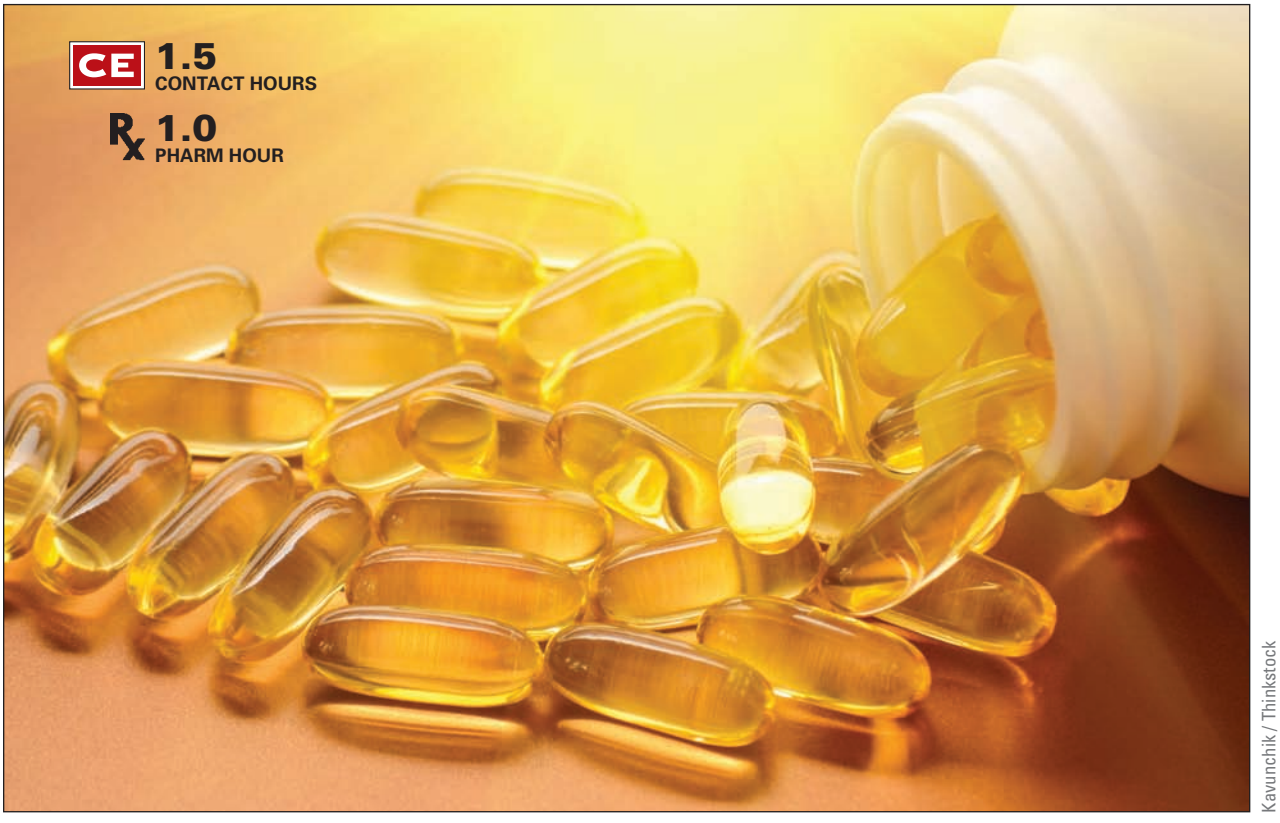

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Implications of vitamin D toxicity & deficiency

