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# Vitamin D Deficiency: Implications Across the Lifespan

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## Abstract and Introduction

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### Abstract

Vitamin D deficiency can occur in infancy, childhood, midlife, and aging. Research is emerging regarding vitamin D deficiency and its effect on neuromuscular function, cancer, cardiovascular disease, inflammatory illnesses, and bone mineralization. Recent evidence has shown that there is a need for increased vitamin D supplementation across the lifespan. Nurse practitioners must understand the effect of vitamin D deficiency on multiple body systems, assessment for deficiency, treatment, and prevention.

### Introduction

The role of vitamin D and calcium absorption in the elderly with osteoporosis has been well documented. However, as more evidence is developed, it is becoming clear that vitamin D deficiency is not only affecting the elderly population, it has negative effects across the lifespan. It is estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.<sup>[1]</sup> Review of research in medical, nursing, and nutritional literature reveals the need for vitamin D education, supplementation, and follow-up in all ages and treatment settings.

### Vitamin D: An Overview

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Vitamin D is a fat-soluble vitamin that is metabolized by the body by either sun (ultraviolet light) exposure or dietary intake. There are 2 molecules that make up vitamin D: ergocalciferol (D<sub>2</sub>) and cholecalciferol (D<sub>3</sub>).<sup>[2]</sup> Ultraviolet B (UVB) radiation is absorbed by the skin and converts 7-dehydrocholesterol to vitamin D<sub>3</sub>.<sup>[3]</sup> Vitamin D<sub>3</sub> then goes into the capillary bed, where it binds to vitamin D binding protein (DBP). Vitamin D<sub>2</sub> and vitamin D<sub>3</sub> are also ingested through the diet from fortified milk, fatty fish (salmon), and fortified cereals. Once ingested, they are incorporated into chylomicrons. The chylomicrons are transported through the lymphatic system and then are released into venous circulation, where vitamin D is bound to lipoproteins and DBP.<sup>[3]</sup> Both vitamin D from the sun and diet then enter the liver and are converted to 25-hydroxyvitamin D [25(OH)D<sub>3</sub>] (calcidiol);<sup>[3]</sup> 25(OH)D<sub>3</sub> (calcidiol) is the major circulating form of vitamin D and is used to determine vitamin D status. To become biologically active, it requires additional hydroxylation in the kidneys to form active 1,25-hydroxyvitamin D [1,25(OH)<sub>2</sub>D] (calcitriol); however, 1,25(OH)<sub>2</sub>D is not used to determine vitamin D status because it circulates at 1000 times less concentration than 25(OH)D<sub>3</sub> and it has a half life of 6 hours in comparison to 2 weeks for 25(OH)D<sub>3</sub>.<sup>[3]</sup>

Once reaching the form of calcitriol, vitamin D acts as a hormone. Calcitriol is important in the function of intestine, bone, and kidney that result in the maintenance of plasma calcium, phosphorus, and magnesium. It has been recently determined that there are vitamin D receptors in a variety of cells and therefore, vitamin D has a biological effect on more than mineral metabolism.<sup>[4,5]</sup>

Vitamin D has its greatest effect on the maintenance of adequate levels of serum calcium. Calcitriol works with parathyroid hormone to maintain adequate calcium and phosphorus levels in the blood. When serum calcium is too low, parathyroid hormone stimulates calcitriol to act to increase the intestinal absorption of calcium, increase the resorption of calcium by the kidneys, and stimulate the release of calcium from the bone. In response to elevated serum calcium, calcitriol decreases intestinal absorption and stimulates bone to take up calcium, decreasing serum calcium.<sup>[5]</sup>

