses used.[6] The other four controlled trials examined vitamin D_3 supplementation and reported an overall positive effect of vitamin D_3 supplementation on muscle strength, with two of the controlled trials reporting a significant improvement in muscle strength and the other two controlled trials reporting a trend toward improvement in muscle strength.[6]

In older adults, low vitamin D levels are associated with osteoporotic fractures. Fragility fractures are defined by a low-energy mechanism of injury, such as a fall from no more than a standing height, and are common, with 1.5 million osteoporotic fractures reported each year in the United States.[7] Osteoporotic fractures can result in marked morbidity and mortality, with a single

vertebral compression fracture associated with a 1.2-fold greater age-adjusted mortality rate in women and five vertebral compression fractures associated with a 2.3-fold greater age-adjusted mortality rate in women.[8] Therefore, orthopaedic surgeons must be increasingly suspicious of conditions that result in bone fragility and be familiar with current strategies for the diagnosis, prevention, and management of osteoporosis. The effect of vitamin D supplementation on the rate of fracture has been examined in several randomized controlled trials.[9-18] In a meta-analysis of randomized controlled trials that examined the effect of vitamin D supplementation on the rate of fracture, Bischoff-Ferrari et al[18] reported that vitamin D supplementation reduced the risk for hip fracture by 26% and reduced the risk for any nonvertebral fracture by 23%.

Bone Health and Workup

Bone health throughout an individual's life is believed to be largely determined by PBM, which is a reflection of bone acquisition during childhood and adolescence. Eighty percent to 90% of PBM is attained by age 25 years. PBM is considered a major determinant for the development of osteoporosis.[19] A 10% increase in PBM has been estimated to reduce an individual's risk for osteoporosis by 50%.[20,21] Efforts to enhance bone acquisition and optimize PBM are believed to improve bone health and minimize an individual's risk for fracture during childhood and reduce an individual's risk for osteoporosis and fragility fracture during adulthood.

Bone development and maintenance is a complex and dynamic process that involves bone formation and bone resorption. During bone development, which is the period in which bone formation exceeds bone resorption, numerous changes in the length, volume, and microarchitecture of the skeleton contribute to increased size and strength. In addition an increase in length, the long bones undergo an increase in cortical thickness and expansion of the medullary cavities. In vertebral bodies, growth includes an increase in trabecular size, orientation, and thickness. Substantial changes in bone composition also are observed during bone development, with bone mineralization occurring at a rapid rate. A typical infant with a total-body calcium level of 25 g will transition to an adult with a total-body calcium level of 1,200 g by age 25 years. Conversely, during aging, bone resorption exceeds bone formation, and age-related changes occur at multiple levels. These age-related changes include decreased bone mineral density; a decrease in trabecular thickness, number, and connectivity; decreased mechanical strength; and increased cortical thinning and porosity.[22] Similar to insufficient bone acquisition during childhood, these age-related changes in bone are associated with an increased risk for fracture.

Understanding the bone acquisition curve helps determine the windows of opportunity to optimize bone health during childhood and adulthood. Bone acquisition during bone development is not linear and, although bone acquisition is rapid during childhood, it appears to further accelerate during adolescence. The speed of bone mineral acquisition during adolescence is more closely linked to pubertal development than to chronologic age. Studies estimate that in the 4 peripubertal years, individuals gain 40% of their PBM, which is essentially more than they will lose in a lifetime.[23] Another phenomenon of note that occurs during pubertal development is that peak height velocity precedes PBM accrual by approximately 6 months.[23] By the age at which adolescents reach their peak height velocity (11.6 years for girls and 13.5 years for boys), they will have reached 90% of their adult height but only 60% of their adult total-body bone mineral content (BMC).[24] The discrepancy between bone size and BMC that occurs during the adolescent growth spurt results in a transient period of relative bone weakness, which corresponds with the increased incidence of fractures in adolescents.[25]