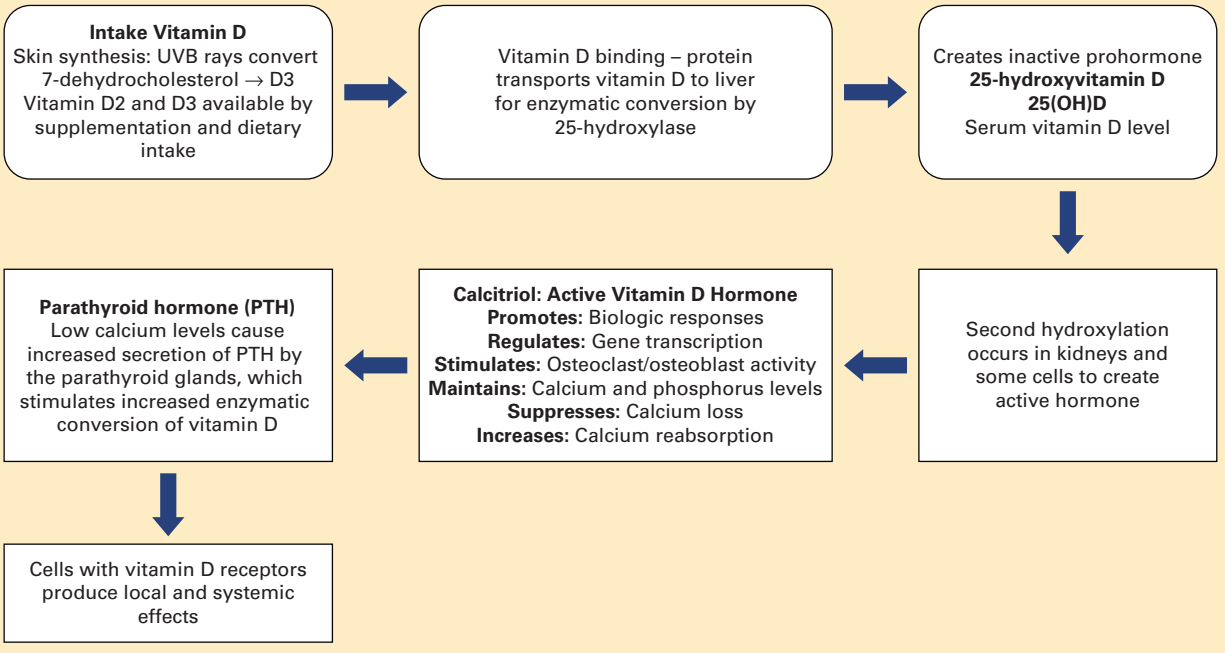
Abstract: Vitamin D deficiency is an increasing problem affecting all ages. Patients should be assessed for risk factors as part of preventive health maintenance. Vitamin D toxicity is a rare occurrence caused by oversupplementation and errors in food fortification. The connection between vitamin D deficiency and osteoporosis, is well established. However, a cause and effect relationship has yet to be established between vitamin D deficiency and many chronic illnesses. An evidence-based approach is treating patients for an underlying vitamin D deficiency in hopes of improving many chronic illnesses.

By Susan Waterbury, MSN, FNP-BC, ACHPN

Interest in vitamin D has increased, making it one of the most studied vitamins in the 21st century. There has been a rise in vitamin D testing and supplement sales, with supplement sales reported at $713 million in 2013.[1] Vitamin D has well-known benefits to the musculoskeletal system. However, the association of vitamin D with other disease processes remains less clear. Vitamin D has been promoted for use in nonmusculoskeletal diseases, such as dementia, obesity, and diabetes. Many diseases are associated with low vitamin D levels, yet a causative role has yet to be established. This introduces the possibility that a deficient vitamin D level may also represent a biomarker for overall poor health. Treatment

Keywords: calcitriol, cholecalciferol, hypercalcemia, vitamin D3, vitamin D deficiency, vitamin D toxicity

Metabolic conversion of vitamin D to calcitriol[3,5]



of the underlying vitamin D deficiency improves the outcomes of chronic illness.

Self-medicating with megadoses of vitamin D can lead to toxicity, with the risk of life-threatening hypercalcemia. A patient may present with vague symptoms in early vitamin D toxicity; prompt diagnosis and treatments decrease morbidity and mortality.[2]

Types of vitamin D

Vitamin D2 and D3 are most commonly used for supplementation and fortification. Ergocalciferol (vitamin D2) is derived from plant-based sources and irradiation of yeast and mushrooms. Cholecalciferol (vitamin D3) is synthesized by irradiation of lamb's wool and the extraction of fat. Vitamin D2 is available by prescription, whereas vitamin D3 is not. Both vitamins D2 and D3 are available over the counter in varying oral formulations.

Vitamin D3 is also produced by the skin; 7-Dehydrocholesterol is a sterol in the skin that is converted to cholecalciferol by ultraviolet B (UVB) waves.[3] Cutaneous synthesis of vitamin D is estimated to account for 80% to 100% of vitamin D intake. The amount of UVB ray absorption varies according to latitude, season, month, cloud cover, and skin pigmentation, and is affected by the ozone layer.[4] Dietary intake of vitamin D3 is in animal-based foods (such as fatty fish and sardines) or via fortification of foods (such as milk, yogurt, and tofu).