### Deficiency

Deficiency occurs when people do not have adequate exposure to UVB rays or adequate dietary intake. According to the National Institutes of Health (NIH), 10 to 15 minutes of direct sunlight at least twice a week to the face, arms, hands, or back is sufficient to maintain optimum serum Vitamin D levels.<sup>[6]</sup> The common application of sunscreen and decreased outdoor sun exposure can result in inadequate production of vitamin D in the skin. Sunscreen application reduces vitamin D synthesis—SPF 8 by 92.5% and SPF 15 by 99%.<sup>[1,7]</sup> While there are varying opinions on whether or not sunscreen can be a primary cause of deficiency, it has been shown that sunscreen will reduce the synthesis of the vitamin.<sup>[7,8,9]</sup>

People with darker skin pigmentation have a reduction of synthesis by 99% because the UVB rays are being absorbed by melanin. There is a reduction of 7-dehydrocholesterol in the skin as aging occurs—only 25% of vitamin D<sub>3</sub> is synthesized in a 70-year-old.<sup>[10]</sup> Therefore, people with darker skin, and elders, need to ingest more vitamin D in their diets.

Because the sun does not rise high enough in the sky in the winter months, people who live in high latitudes require more dietary intake of vitamin D<sub>3</sub> and D<sub>2</sub>. It has been shown that above 35° north latitude (Atlanta), little or no vitamin D<sub>3</sub> can be produced from November to February.<sup>[10]</sup>

The use of tanning beds has been discussed as an option for increasing UV exposure and, in turn, increasing serum vitamin D. While tanning beds can result in vitamin D photosynthesis, they also increase the incidence of skin cancer and photo aging. Due to the damaging effects of UVB radiation from artificial sources, it is not recommended that people use these devices as a main source of vitamin D.<sup>[11]</sup>

People who are obese also have a more difficult time maintaining optimum vitamin D levels. Vitamin D is fat soluble and therefore easily stores in adipose tissue. This storage results in decreased vitamin D in the bloodstream. It has also been found that release of vitamin D from the skin into circulation is altered in obese women.<sup>[2]</sup> Due to this information, people who are obese should try to obtain more vitamin D from their diet. Intestinally absorbed ergocalciferol (D<sub>2</sub>) is most bioavailable in people with obesity.<sup>[2]</sup>

Vitamin D deficiency is determined by serum 25(OH)D levels. Recommended levels, according to textbooks, of vitamin D from can vary from 9 to 38 ng/mL (20-110 nmol/mL).<sup>[11]</sup> However, according to recent research and recommendations from vitamin D experts, ideal serum levels are between 30 and 60 ng/mL. Insufficiency is 25 to 30 ng/mL, rickets or osteomalacia is evident at less than 20 ng/mL, and frank insufficiency is less than 10 ng/mL.<sup>[2,3,11,12]</sup> Oral vitamin D supplementation will be presented after a description of causes and effects of vitamin D deficiencies.

When vitamin D levels are deficient, dietary calcium is not absorbed adequately. This deficiency disrupts phosphorus and calcium homeostasis, as well as bone mineralization. Recent evidence shows that deficiency in

vitamin D and its effect on calcium absorption causes disruption in neuromuscular function, muscle strength, cancer, diabetes, and inflammatory illnesses.<sup>[13]</sup> The following sections of this article will present issues that are identified throughout the lifespan that are now shown to be affected by vitamin D deficiency.

### Children and Adolescents

Children and adolescents are at high risk for vitamin D deficiency. In studies in Boston and Maine (northern latitudes), it was found that 52% of Hispanic and black adolescents and 48% of white preadolescent girls were vitamin D deficient (less than 20 ng/mL serum 25-OHD).<sup>[10]</sup> It is well documented that vitamin D deficiency and its effect on parathyroid hormone release resulting in diminishing the collagen matrix is the cause of rickets in children. This deficiency can be from hereditary mutations of vitamin D receptors, or insufficient absorption and intake of vitamin D.<sup>[1,2,3,5,7,10,14]</sup> The main causes of vitamin D deficiency in children are inadequate sun exposure, inadequate vitamin supplementation, and breastfeeding without vitamin D supplementation. Vitamin D has been associated with decreased risk of autoimmune disease such as inflammatory bowel diseases (irritable bowel syndrome [IBS], Crohns disease, and ulcerative colitis), and diabetes.<sup>[15]</sup>