Bone acquisition and PBM are determined by many factors, some of which, such as nutrition and physical activity, are modifiable and others, such as genetics, chronic disease, sex, and age, are not modifiable. In a study on the influence of hormones on bone, Drinkwater et al[26] reported that estrogen deficiency at any age results in decreased bone mass. In males, delayed puberty can result in osteopenia, which is more commonly referred to as low bone mass.[27] In healthy males, testosterone is converted to estrogen, which helps prevent excessive bone resorption. Therefore, low testosterone levels in males are associated with decreased bone mineral density and an increased risk for fracture.[28]

Modifiable factors that affect bone acquisition and PBM include nutrition and physical activity. The most common nutritional components that affect bone acquisition and PBM are calcium and vitamin D. Many other dietary components, including adequate calories, adequate protein, and the avoidance of excess dietary sodium, are known to positively influence bone health. Ideally,

Table 1
Serum 25-Hydroxyvitamin D Level and Vitamin D Status

Status	Institute of Medicine (Absolute Minimal Values; ng/mL)[a]	Endocrine Society (ng/mL)[b]
Deficient	<12	<20
Insufficient	12–20	20–29
Sufficient	>20	≥30

[a]To evaluate population statistics for adult bone health.
[b]To set individually applicable values to minimize falls and fractures.

calcium should be obtained from dietary sources such as dairy products; however, adequate calcium supplementation has been reported to be beneficial in all age groups. Wosje and Specker[29] reported that adequate calcium supplementation during childhood and adolescence was associated with improved gains in bone mineral density especially if the supplementation was initiated in the pre-teenage years. Studies have reported an association between carbonated beverage consumption and fracture during adolescence. In a study of 460 teenaged girls, Wyshak[30] reported that the risk for fracture was three times higher in girls who drank carbonated beverages and five times higher in girls who drank cola compared with girls who did not drink carbonated beverages. In a study of the dietary trends of US adolescents that was conducted over three decades, Cavadini et al[31] reported that calcium consumption decreased by a mean of 13%, whereas milk consumption (an important source of calcium and vitamin D) decreased by a mean of 40%. The authors also reported that soda consumption increased by 160%. Some dietary trends have reported that 86% of girls and 65% of boys aged 12 to 18 years fail to meet the recommended dietary calcium allowance of 1,200 mg/day.

Vitamin D deficiency and insufficiency are associated with bone deficits throughout an individual's life span. Vitamin D is important for the absorption of calcium and the mineralization of bone. The active form of vitamin D (1,25-dihydroxyvitamin D) is required for vitamin D to be effective. Children with severe vitamin D deficiency suffer from rickets and are predisposed to osteoporosis and fracture during adulthood. Osteomalacia, which is the adult form of vitamin D deficiency, is associated with bone pain and fracture. Vitamin D also is responsible for numerous extraskeletal functions, including the regulation of blood calcium/phosphorus levels and immunomodulatory function, and adequate vitamin D levels have been associated with a decreased risk for cancer (breast, prostate, colon), autoimmune disease, macular degeneration, and mortality from cardiovascular events.[32]

A serum 25(OH)D assay is the current screening tool used to determine an individual's vitamin D level. A serum 25(OH)D assay measures a composite of 25(OH)D from diet, supplements, and synthesis. Serum 25(OH)D levels are measured in ng/mL or nmol/L, with 30 ng/mL equal to 75 nmol/L (conversion, 2.496). The half-life of serum 25(OH)D is 2 to 3 weeks. The form of vitamin D derived from plants or yeast is D_2 (ergocalciferol), whereas the form of vitamin D derived from animals/fish is D_3 (cholecalciferol). Of the two forms of vitamin D, vitamin D_3 is superior because of its increased activity and longer duration of activity.[33] The active form of vitamin D (1,25-dihydroxyvitamin D) has a half-life of 4 hours and is 1,000 times less concentrated than serum 25(OH)D.

