

## How I Treat Vitamin D Deficiency

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### Importance of Vitamin D

Vitamin D is important in a number of physiologic processes, including calcium absorption, innate and adaptive immunity, and homeostasis of a number of organs. Chronic vitamin D deficiency in adults results in osteoporosis, osteomalacia, muscle weakness, and increased risk of falls.<sup>1-4</sup> Poor vitamin D intake and low blood levels of vitamin D metabolites are associated with increased incidence and severity of several autoimmune diseases involving the T helper type 1 lymphocyte,<sup>5,6</sup> including multiple sclerosis,<sup>7</sup> rheumatoid arthritis,<sup>8</sup> type I diabetes,<sup>9</sup> systemic lupus erythematosus,<sup>10</sup> and psoriasis.<sup>11,12</sup> Lower levels of vitamin D, adjusted for body mass index, are also associated with increased risk of hypertension, myocardial infarction, and death as a result of cardiovascular disease.<sup>13-16</sup>

Of particular interest to oncologists is the reduced incidence of some epithelial malignancies, particularly breast and colon, with higher intake or blood levels of vitamin D.<sup>17-23</sup> In some observational studies, higher levels of vitamin D have also been associated with reduced recurrence and mortality from breast, colon, and ovarian cancers.<sup>24-28</sup> Although there is evidence that vitamin D supplementation can improve muscle strength and reduce the number of falls among the elderly and fractures resulting from osteoporosis,<sup>1,29-32</sup> there is little direct evidence that low-dose vitamin D supplementation can significantly reduce cancer incidence or recurrence. Reduction in cancer incidence was observed in a small placebo-controlled trial for calcium and vitamin D (1,100 IU/d), and this reduction seemed greater than that seen with calcium alone, when cancers arising in the first year of the trial were censored.<sup>33</sup> However, no reduction in breast or colon cancer was observed for the calcium and vitamin D arm in the Women's Health Initiative trial, in which the dose of vitamin D for the treatment arm was only 400 IU, and both the placebo and treatment arms were allowed to ingest nonstudy vitamin D up to 1,000 IU/d.<sup>34-36</sup>

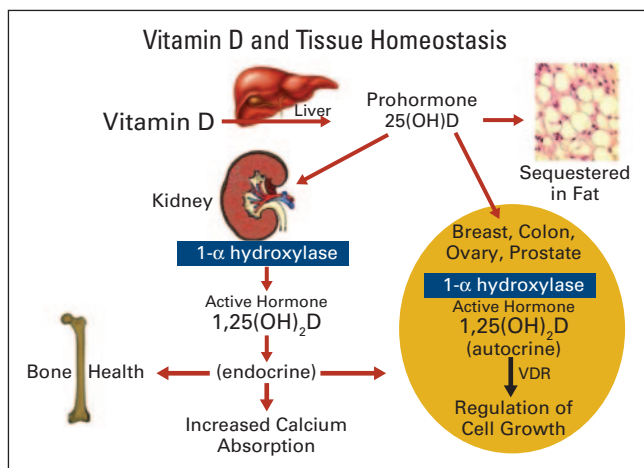
Regardless of whether vitamin D helps prevent cancer or its recurrence, the high frequency of vitamin D inadequacy in the US population<sup>37,38</sup> and the adverse impact on bone health of both vitamin D depletion and many of today's systemic cancer treatments makes it important for oncologists to understand vitamin D physiology and recognize, treat, and prevent vitamin D deficiency.

### Vitamin D Metabolism and Its Role in Breast and Colon Homeostasis

Cholecalciferol (vitamin D<sub>3</sub>), either ingested or manufactured in the skin in response to sun exposure, must first be converted to the prohormone 25(OH)D in the liver and then to the active hormone 1,25(OH)<sub>2</sub>D by tissues containing the 1- $\alpha$ -hydroxylase enzyme. The active form of vitamin D—1,25(OH)<sub>2</sub>D—may function in an endocrine fashion, as in the case of 1,25(OH)<sub>2</sub>D produced in the kidney, or an autocrine/paracrine manner, as in the case of 1,25(OH)<sub>2</sub>D produced in several other organs in which vitamin D plays an important role in homeostasis (Fig 1). The breast and colon are two of these organs, and epithelial cells from both make 1,25(OH)<sub>2</sub>D from circulating precursors. In the breast, vitamin D seems to be important in limiting proliferation and neoangiogenesis in response to hormones and growth factors and promoting differentiation.<sup>39-47</sup> In the colon, vitamin D limits proliferation in response to bile acids and other carcinogens and promotes differentiation and expression of adhesion and cell-junction proteins.<sup>48-50</sup>