**Autoimmune Disease.** It is important to understand the relationship between helper T cells and vitamin D in relation to all of these autoimmune disease processes. Helper T cells (Th) are key components to antigen-specific immunity.<sup>[15]</sup> There are 2 subtypes, Th1 and Th2. They regulate each other and, in normal immune responses, the host responds to a balance of Th1 and Th2. In autoimmune disease, Th1 is misdirected against self-proteins. Examples of these Th1-driven diseases are diabetes mellitus type 1 and irritable bowel syndrome (IBS). Th1 and Th2 are targets of 1,25(OH)<sub>2</sub>D<sub>3</sub>. There are vitamin D receptors on Th cells. Vitamin D works with mediators for the suppression of autoimmune disorders. With inadequate vitamin D, this suppression can cease to occur, increasing the instance of Th1-driven diseases.<sup>[15]</sup> The relationship with vitamin D and IBS is cyclic. Autoimmune disorders are associated with vitamin D deficiency, but then can also cause vitamin D deficiency. The malabsorption caused by IBS results in deficiency of vitamins absorbed in the intestines, which includes vitamin D.

**Diabetes Mellitus Type 2.** The incidence of diabetes mellitus type 2 (DM type II) is rising in children and adolescents. Thus, it is important to examine the role of vitamin D and calcium in this population. DM type II is most prevalent in children with obesity and, as previously discussed, vitamin D is poorly absorbed and circulated in people with obesity. Research has shown that vitamin D and calcium influence pancreatic β-cell function, insulin sensitivity, and systemic inflammation. It has also been found that patients with DM type II are found to have a lower serum 25-OHD concentration compared to controls without diabetes.<sup>[13]</sup>

**Recommendations.** Children should maintain a serum 25-OHD concentration above 32 ng/mL.<sup>[2]</sup> The most effective way of maintaining this level is exposure to UVB light, but without sunscreen. Vitamin D exposure via sunlight may be inconsistent and will vary with residential latitude. Therefore, supplemental dietary intake is recommended. Because D<sub>3</sub> is most efficient at maintaining serum levels, it is recommended that children intake 400 to 1000 international units (IU) of vitamin D<sub>3</sub> per day.<sup>[1,12]</sup> If the child is not getting adequate sun exposure (less than 10 to 15 minutes per day) or living in higher latitudes in winter months, are advised to ingest the higher dose of 1000 IU per day.<sup>[12]</sup>

### Adults

The main causes of vitamin D deficiency in adults are inadequate sun exposure, insufficient supplementation, pregnant/lactating, and obesity. Illnesses that are associated with vitamin D deficiency in adults include autoimmune diseases (such as rheumatoid arthritis [RA], diabetes, inflammatory bowel syndromes, and multiple sclerosis [MS]), hyperparathyroidism, low bone density, cardiovascular disease, and cancer.<sup>[1,2,12,15]</sup>

**Autoimmune Diseases.** Autoimmune diseases are associated with vitamin D deficiency due to lack of suppression of Th1 cells that are misdirected against self proteins.<sup>[15]</sup> In adults, we see this with RA, MS, and IBS. It is common to find serum deficiencies in these patients.<sup>[12,15]</sup>

**Hyperparathyroidism.** Low levels of serum vitamin D and calcium result in stimulation of the release of parathyroid hormone (PTH). As deficiency progresses, the parathyroid is overstimulated and causes secondary hyperparathyroidism. This release of PTH causes an increase in the metabolism of 25-OHD to 1,25 dihydroxyvitamin D, and this further exacerbates vitamin D deficiency.<sup>[1,12,15]</sup> This release of PTH also results in phosphatemia, low levels of serum phosphorus that cause diminished mineralization of the collagen matrix, resulting in osteomalacia, and eventually osteoporosis.