Determining adequate serum 25(OH)D levels and required vitamin D supplementation is controversial because of disagreements between the Institute of Medicine and the Endocrine Society (**Table 1**). In 2011, the Institute of Medicine established the recommended dietary vitamin D allowance as 600 IU/day, which appears to be too low to maintain optimal serum 25(OH)D levels in healthy individuals.[34] In fact, Bischoff-Ferrari et al[18] reported a 35% reduced risk of falls in older adults who received 800 IU/day vitamin D. The authors reported that 800 IU/day vitamin D significantly reduced the risk for hip fracture (26%) and any nonvertebral fracture (23%) compared with calcium or a placebo, whereas lower doses of vitamin D (400 IU/day) did not reduce the risk of fracture compared with calcium or a placebo. The Endocrine Society uses a more individualized approach for vitamin D intake, suggesting a sliding recommended dietary vitamin D allowance that ranges from 800 to 4,000 IU/day based on serum 25(OH)D levels.[35,36]

Physical activity, which is an important factor that affects bone acquisition and PBM, generally is modifiable. According to the Wolff Law, bone will adapt to the loads under which it is placed; therefore, appropriate physical activity may be an effective method to

optimize bone acquisition and maintenance. Several studies have reported an association between physical activity and bone accrual in children, with increased bone accrual observed in children in whom calcium supplementation was used in combination with physical activity.[37,38] Adults also benefit from physical activity, and walking briskly, running, and strength training have been reported to attenuate bone loss and reduce the risk for fracture and falls.[39]

Determinants for bone health in athletes include body mass, menses, and the skeletal site considered. The sport in which an athlete participates also is important, with sports that involve greater weight bearing, such as gymnastics, having a greater effect on bone mass compared with sports such as swimming.[40,41] High-demand female athletes may have low bone mass and amenorrhea, which are associated with reduced bone mass in the spine, proximal femur, femoral shaft, and radius and an increased incidence of stress fracture. In a study of 127 young female cross-country runners, Kelsey et al[42] reported that the risk factors for stress fracture included previous stress fracture (fivefold greater risk for refracture) and low BMC (twofold greater risk for stress fracture for each standard deviation decrease observed in whole-body BMC). The authors reported that stress fracture also was associated with low calcium/dairy intake, lower lean body mass, lower weight, and younger age at menses.

Numerous factors affect bone fragility. Templeton[43] published a study on the factors that contribute to secondary osteoporosis. **Table 2** lists factors that substantially decrease bone mass. **Table 3** lists recommendations for low bone mass screening.

Video 41.2: What Constitutes Orthopaedic Management When a Patient Presents With a Fragility Fracture? J.M. Lane, MD (29 min)

Vitamin D Level Goals and Osteoporotic Drugs

Vitamin D_3 is produced by the skin as a result of exposure to ultraviolet light and is converted in the liver to 25(OH)D. Under the stimulation of parathyroid hormone (PTH), 25(OH)D is converted mostly in the kidney to the active form of vitamin D (1,25-dihydroxyvitamin D), which is responsible for the main benefits that are associated with vitamin D, including the induction of calcium absorption in the intestines, enhanced bone mineralization, improved fracture healing, and increased muscle strength. Low vitamin D levels result in an increased risk for fracture and decreased muscle strength.

As already mentioned, vitamin D supplementation is associated with a decreased risk for fracture. However, the effect of low vitamin D levels on healing in patients with a fracture is less clear. In a study of 37 patients in whom a fracture nonunion occurred without any obvious technical error or deviation from the standard of treatment, Brinker et al[44] reported that 68% of the patients were vitamin D deficient. Although a large number of the patients in the study by Brinker et al[44] were vitamin D deficient, the prevalence of vitamin D deficiency in the study by Brinker et al[44] did not substantially differ from the estimated prevalence of vitamin D deficiency in the overall US population.[45] Whether vitamin D deficiency also was prevalent in the patients in whom fractures successfully healed is impossible to determine without a control group for comparison. Although most animal studies report