Vitamin D2 and D3 are inactive compounds that must be enzymatically converted to 25-hydroxyvitamin D (25[OH]D). This occurs in the liver via a cytochrome P450 enzyme, 25-hydroxylase, and the hydroxylation forms 25(OH)D. A second hydroxylation occurs in the kidneys, producing the active vitamin D hormone, calcitriol (1,25-dihydroxyvitamin D [1,25$[OH]_2$D)]; see *Metabolic conversion of vitamin D to calcitriol*). Cells with vitamin D receptors (VDRs) have the ability to convert 25(OH)D to calcitriol, which is a local effect that does not increase circulating vitamin D levels.[5]

Calcitriol is chemically similar to steroid hormones such as estradiol, testosterone, aldosterone, and cortisol. Specifically, the body can create these hormones, and they share the ability to bind with a target receptor to produce a biologic response.[6]

Calcitriol promotes biologic responses in bone, circulation, and in cells that contain the VDR. It stimulates osteoclast and osteoblast activity and reabsorption of calcium into the bones. Calcitriol suppresses calcium loss in the kidneys by increasing calcium reabsorption; calcitriol stimulates the intestinal absorption of calcium and phosphorus.[3,5]

In conjunction with the parathyroid glands and parathyroid hormone (PTH), calcitriol maintains calcium and phosphorus homeostasis. In response to low calcium levels, the parathyroid glands are signaled to produce increased PTH, which stimulates the kidneys to increase production of the active vitamin D metabolite and conserve calcium. Calcium levels in the body are closely regulated by controlling factors and feedback mechanisms.[3]

Recommended daily intake

One difficulty in establishing the recommended daily intake (RDI) for vitamin D is the lack of ability to predict how much vitamin D an individual receives from sun exposure.[7] The variables that affect UVB ray absorption include latitude, altitude, skin color (darker skin requires more exposure), time of day, season, age (older skin is less efficient at conversion), the use of sunscreen, and shielding or coverings.[7]

The Institute of Medicine's (IOM's) RDI for most adults is 600 international units (IU) a day, which increases to 800 IU in individuals over age 70 years. The upper level of safe intake for adults is 4,000 IU daily.[8] The American Geriatrics Society recommends vitamin D and calcium supplementation for community-dwelling older adults age 65 and older to reduce the risk of fractures and falls.[9] Dietary reference intakes for calcium and vitamin D vary according to age and gender. Supplementation is recommended for pregnant women and breast-fed infants. Human breast milk does not contain sufficient levels of vitamin D (see *Dietary reference intakes for calcium and vitamin D*).

The U.S. Preventive Services Task Force (USPSTF) does not recommend sun exposure to treat vitamin D deficiency due to the risk of skin cancer.[10] Tanning beds are not acceptable sources of vitamin D, as they deliver both UVB and UVA rays. The UVA rays do not provide vitamin D conversion yet increase risk of cancer.

Nutritional sources of vitamin D

The natural sources of vitamin D are limited and few. They are animal based, with fatty fish as the best

Dietary reference intakes for calcium and vitamin D

	Calcium			Vitamin D		
Life stage group	Estimated average requirement (mg/day)	Recommended dietary allowance (mg/day)	Upper level intake (mg/day)	Estimated average requirement (IU/day)	Recommended dietary allowance (IU/day)	Upper level intake (IU/day)
Infants 0 to 6 months	*	*	1,000	**	**	1,000
Infants 6 to 12 months	*	*	1,500	**	**	1,500
1-3 years old	500	700	2,500	400	600	2,500
4-8 years	800	1,000	2,500	400	600	3,000
9-13 years old	1,100	1,300	3,000	400	600	4,000
14-18 years old	1,100	1,300	3,000	400	600	4,000
19-30 years old	800	1,000	2,500	400	600	4,000
31-50 years old	800	1,000	2,500	400	600	4,000
51-70 years old males	800	1,000	2,000	400	600	4,000
51-70 years old females	1,000	1,200	2,000	400	600	4,000
>70 years old	1,000	1,200	2,000	400	800	4,000
14-18 years old, pregant/lactating	1,100	1,300	3,000	400	600	4,000
19-50 years old, pregant/lactating	800	1,000	2,500	400	600	4,000