**Low Bone Density.** Low bone density is common in adults. The clinical criterion for low bone density is a bone mineral density that is a t-score of more than 1 but less than 2.5 standard deviations (SDs) below the mean for young adults measured via dual-energy x-ray absorptiometry (DEXA). To put this into perspective, osteoporosis is valued at a t-score of 2.5 SD or more below the mean for young adults.<sup>[16]</sup> If a patient has low bone mineral density, he or she is at a greater risk of fracture, primarily hip and vertebrae. Greater than 33.6 million Americans have low bone density, and 80% of those people are women.<sup>[16]</sup> A meta analysis of 25 trials involving postmenopausal women showed that vitamin D supplementation (300-2000 IU daily) reduced the risk of vertebral fracture.<sup>[16]</sup> Vitamin D supplementation can help decrease the incidence of low bone density and, in turn, fractures.

**Cardiovascular Disease.** As in most cells, there are vitamin D receptors in the heart muscle. Because of these receptors, vitamin D is reported to be involved in the pathogenesis of many cardiovascular problems.<sup>[17]</sup> Vitamin D has been found to affect cardiac contractility, vascular tone, cardiac collagen content, and cardiac tissue maturation.<sup>[18]</sup> Vitamin D has also been found to play a vital role in the renin angiotensin aldosterone system, and vitamin D deficiency has been connected to end-stage renal disease and cardiac disease. Maintaining adequate levels of vitamin D can help delay the progression of cardiac disease and renal disease.<sup>[18]</sup>

**Cancer.** There are vitamin D receptors in brain, prostate, breast, and colon tissues.<sup>[1]</sup> These vitamin D receptors are a "critical determinant of the ability of proliferating cells to regulate their response to various stimuli."<sup>[1,19]</sup> Recent studies have shown a correlation between serum 25 (OH)D levels and breast and colorectal cancer. It has been documented that patients with the highest serum vitamin D levels had a 50% reduced risk of breast and colorectal cancer.<sup>[19,20]</sup> A serum level of 52 ng/mL was associated with the greatest risk reduction of breast cancer. In colorectal cancer, it has been found that a serum 25(OH)D level of 34 ng/mL can reduce the incidence by half, and at serum levels of 46 ng/mL, the risk of colorectal cancer can decrease by two thirds.<sup>[16]</sup> These serum levels could be obtained through a daily intake of 2000 IU of vitamin D<sub>3</sub> through diet in addition to sun exposure of 10 to 15 minutes per day.<sup>[20]</sup>

**Recommendations.** Adults are recommended to maintain a serum 25(OH)D level between 30 and 60 ng/mL. As the research shows, the higher the level, the lower the risk for autoimmune deficiency, hyperparathyroidism, low bone density, cardiovascular disease, and cancer. Women are especially encouraged to maintain higher serum levels due to their risk for osteoporosis post-menopause. A dietary intake of between 1000 to 2000 IU/day of vitamin D<sub>3</sub> is recommended.<sup>[1,20]</sup> This intake can be obtained through diet, supplements, and sun exposure. Practitioners must assess risks of malabsorption such as obesity and darker skin pigmentation; patients having these risk factors may require higher dosages through supplements, as they do not absorb vitamin D from UVB radiation.

### Pregnant and Lactating Women Vitamin D Levels

It is important to examine vitamin D levels during pregnancy, as it has been found that deficiency in maternal vitamin D can affect the fetus. Low maternal serum vitamin D has been associated with infantile rickets, low birth size, poor childhood growth, and later risk of hip fracture as the children mature into older adults.<sup>[14,21]</sup> In utero and early-life vitamin D deficiency has been linked to type one diabetes mellitus<sup>[22]</sup> and asthma.<sup>[23]</sup>