Table 2
Factors That Substantially Decrease Bone Mass

Lifestyle
Diet (limited intake of vitamin D and calcium, inadequate or excessive protein intake)
Smoking
Excessive alcohol consumption
Immobility
Endocrinopathies
Hyperthyroidism
Hyperparathyroidism
Cushing syndrome
Type 1 diabetes mellitus
Hypogonadism
Systemic diseases
Gaucher disease
Mastocytosis
Rheumatoid arthritis
Ankylosing spondylitis
Psoriasis
Organ dysfunction/inflammatory disorders
Asthma
Chronic obstructive pulmonary disease
Renal failure
Primary biliary cirrhosis
Inflammatory bowel disease
Celiac sprue
Organ transplantation
Genetic disorders
Cystic fibrosis
Thalassemia and sickle cell anemia
Osteogenesis imperfecta
Prescription medications
Oral glucocorticoids
Diuretics
Antiepileptics
Methotrexate
Cyclosporine
Chemotherapy
Neoplastic conditions
Multiple myeloma

Table 3
Recommendations for Low Bone Mass Screening

Bone health history
Family history (osteoporosis or fracture)
Medical history
Medications (steroids, seizure medications, warfarin, gastrointestinal medications)
Diet (calorie, protein, vitamin D, and calcium intake)
Activity patterns
Fracture history
Fall history
Loss of height
Gait, posture, and balance deficits
Initial laboratory tests
Complete blood count
Comprehensive metabolic panel (including calcium, phosphate, magnesium, albumin, and alkaline phosphatase levels)
25-hydroxyvitamin D assay
Intact parathyroid hormone blood test
Also can evaluate thyroid-stimulating hormone, free thyroxine, estrogen, testosterone, and urine calcium/creatinine levels
Initial imaging tests
Bone densitometry scan
Use T score for adults at spine and hip
Good correlation with whole-bone strength at spine, radius, and femur
Strong predictor of fracture risk in adults
Use of Z score is preferred in premenopausal females and males <50 years
The pediatric protocol (whole body, spine, and hip if >11 years) should be used in patients <21 years
Genetic studies for osteogenesis imperfecta
In adults with suspected malignancy
Evaluate serum protein electrophoresis level
Evaluate urine protein electrophoresis level (multiple myeloma)
Evaluate bone turnover markers
Formation: Serum bone–specific alkaline phosphatase, serum osteocalcin, serum type 1 N-terminal procollagen levels (low levels indicate slow bone formation)
Resorption: Serum collagen type 1 cross-linked C-telopeptide, urine collagen type 1 cross-linked N-telopeptide (levels >35 nmol/L indicate bone loss, levels 20–30 nmol/L are sufficient, levels <20 nmol/L indicate slow bone resorption)
Bone biopsy: Reserved for patients with metabolic bone disease, such as those with renal osteodystrophy, osteomalacia, and/or osteogenesis imperfecta; tetracycline labeling and bone histomorphometric analysis are used

a trend toward improved fracture healing with vitamin D supplementation, clinical data that demonstrate an effect of low vitamin D levels or vitamin D supplementation on fracture healing in humans remain elusive. Several meta-analyses and systematic reviews failed to conclusively determine the benefit of vitamin D supplementation for fracture healing.[46-48] Whether the lack of human studies on the benefit of vitamin D supplementation for fracture healing is because of methodological difficulties or negative study results that have been suppressed has been questioned.[46]

An individual's vitamin D status is largely determined via the measurement of 25(OH)D levels. As already mentioned, adequate vitamin D levels are controversial. Calcium also is important for bone health. Calcium is important for intracellular signaling and is a major component of bone. PTH prevents plasma calcium deficiency and is an excellent marker of total-body calcium level. An individual's calcium level and intact PTH level must be evaluated to determine his or her calcium status. PTH levels greater than 50 pg/mL indicate calcium deficiency. PTH levels less than 20 pg/mL indicate excessive calcium. PTH levels between 25 and 45 pg/mL indicate normal calcium homeostasis. Low calcium levels can result from inadequate calcium intake and decreased vitamin D levels. Poor calcium absorption may occur in individuals with celiac sprue or other disorders of the intestinal tract and individuals who are being treated with proton pump inhibitors. Excessive renal loss also may affect calcium absorption. Calcium supplements are available as either citrate or carbonate forms of calcium. Calcium citrate supplements are preferred because they are associated with a decreased risk for kidney stones. In a meta-analysis of 15 calcium supplementation studies, Bolland et al[49] reported that calcium supplementation is associated with an increased risk for cardiovascular events. This conclusion has been challenged because most of the studies included in the meta-analysis by Bolland et al[49] did not administer calcium in combination with vitamin D and, therefore, do not accurately represent current clinical practices.[50] In addition, concern existed that the patients in the studies included in the meta-analysis by Bolland et al[49] may have been taking personal