*For infants, adequate intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age.
**For infants, adequate intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age.
Reprinted with permission from the National Academies Press, Copyright 2018, National Academies of Sciences. www.nationalacademies.org/hmd/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx.

source. A serving of salmon provides between 600 and 1,000 IU of vitamin D, while an egg yolk provides 40 IU, and tofu supplies around 100 IU. The majority of vitamin D obtained nutritionally comes from fortified foods.[11] Some commonly fortified foods include milk, margarine, cheese, and cereal. Meeting vitamin D requirements through diet alone is difficult.

Measurement of vitamin D levels

Serum 25(OH)D levels represent the total vitamin D intake by both sun exposure and oral intake of vitamin D2 or D3. Lab measurement of calcitriol is not used to diagnose vitamin D deficiency due to its short half-life and close regulation via parathyroid glands. Calcitriol levels may be at a normal range until the deficiency is severe.[11]

Vitamin D levels are reported in two different measures: ng/mL and nmol/L (most commercial labs use the ng/mL measure; see *Serum 25(OH)D level categories.*)

Serum 25(OH)D level categories[11,43*,45]

Category	National Institutes of Health	Endocrine Society
Deficiency	<12 ng/mL	<20 ng/mL
Insufficiency	12 to <20 ng/mL	21 to 29 ng/mL
Sufficiency	≥20 ng/mL	≥30 ng/mL
Excess	>50 ng/mL	>100 ng/mL

* Vitamin D intoxication may be linked to serum 25(OH)D levels greater than 150 ng/mL.

Vitamin D intoxication and toxicity

Vitamin D intoxication is measured as an elevated 25(OH) D level, and toxicity is determined by the dosage ingested. Severe intoxication may lead to toxicity. Toxicity also relates to poisoning. Vitamin D toxicity causes hypercalcemia and potential acute kidney injury. Key diagnostic findings in vitamin D intoxication include elevated 25(OH)D and calcium levels. Hypercalcemia at levels above 14 mg/dL causes adverse reactions, including fatalities from calcium's effects on cardiac, central nervous system, and kidney function.

Mild hypercalcemia may be asymptomatic, whereas chronic hypercalcemia can lead to vascular or soft tissue calcifications. Signs and symptoms of hypercalcemia include nausea, vomiting, constipation, loss of appetite, abdominal pain, polyuria, thirst, somnolence, metallic taste, muscle or bone pain, hematuria, nephrolithiasis, pruritus, and muscle weakness. Late findings include confusion, psychosis, cardiac dysrhythmias, hyperthermia, hypertension, and coma.[12]

The diagnosis of vitamin D intoxication is derived from the history, physical, and diagnostic findings. Self-administration of vitamin D supplements is the primary cause of toxicity, which should be identified in the history. Physical exam findings may include lethargy, abdominal pain, muscle or bone pain, skin excoriations, and weight loss. The diagnostic findings for vitamin D intoxication include 25(OH)D greater than 150 ng/mL and calcium levels between 12 and 16 mg/dL. Other findings can include an elevated blood urea nitrogen, elevated creatinine level, elevated phosphorus level, hypercalciuria, low PTH, ECG changes including a shortened QT interval and atrioventricular block, calcium deposits, and/or bony abnormalities on X-ray.[12]

Treatment of vitamin D intoxication

Treatment considerations for vitamin D intoxication include the patient's comorbidities, age, duration, and severity of hypercalcemia. Treatment approaches include discontinuing calcium and vitamin D intake, low calcium diet, isotonic I.V. fluids (usually 0.9% sodium chloride to maintain a urine output of at least 100 mL/hour), calcitonin, bisphosphonates, and corticosteroids. Calcitonin and bisphosphonates inhibit bone resorption and circulatory release of calcium. Corticosteroids (prednisone) reduce the production of calcitriol, which decreases calcium reabsorption in the kidneys.