If mothers are pregnant or lactating, they need more vitamin D for themselves and their fetus/infant. To maintain the recommended serum 25(OH)D levels of above 30 ng/mL, a pregnant or lactating woman requires 1000 to 2000 IU of vitamin D<sub>3</sub> per day. This is especially important in women living in higher latitudes during the fall and winter

months, as they do not get adequate sun exposure.<sup>[1]</sup> Infants who are breastfeeding without supplementation or with inadequate sun exposure are recommended to receive 400 to 1000 IU of vitamin D<sub>3</sub> per day.<sup>[1,12]</sup>

### Older Adults

Older adults need to maintain serum 25(OH)D levels at 30 to 60 ng/mL.<sup>[2,12]</sup> When deficient in vitamin D, the older adult can have all of the problems previously discussed, including cardiovascular disease, cancer, autoimmune deficiencies, low bone density, and more. In addition to these disease processes, older adults with vitamin D deficiency are at risk for osteoporosis, increased falls, and periodontal disease.

**Osteoporosis.** As previously noted, decreased serum vitamin D causes decreased levels of calcium and phosphorus. The lower amount of vitamin D, calcium, and phosphorus results in demineralization of the collagen matrix of the bone. Approximately 33% of women 60 to 70 years of age and 66% of women over 80 years of age have osteoporosis.<sup>[24]</sup> In addition, 47% of women and 22% of men 50 years or older will sustain an osteoporotic fracture in their remaining lifetime.<sup>[1,24]</sup> Optimal prevention of nonvertebral and hip fractures occurred when serum 25(OH)D levels are at 40 ng/mL.<sup>[12]</sup> To maintain the recommended level of above 30 ng/mL for older adults, they must consistently take dietary supplementation of vitamin D along with calcium.<sup>[1]</sup>

**Fall Risk.** Vitamin D is associated with fall risk due to receptors on skeletal muscle. In addition, vitamin D's role in calcium homeostasis results in a direct effect between vitamin D levels and muscle strength.<sup>[1,25]</sup> Muscle performance speed and proximal muscle strength showed great improvement when serum 25(OH)D increased from 16 ng/mL to 40 ng/mL.<sup>[12]</sup> In a meta-analysis of 5 randomized trials, it was shown that increased vitamin D intake reduced the risk of falls by 22%.<sup>[12]</sup> In a randomized control study over a 5-month period in a nursing home, it was shown that residents receiving 800 IU of vitamin D per day plus calcium had a 72% reduction in the risk of falls as compared to placebo.<sup>[26]</sup> It is clear through this research that vitamin D supplementation can help in decreasing the risk of falls in the elderly population.

**Periodontal Disease.** Periodontal disease is the leading cause of tooth loss in older adults. This inflammatory disease causes loss of periodontal attachment, including ligaments and alveolar bone.<sup>[23]</sup> Poor bone quality is thought to be a risk factor of periodontal disease, and it has been shown that vitamin D supplementation can reduce tooth loss.<sup>[23]</sup> Elevated serum 25(OH)D levels through vitamin D and calcium supplementation has been shown to decrease tooth loss and may reduce periodontal disease.<sup>[27]</sup>

## Clinical Implications

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### Dietary Intake

In clinical practice, nurse practitioners can recommend diets that are higher in vitamin D. These foods include milk fortified with vitamin D, fortified cereals, and oily fish. Oily fish are the best sources of vitamin D. A key point with these fish is that there is a difference in vitamin D content in farm-raised versus wild fish.<sup>[28]</sup> The only cooking style that affected vitamin D content was frying in vegetable oil, which significantly reduced the vitamin D content ( Table 1 , Table 2 ).

**Table 1. Vitamin D Content in Fish<sup>[28]</sup>**

Type of Fish	IUD of Vitamin D per 3.5-oz. Serving
Farmed salmon	249
Wild salmon	981
Bluefish	415
Mahi	342

Swordfish	447
Cod	80
Farmed trout	371

**Table 2. Effect of Cooking on Vitamin D Content in Farmed Salmon<sup>[28]</sup>**

Cooking Style	IU of Vitamin D per 3.5 oz. Serving
Raw	274
Microwaved	272
Baked	248
Fried	142

In comparison to fish, milk provides 97.60 IU of vitamin per 8-ounce serving; therefore, 2 servings of milk a day will provide approximately 200 IU of vitamin D.<sup>[19]</sup> While these foods are helpful in maintaining adequate levels of vitamin D, daily supplementation is still recommended to ensure consistency in serum vitamin D levels.