calcium supplements and, therefore, exceeded the regimens being tested.[50] In a recent study of a controlled trial of 1,460 older women who were randomized to receive 1,200 mg of calcium supplementation or a placebo, Lewis et al[51] reported no differences in the amount of carotid atherosclerosis between the women in the two groups, and that women with the highest total calcium intake had decreased carotid atherosclerosis compared with women who had much lower total calcium intake. Other studies have reported that, dissimilar to calcium supplementation, a high calcium intake obtained from dietary sources did not appear to increase an individual's risk for cardiovascular events.[52-54] Studies on the exact risks of both forms of calcium supplementation are ongoing; therefore, only 800 to 1,200 mg/day calcium in combination with vitamin D supplementation is recommended. Dietary sources and, if necessary, calcium citrate supplementation are the preferred methods to manage decreased calcium levels.

Osteoporotic drugs include antiresorptive agents (diphosphonates, denosumab, selective estrogen receptor modulators, and estrogen) and anabolic agents (PTH 1-34). Antiresorptive agents immediately reduce or stop bone resorption via osteoclasts and simultaneously prevent bone formation. Anabolic agents initially stimulate bone formation; however, bone resorption increases within 3 months. The initial 3-month period of bone formation is referred to as the anabolic window. Antiresorptive agents lead to a large fracture callus but delayed maturation. The large fracture callus compensates for the delay in fracture healing and mechanically promotes the repair process as long as some motion is present. In rigidly fixed fractures, antiresorptive agents lead to delayed fracture healing, particularly in patients with stress fractures. Conversely, anabolic agents have demonstrated enhanced fracture healing in the distal radius, the pelvis, patients who undergo spine fusion, and patients who undergo instrument fixation. Clinical trials on the use of osteoporotic drugs in patients with hip fractures and patients who undergo spine fusion have helped define the relative roles of diphosphonates and teriparatide (PTH 1-34).[55,56] In a study of 1,065 patients who underwent treatment for a hip fracture and were randomized to receive zoledronic acid, Lyles et al[55] reported a marked decrease in fracture risk if zoledronic acid was administered within 6 weeks of hip fracture. In a study of 62 women with osteoporosis and degenerative spondylolisthesis who underwent spine fusion and were randomized to a placebo (control), risedronate (diphosphonate), or teriparatide (anabolic), Ohtori et al[56] reported that the patients in the anabolic group had a 50% lower rate of failed fusion and pedicle screw pullout compared with the patients in the diphosphonate group. The authors reported no differences between the patients in the control group and the patients in the diphosphonate group.

Long-term diphosphonate use has been recently linked to insufficiency femoral fractures, which often are referred to as atypical femoral fractures. Although the pathogenesis of insufficiency fractures is not completely understood, studies have hypothesized that intense osteoclast inhibition suppresses bone turnover and bone remodeling, which results in skeletal fragility.[57,58] Numerous studies have linked the use of antiresorptive drugs to atypical femoral fractures.[59-64] Therefore, antiresorptive drugs should be used with caution, and patients who are being treated with antiresorptive drugs should be closely monitored by clinicians. Patients with thigh pain who are being treated with diphosphonates should undergo imaging studies, such as plain radiography, CT, or MRI. For patients who are being treated with diphosphonates and in whom an insufficiency fracture occurs, serum calcium and vitamin D levels should be corrected, the use of diphosphonates should be discontinued, and the use of an anabolic agent should be considered. However, the antifracture benefits of diphosphonates considerably outweigh their potential for harm in patients who have a high risk for fracture.[65] The use of PTH 1-34, specifically, is preferred in patients who have undergone prolonged treatment with diphosphonates, patients with difficult fractures, patients who undergo spine fusion, patients being treated with steroids and/or diabetes medications, and individuals who have a very low bone mineral density (T score ≤3.5). Serum vitamin D and calcium levels must be corrected before the initiation of osteoporotic drug therapy.

