Vitamin D Supplementation to Reduce the Risk of Falls and Fractures: The Dosing Dilemma

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Many tissues in the body have vitamin D receptors. Maintenance of adequate vitamin D serum levels has been linked to a variety of health benefits. Vitamin D deficiency, defined as a serum 25-hydroxyvitamin D level <20 ng/mL, is becoming a common issue as our population ages and sun exposure is minimized. Vitamin D deficiency can lead to osteoporosis, muscle weakness, and increased risk of falls and fractures. Therefore, adequate vitamin D supplementation is essential. With many dosing options available, it is important for clinicians to know how best to treat vitamin D deficiency without causing harm to minimize the risk of falls and fractures.

VITAMIN D BACKGROUND

Vitamin D is a fat soluble, organic substance with a 4-ringed cholesterol backbone. Humans cannot innately synthesize vitamin D; consequently, it must be obtained from outside sources. Humans obtain vitamin D from sunlight exposure, diet, and dietary supplements. These sources provide vitamin D in an inactive form and the body subsequently metabolizes it into an active form.1

Sun and ultraviolet light convert a provitamin D to cholecalciferol (vitamin D3). Vitamin D3 can also be obtained from diet and dietary supplements. Another form of vitamin D can be obtained from diet and supplements, ergocalciferol (vitamin D2). Cholecalciferol and ergocalciferol are hydroxylated by the liver into calcidiol (25-hydroxyvitamin D), the major circulating form of vitamin D. Calcidiol is then further hydroxylated in the kidneys to calcitriol (1,25-dihydroxy vitamin D). Calcitriol is the physiologically active form of vitamin D.1 Calcitriol raises serum calcium by increasing the intestinal absorption of calcium, causing bone resorption, and decreasing renal calcium and phosphate excretion.2 Therefore, adequate vitamin D is necessary to maintain calcium homeostasis.

There are many causes of vitamin D deficiency. Few foods are rich in or fortified with vitamin D. Therefore, calcium absorption is impaired in the setting of vitamin D deficiency. Without adequate calcium, bone mineralization is decreased, leading to impaired bone integrity. Additionally, it appears that myocytes in skeletal muscles have vitamin D receptors and that vitamin D deficiency leads to muscle weakness and, consequently, falls.4,6

VITAMIN D DEFICIENCY

Vitamin D deficiency is a common problem, especially in the elderly. It is suspected that 40% to 100% of American and European elderly men and women have vitamin D deficiencies.1 Vitamin D deficiency can lead to secondary hyperparathyroidism, increased bone turnover leading to osteoporosis, and increased risk of fractures.7

Several trials have been performed to assess the potential benefits of vitamin D on musculoskeletal health. Most, but not all, have revealed that vitamin D supplementation improves strength and reduces falls and fractures.

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reduced skin synthesis from limited sun exposure or heavy sunscreen use. Given that vitamin D must be metabolized in the liver and kidneys to the physiologically active form, patients with kidney and liver disorders may need to be supplemented with active calcitriol depending on the severity of their disease. Vitamin D is a fat soluble vitamin, therefore, patients with fat malabsorptive disorders, such as cystic fibrosis and Crohn’s, may have inadequate absorption of vitamin D, leading to deficiency.\(^1\) Finally, certain drugs may increase the catabolism of calcitriol, including phenytoin, phenobarbital, carbamazepine, isoniazid, theophylline, and rifampin.\(^8\,9\)

Vitamin D sufficiency is measured by obtaining a serum calcidiol, 25-hydroxyvitamin D, level. Patients at high risk for developing vitamin D deficiency should be screened, including elderly patients, patients with malabsorptive syndromes, patients on drugs known to increase calcitriol catabolism, patients with chronic kidney disease, and patients with inadequate sun exposure. While no consensus exists on the optimal 25-hydroxyvitamin D level, there are widely accepted definitions for insufficiency and deficiency.\(^6\)

Vitamin D insufficiency is defined by most as levels 20 to 30 ng/mL and deficiency as levels <20 ng/mL. Debate exists over how much vitamin D is considered sufficient with regards to supplementation.\(^1\,10\) Some references recommend achieving 25-hydroxyvitamin D levels of >30 ng/mL with supplementation while others recommend 20 to 30 ng/mL.\(^6\) Levels >20 ng/mL have been shown to be effective at reducing risk of fractures and levels of 20 to 30 ng/mL seem to be necessary to decrease the risk of falls.\(^6,11,12\)