Judicious use of loop diuretics for hypercalcemia may be considered in hypercalcemic patients with heart and kidney failure. Due to potential adverse reactions, use of this treatment is limited. Calcium levels at 14 mg/dL or greater can cause a hypercalcemic crisis in which dialysis and bisphosphonates are lifesaving treatments.[12]

Risk factors for vitamin D deficiency

Risk factors cause increased demands or utilization of vitamin D and interfere with the intake or absorption. Risk factors also lead to decreased bioavailability of the active vitamin D compound, leading

to hypovitaminosis D. Any patients with risk factors should be tested for serum 25(OH)D and calcium levels. Pertinent risk factors include liver or kidney disease, pregnancy, breast-fed infants, reduced sun exposure (sunscreen and clothing), malabsorption, poor nutritional intake, drug interactions, highly pigmented skin, geographic location, age, and high body mass index (BMI; see *Risk factors for vitamin D deficiency.*)

Vitamin D deficiency is common among Black individuals, as this population has lower 25(OH)D levels as compared with White individuals; this may be due to a genetic variation in the vitamin D–binding protein.[13] Assays that measure the bioavailable 25(OH)D should be developed along with genotype-specific standards.[13] Due to test variability, necessity, and cost, routine testing for vitamin D levels in the general population (without risk factors) is not recommended.[10] Patients with comorbidities or malabsorption may require higher doses to achieve vitamin D sufficiency.

Cellular and immune system effects

In addition to its known role in calcium regulation, vitamin D is becoming known for its effects on the immune system. Calcitriol has a downregulating effect on the renin-angiotensin system (RAS) and inflammatory cytokines.[14] Inflammation is stimulated by a low vitamin D level, which may explain why so many patients with chronic illnesses are vitamin D deficient. The inhibiting effect of calcitriol on RAS and inflammation has led to speculation regarding possible cancer-fighting properties of vitamin D.[14]

Vitamin D plays a role in the innate and adaptive immune systems, with vitamin D synthesis occurring at a cellular level. Vitamin D has a protective effect on immune system function and has historically been used for the treatment of diseases such as tuberculosis and leprosy.[15]

VDRs have been found in many cells, such as monocytes, macrophages, and dendritic cells. Macrophages, when challenged with a pathogen, have been shown to increase production of calcitriol, with resultant antimicrobial effects. Extrarenal production of calcitriol was first discovered in patients with sarcoidosis, which causes increased cellular production of calcitriol via macrophages.[15]

Calcitriol inhibits growth and promotes differentiation. It exerts an anti-inflammatory effect by reducing production of inflammatory cytokines. Calcitriol has protective effects on the kidneys and the cardiovascular system by modulating the RAS.[15] Calcitriol works with PTH to stimulate reabsorption of calcium into bone and acts in the kidneys to increase tubular reabsorption of calcium. Increased calcitriol stimulates the parathyroid glands to reduce the secretion of PTH; decreased levels cause elevation of PTH, leading to secondary hyperparathyroidism.

Risk factors for vitamin D deficiency[11,44]

Risk factors	Considerations
Reduced sun exposure	Sunscreen, clothing/veiling, decreased outdoor activities, darker skin color, higher latitude, sun avoidance, skin cancer
Liver and kidney disease	Decreased synthesis of active vitamin D metabolite
Older age	Decreased ability of skin to convert UVB rays, decreased appetite, increased kidney or liver disease
Malabsorption	IBD, cystic fibrosis, gastric bypass
Poor nutritional intake	Lack of supplemented foods (milk), poor appetite, plant-based diet
Pregnancy or breast-fed infant	Vitamin D deficiency occurs in antenatal, pregnant, and lactating women and is associated with poor maternal outcomes (human milk does not meet daily requirements)
Obesity	Vitamin D is fat soluble and is sequestered into adipose tissue, decreasing bioavailability
Drug interactions	Antiepileptic drugs, corticosteroids, cholestyramine

Rickets and osteomalacia

Rickets is a childhood illness that causes bony deformities due to a defect in bone calcification and mineralization.[16] In the late 17th century, an increase in rickets was noted in crowded, polluted cities such as London and New York due to overpopulation, residences built close to each other, poverty, and the burning of coal and wood (which blocked sun exposure). Rickets is secondary to a deficiency of vitamin D and calcium and causes bowed legs, knock-knees, and pelvic and spinal and chest deformity.[16] Even with sufficient vitamin D, adequate calcium intake is needed to build bones.

Vitamin D deficiency causes osteomalacia, a softening of the bones in adults with fused growth plates.