Video 41.3: The Answer is Vitamin D Conclusion. Barbara Minkowitz, MD (11 min)

Vitamin D Toxicity

According to the Endocrine Society, the goal of vitamin D supplementation is to achieve a serum 25(OH)D level of 40 to 60 ng/mL. Orthopaedic surgeons must understand how much vitamin D supplementation is necessary to

Table 4
Bone Health Protocol for Healthy Pediatric Orthopaedic Patients

Vitamin D and calcium supplements are needed by everyone, every day.

Vitamin D recommendations to obtain serum vitamin D levels of 40–60 ng/mL in children without liver/kidney dysfunction (based on serum 25-hydroxyvitamin D level)

Age	**Vitamin D Recommendation (IU/day)**
0–1 years	400
1–8 years	600–1,000
8–13 years	1,000–1,500
13–18 years	1,500–2,000
Adults	2,000
Weight	**Vitamin D Recommendation (IU/day)**
20–50 lb	500–1,000
50–90 lb	1,500
90 lb	2,000

Vitamin D should always be taken with calcium.

Age	**Calcium Recommendation (mg/day)**
1–4 years	700
4 years	1,000

Children are encouraged to take a multivitamin with their supplement; this can be counted toward the total dose of vitamin D given. Children's multivitamins may include 200–800 IU of vitamin D. Parents should read the label several times to determine how much vitamin D is being given to their child and pay close attention to the serving size (daily dose may be two to three tablets and child may be getting only one tablet).

No fracture present: Supplementation recommendations based on serum vitamin D level in patients without fracture. Laboratory tests must be repeated 2 to 6 months after the initiation of supplementation, depending on the dose given and to validate the dose being used for maintenance. Children with absorption problems require higher maintenance levels.

Serum Vitamin D Level	**Supplementation Recommendation**
30–40 ng/mL (considered vitamin D sufficient by laboratory tests; however, the Endocrine Society considers 40–60 ng/mL vitamin D sufficient)	500 IU/day vitamin D + calcium
20–30 ng/mL (considered vitamin D insufficient)	1,000 IU/day vitamin D + calcium
12–20 ng/mL (considered vitamin D deficient)	2,000 IU/day vitamin D + calcium
<12 ng/mL (considered vitamin D deficient)	7,000 IU/day vitamin D + calcium (if serum vitamin D level is <10 ng/mL, may give 14,000 IU/day vitamin D). This is equivalent to 50,000 IU/week and 100,000 IU/week vitamin D, respectively. Repeat laboratory tests 2 months after the initiation of supplementation; decrease dose if serum vitamin D level is in range, or send to an endocrinologist if not responsive.

Fracture present: Supplementation recommendations based on serum vitamin D level in patients with a fracture. A higher initial dose can be given for 2 to 3 months, after which laboratory tests must be repeated; decrease dose if serum vitamin D level is in range, or send to an endocrinologist if not responsive. This is most important for patients with bone fractures that require a long time to heal even under the best circumstances.

Serum Vitamin D Level	**Supplementation Recommendation**
30–40 ng/mL (considered sufficient for healing by laboratory tests; however, the Endocrine Society considers 40–60 ng/mL sufficient for healing)	500–1,000 IU/day vitamin D + calcium

Table 4 (*continued*)
Bone Health Protocol for Healthy Pediatric Orthopaedic Patients

20–30 ng/mL (considered insufficient for healing)	4,000 IU/day vitamin D + calcium
16–20 ng/mL (considered insufficient for healing)	4,000 IU/day vitamin D + calcium
<16 ng/mL (considered deficient for healing)	7,000 IU/day vitamin D + calcium (if serum vitamin D level is <10 ng/mL, may give 14,000 IU/day vitamin D). This is equivalent to 50,000 IU/week and 100,000 IU/week vitamin D, respectively.
	Repeat laboratory tests 2 months after the initiation of supplementation; decrease dose if serum vitamin D level is in range, or send to an endocrinologist if not responsive.