**VITAMIN D SUPPLEMENTATION**

Vitamin D is commonly supplemented in 2 forms: ergocalciferol (vitamin D\(_2\)) and cholecalciferol (vitamin D\(_3\)). Many over the counter vitamin D supplements contain ergocalciferol and it is currently the only prescription strength product available.\(^10,13\) For many years, vitamin D\(_2\) and D\(_3\) were deemed to be equipotent. However, more recent evidence indicates that vitamin D\(_3\) is more potent and better at raising and maintaining serum vitamin D levels.\(^13,14\) It has been demonstrated that vitamin D\(_3\) is approximately 30\% more potent than vitamin D\(_2\).\(^7\)

For supplementation without deficiency, most experts recommend 400 to 800 IU daily for patients younger than 50 years and 800 to 1000 IU daily for elderly patients.\(^14,15\) Doses of 800 IU daily combined with calcium may be necessary to reduce the risk of fractures and doses of 1000 IU daily may be necessary to reduce falls.\(^10,16,17\)

Vitamin D dosing for treating deficiency is dependent on the initial serum 25-hydroxyvitamin D level. Many dosing strategies have been used, including 400 to 2000 IU daily and 50,000 IU weekly to monthly.\(^14,17\) To increase compliance, annual high dose vitamin D supplementation has also been studied.\(^18,19\) Patients with advanced renal disease (chronic kidney disease stage 3 and 4) cannot adequately convert D\(_2\) to the active form, calcitriol, therefore, these patients typically require supplementation.\(^20,21\)

Patients with low serum 25-hydroxyvitamin D levels (<15 ng/mL) need high dose supplementation (50,000 IU) weekly for a number of weeks depending on the initial serum level (Table). Vitamin D requirements generally increase as age increases due to decreased synthesis from the skin and decreased renal conversion to the active form.\(^10\) After receiving supplementation, patients’ vitamin D levels should be reassessed in 3 months to confirm the deficiency has been corrected.\(^6\)

Although rare, multiple serum 25-hydroxyvitamin D levels >150 ng/mL suggest intoxication.\(^1\) Symptoms of intoxication include nausea, vomiting, constipation, weakness, falls, and weight loss.\(^22\)
Intoxication can also lead to hypercalcemia and hyperphosphatemia, which can cause mental status changes and arrhythmias. Excessive sun exposure will not lead to intoxication because of photodegeneration of vitamin D in the skin.22,23

FALLS AND FRACTURES
Several trials have been performed to assess the potential benefits of vitamin D on musculoskeletal health. Most, but not all, have revealed that vitamin D supplementation improves strength and reduces falls and fractures.16,22,24-26 In studies using doses of 700 to 800 IU of vitamin D₃ daily, the relative risk of hip fracture and nonvertebral fracture was reduced, by 26% and 23% respectively, as compared to calcium and placebo.16 Another study used 800 IU of cholecalciferol + 1200 mg of calcium daily versus 1200 mg of calcium alone. The calcium plus vitamin D₃ group had a 49% reduction in falls.25 A few studies have looked at using lower doses of vitamin D (400 IU daily) to achieve the same benefits.23 These trials have not shown a reduced risk of fractures. Therefore the compilation of these results, as well as the data from other trials, indicate that there is a dose-dependent relationship with vitamin D and that supplementation of at least 800 IU daily, and up to 1000 IU daily, is required to prevent falls and fractures.4,6,24-26

To increase medication compliance, 2 studies examined once yearly high doses of vitamin D.18,19 The most recent trial was a single-center, double-blind, randomized, placebo-controlled study of women 70 years and older at a high risk of hip fracture. Patients were randomly assigned to receive either a single oral dose of cholecalciferol at 500,000 IU or a matched placebo annually for 3 years.18 The study showed that the ergocalciferol group had a statistically significant higher risk of wrist and hip fractures. At the time, this study had no proposed explanation for this other than random chance.19

Both of these studies allude to the fact that too much vitamin D may lead to adverse effects. There are several proposed explanations for the increase in risk of falls and fractures seen with single high dose administration. The most plausible explanation is a negative feedback mechanism that occurs from high dose vitamin D. When presented with high dose vitamin D, the enzymes in the liver that catabolize calcitriol may be upregulated thus leading to decreased levels.27 Although 25-hydroxyvitamin D levels measured in a small subset of patients did not indicate high enough levels for intoxication, it cannot be ruled out that some of these patients experienced symptoms of an overdose early on. These symptoms may include muscle weakness and falls.28