### Sources of Vitamin D and Standard Doses of Vitamin D Supplements

Vitamin D sufficiency is defined in terms of the serum level of the prohormone 25(OH)D required for bone health, which is 30 to 32 ng/mL. Maintenance of a 30 to 32 ng/mL serum level requires approximately 2,200 to 3,000 IU/d of vitamin D from all sources, including ultraviolet light exposure, food, and supplements.<sup>20,51,52</sup> Recommendations from the Institute of Medicine for vitamin D supplementation suggest 200 IU of vitamin D daily from birth through age 50 years, 400 IU/d for individuals age 51 to 70 years, and 600 IU/d for those age 70 years or older.<sup>53</sup> These recommendations presume some sun exposure and vitamin D intake from food and are not adequate to treat vitamin D deficiency.<sup>54,55</sup> Historically, the source of most vitamin D has been ultraviolet light–induced skin manufacture of cholecalciferol. A single whole-body dose of ultraviolet radiation associated with minimal erythema produces 10,000 IU of vitamin D.<sup>55</sup> Thus, 15 to 20 minutes of daily sun exposure without sunscreen in lower midwestern and southern latitudes between 10:00 AM and 3:00 PM is usually sufficient to ensure adequate synthesis of vitamin D metabolites. Large excesses of vitamin D<sub>3</sub> from prolonged sun exposure are destroyed in the skin, making vitamin D toxicity from sun



**Figure 1.** Schematic of vitamin D metabolism and actions related to tissue homeostasis. VDR, vitamin D receptor. Data adapted.<sup>81</sup>

exposure improbable.<sup>54,55</sup> In contrast, with the exception of coldwater ocean fish, food is a poor source of vitamin D.<sup>54</sup> Three ounces of herring, which few individuals eat, provides 1,300 IU of vitamin D, 3.5 oz of the more commonly ingested salmon provides 350 IU, and 1 teaspoon of cod liver oil provides approximately 400 IU. However, the amount of vitamin D in 1 cup of fortified milk or orange juice is only 100 IU, with 50-100 IU per cup of breakfast cereal or tablespoon of margarine.<sup>54,56,57</sup> Today, with more time spent indoors and increased use of sunscreen, higher basal intakes of 1,000 to 2,000 IU/d from supplements are recommended to avoid vitamin D deficiency.<sup>23,58-60</sup> Multiple vitamins generally contain 400 IU of vitamin D, and calcium supplements provide 200 to 400 IU of vitamin D. Vitamin D3 supplements without other additives are readily available over the counter in 400, 1,000, and 2,000 IU strengths at pharmacies and most grocery stores. These supplements are much smaller in size than pills containing calcium and vitamin D and generally cost \$10 or less for a 3-month supply. At similar doses, vitamin D3 may be more potent than vitamin D2 (ergocalciferol), which is obtained from plants.<sup>61</sup> The Institute of Medicine lists 2,000 IU/d as the upper tolerable limit, but in fact, there is little evidence of toxicity unless doses of 10,000 IU of vitamin D3/d are exceeded.<sup>53,62</sup>

### Definition of Vitamin D Deficiency and Incidence in US Population

Vitamin D adequacy is currently defined as a function of calcium homeostasis, with lower vitamin D levels resulting in reduced absorption of calcium from the gut and/or elevations of parathyroid hormone (PTH) considered inadequate. Blood levels of the prohormone 25(OH)D, with a half-life of 2 to 3 weeks, are used to describe vitamin D sufficiency rather than levels of 1,25(OH)<sub>2</sub>D, which has a half-life of only 3 to 4 hours.<sup>54,58</sup> Furthermore, in early vitamin D depletion, blood levels of 1,25(OH)<sub>2</sub>D can be misleading because they may rise initially in response to elevations in PTH, which is sensitive to

reductions in 25(OH)D, before they begin to fall with prolonged precursor depletion.<sup>51,63</sup>

### Vitamin D Deficiency

Currently, 25(OH)D levels below 20 ng/mL (50 nmol/L), with resultant consistent elevation of PTH and reduction in intestinal calcium absorption, are considered indicative of vitamin D deficiency.<sup>52,54</sup> Older classifications considered 25(OH)D levels less than 12 ng/mL to be evidence of deficiency because symptoms were uncommon when levels were higher than this.<sup>38</sup> Today, 25(OH)D less than 12 ng/mL is considered evidence of severe vitamin D deficiency.