Fracture present but no serum vitamin D level available: Supplementation is initiated while waiting for serum vitamin D level laboratory results. Supplementation is increased or decreased based on serum vitamin D level laboratory results.

Age/Weight	Supplementation Recommendation
≤12 years or <90 lb	2,000 IU/day vitamin D + calcium
≥12 years or >90 lb	4,000 IU/day vitamin D + calcium

The noncompliant child: A weeks' worth of vitamin D can be given once a week and calcium given daily.

Some children have absorption problems that are recognized, and some children have absorption problems that are not recognized. Children with absorption problems may require up to 7,000 IU/day vitamin D for maintenance (the equivalent of 50,000 IU/week vitamin D). Repeat laboratory tests aid in the discovery of absorption problems and allow for customization of supplementation.

Serum vitamin D levels are the highest at the end of the summer, and serum vitamin D levels are the lowest in early spring.

Although vitamin D toxicity is not encountered often, serum vitamin D levels should be reevaluated after every change in supplementation. A level of vitamin D excess that is not considered vitamin D toxicity exists and can be easily managed by reducing dosage.

Vitamin D sources (Should be United States Pharmacopeial or Good Manufacturing Practice grade vitamin D_3. Prescription vitamin D is vitamin D_2, which is not absorbed as well as vitamin D_3.)

Vitamin D drops: 1,000–5,000 IU vitamin D per drop; tasteless.

Vitamin D gummy (for adults): Can be used for children; however, read label for correct dosage.

Vitamin D + calcium gummy: Most pediatric gummies have little vitamin D per gummy and are expensive.

Vitamin D caplets or pills with calcium

Calcium sources

Calcium can be taken as part of daily diet.

Calcium carbonate: Read label for correct dosage.

Calcium pills

Calcium/vitamin D gummy (for adults): Can be used for children; however, read label for correct dosage.

Other calcium + vitamin D candy/chocolate: Read label for correct dosage.

International Osteoporosis Foundation Calcium Calculator

Estimating daily calcium intake		
Glasses of milk (8 oz)	_____ × 300 mg	= _____ mg
Servings of yogurt (8 oz)	_____ × 300 mg	= _____ mg
Ounces of cheese	_____ × 200 mg	= _____ mg
Orange juice with calcium	_____ × 300 mg	= _____ mg
General diet excluding above sources		= 250 mg
Calcium supplements		= _____ mg
Total daily calcium intake		= _____ mg

Table 5
Online Resources for Education on Bone Health and Fracture Prevention

Resource	Website
National Bone Health Alliance	http://nbha.org
Fracture Prevention Central	http://www.fracturepreventioncentral.org
American Academy of Orthopaedic Surgeons	http://www.aaos.org
Own the Bone	http://www.ownthebone.org
National Osteoporosis Foundation	http://www.nof.org
United States Bone and Joint Initiative	http://www.usbji.org

achieve a serum 25(OH)D level of 40 to 60 ng/mL. The vitamin D recommendations listed in **Table 4** were devised for vitamin D supplementation in healthy children and have been used as a starting point for vitamin D supplementation in healthy adults. The validation of vitamin D supplementation regimens via serum 25(OH)D level testing is necessary because each individual may respond differently to the standard amount of vitamin D supplementation and may have different vitamin D supplementation requirements.