### Supplementation

Current research has determined that the daily recommended intake for most people is 1000 IU.<sup>[1,2,11,12]</sup> Supplementation of vitamin D can be obtained through daily multivitamins in addition to diet. The average daily adult multivitamin contains 400 IU of vitamin D. Children's vitamins vary their formularies between 200 to 400 IU per tablet or teaspoon. Depending on the patient's diet and the formulary of their multivitamin, practitioners can recommend 1 to 3 vitamins daily, 1 vitamin every 8 to 12 hours. If the patient presents with a frank insufficiency (serum level less than 10 ng/mL) they can be treated with a prescription of vitamin D<sub>2</sub> 50,000 IU once per week for 6 to 8 weeks, with serum levels drawn afterward to ensure a level greater than 32 ng/mL.<sup>[2]</sup>

### Medications That Prevent Vitamin D Absorption

There are multiple drugs prescribed on a regular basis in primary care that can inhibit the absorption of vitamin D. These medications include anticonvulsants, thiazide diuretics, corticosteroids, nicotine, cimetidine, cholesterol-lowering agents (ezetimibe), heparin, and diet agents (Xenical and Alli) ( Table 3 ).

**Table 3. Medications That Prevent Vitamin D Absorption**

Medication	Effect
Anticonvulsants: (phenytoin, carbamazepine, Phenobarbital)	Induce hepatic p450 enzymes to accelerate the catabolism of vitamin D <sup>[29]</sup>
Thiazide diuretics	Metabolized by hepatic p450 enzymes, can accelerate the catabolism of vitamin D
Corticosteroids	Metabolized by hepatic p450 enzymes, can accelerate the catabolism of vitamin D
Nicotine	Metabolized by hepatic p450 enzymes, can accelerate the catabolism of vitamin D

Cholesterol-lowering medications: (Cholestyramine, colestipol, ezetimibe)	By blocking the absorption of lipids in the intestines, these medications also block the absorption of vitamin D and other fat-soluble vitamins
Cimetidine	Metabolized by hepatic p450 enzymes, can accelerate the catabolism of vitamin D
Heparin	Metabolized by hepatic p450 enzymes, can accelerate the catabolism of vitamin D
Diet agents (xenical, Alli)	While blocking the absorption of fat in the intestines, this medication also blocks the absorption of vitamin D and other fat-soluble vitamins

## Summary

Vitamin D deficiency affects people of all races, age, religions, and regions of the world. If practicing in an area of northern latitude, it is important to help patients understand that sun exposure in the winter does not provide vitamin D absorption. In addition, use of sunscreen greater than SPF 8 will block the absorption of vitamin D. While sunscreen is important to prevent skin cancer, patients who obtain 15 minutes of sun exposure 2 to 4 days week without sunscreen can increase their vitamin D levels.

Recommendations from 1997 for vitamin D intake are 200 IU/day for young adults, 400 IU/day for ages 51 to 70, and 600 IU for those greater than 70 years of age.<sup>[12]</sup> It has been shown that to maintain adequate serum levels of vitamin D requires higher daily intake. Through current research, it has been determined that the average recommended supplement intake is 1000 IU of vitamin D3 daily for all ages.<sup>[12]</sup> Vitamin D supplements are relatively safe. To reach vitamin D toxicity, the serum 25(OH)D has to be at 150 ng/mL or above—this serum level would require supplementation greater than 10,000 IU.<sup>[10]</sup> Vitamin D affects disease processes in the heart, muscle, lungs, skin, bones, and GI tract. In clinical practice, it is important to encourage vitamin D supplementation daily for all patients.

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