### Vitamin D Insufficiency

Because increases in intestinal calcium absorption continue until 25(OH)D reaches a minimum of 30 ng/mL, and PTH continues to decrease until this level is reached,<sup>64,65</sup> a 25(OH)D serum level of 30 to 32 ng/mL is considered sufficient and levels of 20 to 29 ng/mL insufficient.

### Optimal Vitamin D Status

At the present time, 25(OH)D levels in the range of 30 to 60 ng/mL are considered optimal, but higher levels up to 100 ng/mL are often seen in individuals with outdoor occupations receiving intense sun exposure without ill effects.<sup>55</sup> Correlative studies of 25(OH)D with muscle strength or risk of breast or colon cancer have prompted several investigators to suggest that the optimal 25(OH)D target for multiple health outcomes is 40 to 50 ng/mL.<sup>19,20</sup> Garland et al<sup>23</sup> suggest that increasing 25(OH)D to a range of 40 to 60 ng/mL from the current US average could reduce risk of breast cancer by 25% and colon cancer by 27%. Intakes of at least 4,000 IU daily from all sources would be needed to maintain 25(OH)D levels of 40 to 60 ng/mL. Practically speaking, supplements of 2,000 IU daily plus some sun exposure would probably be required to maintain a 25(OH)D level of 40 to 60 ng/mL year round.<sup>23</sup>

### Vitamin D Toxicity

Vitamin D intoxication with renal stones and hypercalcemia may be observed when serum levels of 25(OH)D are greater than 150 ng/mL (374 nmol/L). For a good margin of safety, levels greater than 100 ng/mL should probably be avoided.

### Prevalence of Vitamin D Deficiency

The incidence of vitamin D deficiency (ie, 25(OH)D < 20 ng/mL) in US adults is approximately 25% for men and approximately 35% for women.<sup>38</sup> Postmenopausal women with osteoporosis are especially likely to exhibit deficiency.<sup>1,63</sup> The problem is not limited to older women. Seventy-four percent of a cohort of newly diagnosed premenopausal patients with breast cancer from the New York City area<sup>66</sup> and 50% of a cohort of premenopausal women from the Kansas City area at high risk for the disease were reported as exhibiting vitamin D deficiency.<sup>67</sup>

## Who Should Have Serum 25(OH)D Levels Assessed?

### Individuals About to Initiate Treatment With Antihormonal Effects

We suggest obtaining a baseline 25(OH)D level in all individuals who are initiating therapy that could impact bone mineralization. This means that premenopausal women undergoing chemotherapy or medical or surgical ovarian ablation and postmenopausal women beginning aromatase-inhibitor therapy should be tested. Estrogen upregulates both the 1- $\alpha$ -hydroxylase enzyme that converts 25(OH)D to 1,25(OH)<sub>2</sub>D and increases levels of vitamin D receptor protein.<sup>68,69</sup> Thus, depletion of estrogen may unmask a subclinical vitamin D deficiency, which may increase the severity of muscle and joint symptoms experienced by women entering menopause or undergoing aromatase-inhibitor therapy. For cancer survivors, 25(OH)D levels drawn in late winter or early spring will provide an estimation of trough levels of vitamin D.