Vitamin D toxicity, which results from excessive vitamin D supplementation, is rarely observed. Currently, many scientists consider a serum vitamin D level of 100 ng/mL an acceptable upper limit for healthy individuals who take vitamin D_3 (cholecalciferol) supplements.[66,67] Patients with serum vitamin D levels higher than 100 ng/mL are considered in the zone of vitamin D excess until symptoms of vitamin D toxicity occur. Individuals with vitamin D toxicity demonstrate symptoms of hypercalcemia, which include nausea, dehydration, lethargy, loss of appetite, weight loss, excessive urination, constipation, irritability, nervousness, ringing in the ear (tinnitus), muscle weakness, dizziness, confusion, disorientation, high blood pressure, and heart arrhythmia.[68] The long-term complications of unmanaged hypervitaminosis D include kidney stones, kidney damage, kidney failure, excessive bone loss, and calcification (hardening) of the arteries and soft tissues. In a recent study of 48 randomized controlled trials that examined the side effects of vitamin D supplementation, Malihi et al[68] reported that vitamin D supplementation is associated with an increased risk for hypercalcemia but is not associated with an increased risk for kidney stones.

The monitoring of patients for hypervitaminosis D should include a measurement of serum 25(OH)D levels (the storage form of vitamin D), serum calcium and phosphorus levels, and urine calcium levels. Although the exact serum 25(OH)D level that results in hypercalcemia symptoms is unknown, serum 25(OH)D levels must exceed 240 ng/mL for acute vitamin D toxicity to occur. In healthy adults, the lowest reported dose of vitamin D that resulted in hypercalcemia was 40,000 IU/day of vitamin D_2 (ergocalciferol) that was taken for a prolonged period of time.[66] In a recent retrospective study that was conducted over 10 years and included more than 20,000 25(OH)D level measurements, Dudenkov et al[69] reported only one patient with vitamin D toxicity. The authors reported that the patient was taking 50,000 IU/day vitamin D for more than 3 months and had a serum 25(OH)D level of 364 ng/mL.

Vitamin D toxicity is one of the rarest medical conditions and typically is the result of the intentional or inadvertent intake of extremely high doses of vitamin D (range, 50,000 to 100,000 IU/day) for months or years.[70,71] Vitamin D supplementation can be easily reduced or discontinued temporarily if circulating 25(OH)D levels exceed 100 ng/mL so that vitamin D excess does not result in vitamin D toxicity. Serum 25(OH)D levels should be monitored in individuals in whom vitamin D supplementation is reduced or discontinued because vitamin D supplementation regimens may affect each individual differently. Healthcare and professional organizations offer helpful online resources that provide education on bone health and fracture prevention (**Table 5**).

Summary

Vitamin D deficiency occurs in all age groups. An individual's PBM should be optimized during childhood to minimize the risk for osteoporosis and fragility fracture during adulthood. Severe fractures in pediatric patients are related to vitamin D levels less than 40 ng/mL. Decreased bone mineral density and changes in bone structure occur during aging. Bone acquisition and PBM are determined by many factors, some of which are modifiable and some of which are not modifiable. Modifiable factors that affect bone acquisition and PBM include nutrition (three to four servings of dairy per day

are recommended), vitamin D supplementation (to increase bone mass), and physical activity (1 hour per day to increase bone mass). Estrogen deficiency in females and testosterone deficiency in males result in decreased bone mass. Patients with fractures provide orthopaedic surgeons with an opportunity to discuss bone health. An evaluation of an individual's vitamin D level should be comprehensive and include a measurement of serum 25(OH)D levels. According to the Endocrine Society, multivitamins do not contain adequate vitamin D. Although serum 25(OH)D levels greater than or equal to 30 ng/mL are considered sufficient, serum 25(OH)D levels greater than 45 ng/mL are associated with increased speed, balance, and strength. Antiresorptive and anabolic agents reduce the risk for fracture in patients with osteoporosis; however, an individual's serum vitamin D and calcium levels must be corrected before the initiation of osteoporotic drug therapy. Antiresorptive agents, which include diphosphonates, help prevent fracture; however, an increased risk for fracture has been reported in a small subgroup of patients being treated with diphosphonates. Anabolic agents enhance fracture healing and spine fusion. Orthopaedic surgeons should remember that serum 25(OH)D levels increase and decrease throughout the year based on sun exposure, weight gain or loss, and other factors.

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