### Individuals at High Risk for Vitamin D Deficiency

Individuals most likely to have vitamin D deficiency are those who do not take supplements, are elderly,<sup>54</sup> are darkly pigmented,<sup>70</sup> are obese,<sup>71</sup> have osteoporosis or osteopenia,<sup>1</sup> avoid any sun exposure without sunscreen,<sup>72,73</sup> are typically veiled,<sup>74</sup> live in a highly polluted environment,<sup>75</sup> or have Crohn's disease or other reasons for fat malabsorption.<sup>54</sup>

### Individuals With Symptoms of Vitamin D Deficiency

Symptoms of vitamin D deficiency can be rather nonspecific and include fatigue, altered mood and depression, insomnia, nonradicular back pain, arthralgias (particularly of the wrists, ankles, shoulders, and shins), proximal muscle weakness, headache, and hair loss.<sup>76,77</sup> Symptoms are uncommon with 25(OH)D levels greater than 20 ng/mL, and even individuals with mild to moderate deficiency may not spontaneously complain of symptoms unless they are undergoing treatment that results in reduced formation of 1,25(OH)<sub>2</sub>D or decreased vitamin D receptor activation, such as estrogen depletion as the result of aromatase-inhibitor therapy. In a pilot study, we found that 50,000 IU of vitamin D3 weekly for 12 weeks was effective in treating vitamin D insufficiency in women receiving the aromatase inhibitor letrozole, and higher levels of 25(OH)D were associated with reduced disability from aromatase inhibitor-associated joint pain.<sup>78</sup>

### How to Treat Vitamin D Deficiency

The first step in treating vitamin D deficiency is to obtain a baseline 25(OH)D blood level and then decide on the target replacement level and how quickly that target must be reached (Table 1). Each 1,000 IU of vitamin D3 daily in addition to what the patient is currently ingesting will raise the level of 25(OH)D by 10 ng/mL after a few weeks. Note that more may be required for individuals who are obese, because vitamin D is sequestered in adipose tissue.<sup>79</sup>

**Table 1.** Recommendations for Treatment of Vitamin D Deficiency or Insufficiency

Serum 25(OH)D Level (ng/mL)	Vitamin D3 Supplementation Dose (IU)	Frequency of Vitamin D Supplementation
20-30	1,000-2,000	daily
12-20	2,000	daily
< 12 (asymptomatic)	4,000-5,000	daily
< 12 (symptomatic)	30,000	weekly

NOTE. These doses are in addition to what the patient is ingesting at baseline. Patients receiving more than the equivalent of 2,000 IU of vitamin D3 daily in supplements should have 25(OH)D levels monitored approximately every 12 weeks.

A common example encountered by an oncologist would be that of an asymptomatic postmenopausal woman about to begin aromatase-inhibitor therapy who is found to have mild osteopenia. Her 25(OH)D level is 20 ng/mL. In addition to ensuring adequate calcium intake, if the target 25(OH)D serum level is 40 ng/mL, the simplest treatment is to ask her to take an extra 2,000 IU of over-the-counter vitamin D3, checking the 25(OH)D level again at 3 months. It should be cautioned that 1% of the population may have occult primary hyperparathyroidism, which may be unmasked by vitamin D and calcium supplementation, resulting in hypercalcemia.<sup>80</sup> For individuals of average weight with insufficiency only during the winter months who get appreciable sun exposure during the summer, we usually suggest vitamin D3 supplementation only during the late fall, winter, and early spring.

A different scenario might involve a woman with a body mass index of 35 kg/m<sup>2</sup> ready to begin antihormonal therapy who already complains of fatigue, weakness, and diffuse arthralgias. A 25(OH)D level of 9 ng/mL shows evidence of severe vitamin D deficiency and is likely responsible for some or all of her symptoms. In this case, the 25(OH)D level should be increased as quickly as possible with either 4,000 IU vitamin D3 daily or 30,000 IU weekly, checking the level again at 6 and 12 weeks. When the desired level is achieved, maintenance of 40 ng/mL is usually possible with 2,000 IU per day, but in the case of obese women, higher doses may be needed.<sup>79</sup>

The importance of educating patients, checking compliance, and monitoring 25(OH)D levels every 3 months during treatment of deficiency and early maintenance phases cannot be overstressed. Patients easily get confused. We have observed situations in which weekly high-dose vitamin D was taken daily by mistake. In summary, vitamin D plays an important role in the homeostasis of a variety of organ systems. The precise roles that vitamin D plays in prevention of cancer and recurrence—along with the blood levels necessary to carry out those roles—have yet to be defined. In the meantime, oncologists are encouraged to check vitamin D levels in individuals about to undergo treatment that could impact bone and muscle health, replace deficiencies, and maintain 25(OH)D at levels optimum for musculoskeletal health.

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