Malabsorptive illness caused by gastric bypass surgery or inflammatory bowel disease (IBD) increases the risk of vitamin D deficiency and subsequent osteomalacia. Patients with epilepsy on antiepileptic drugs are at increased risk for drug interactions, causing low vitamin D levels.[17]

Symptoms of osteomalacia are vague and may be mistaken for diseases such as fibromyalgia, dysthymia, degenerative joint disease, arthritis, and chronic fatigue syndrome. Patients may present with a dull, unrelenting, aching sensation in the bones. A helpful diagnostic sign is the application of minimal pressure over the sternum, anterior tibia, or radius and ulna, causing disproportionate pain. Patients with nonspecific musculoskeletal pain who do not respond to usual treatment methods may be vitamin D deficient.[18] Without treatment, osteomalacia can lead to bony demineralization and osteoporosis.

Weight-bearing and resistance exercise is needed to build strong bones. Vitamin D helps regulate bone reabsorption, calcium levels, and exerts a local effect in many cells. Other factors that affect bone health include calcium intake, PTH, phosphorus and magnesium levels, and genetics. Immobility contributes to bone loss. Older adults and disabled or bedridden patients are at increased risk for bone loss, resulting in demineralization and osteoporosis.

Diabetes mellitus

Researchers studied the association between inflammation, in patients with type 1 diabetes mellitus (T1DM), and the effects of calcitriol on diabetic nephropathy and proteinuria. In this prospective study, 31 patients with T1DM with microalbuminuria were enrolled, along with 30 healthy patients as controls. Patients with diabetes may have a high incidence of vitamin D deficiency and higher levels of circulating markers of inflammation, including C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, and interleukin-6 (IL-6). The patients with T1DM who were vitamin D deficient were given calcitriol 0.25 mcg/daily and were followed for 6 months. There was a decrease in inflammatory markers (high-sensitivity CRP, TNF-alpha, IL-6) in the treatment group with lower rates of proteinuria. Improvement in diabetes control was not seen in the treatment group. This suggests that improvements noted were caused by the downregulation of inflammation. Decreased levels of inflammatory cytokines were seen, and proteinuria was reduced. No significant change to glucose metabolism or pancreas beta-cell function was noted.[19]

Fifty children ages 10 to 16 years with metabolic syndrome were given vitamin D3 (300,000 IU capsule) once weekly. Serum insulin, lipid profile, fasting blood glucose, vitamin D level, and BP were monitored. Serum triglycerides and serum insulin levels showed a decrease; however, no significant differences were found for cholesterol, glucose, or BP.[20]

A 24-week study of patients (ages 30 to 69 years) with type 2 diabetes mellitus (T2DM) who were vitamin D deficient received vitamin D3 (1,000 IU) with elemental calcium 100 mg twice daily. Hemoglobin A1C, glucose, and insulin resistance were measured along with anthropometrics. Supplementation of vitamin D had no effect on the glucose control of patients with T2DM with vitamin D deficiency.[21]

Neurologic system

Research findings suggest that vitamin D may play a role in brain function and development and vitamin D deficiency may be associated with neurologic disorders.[22-25] A neuroprotective role of calcitriol is suggested.[25] The presence of vitamin D metabolites, enzymes, and VDRs indicates that vitamin D, like other neurosteroids, is important for maintaining brain functions.[23] Vitamin D plays a crucial role in the functions of neurons and affects the synthesis of neurotransmitters, such as acetylcholine, catecholamines, serotonin, and dopamine.[25]

Patients with vitamin D deficiency have increased risks for all-cause dementia and Alzheimer disease through both vascular and neurodegenerative pathways.[25] Vitamin D lab testing is recommended for individuals diagnosed with psychiatric and neurologic disorders, with resultant supplementation when indicated.[23]

Cardiovascular disease

Vitamin D deficiency is a risk factor for cardiovascular disease (CVD). There is a seasonal increased incidence of CVD in the winter that correlates with lower vitamin D levels. There is some evidence that vitamin D may help maintain lower BP.[26] The vitamin D treatment dose, most commonly 400 IU daily, did not show a significant difference in BP readings.[26]

Cardiomyocytes, vascular cells, phagocytes, and renin-producing renal cells contain the VDR, indicating

a response to calcitriol.[27] The proposed mechanisms of how vitamin D may improve CVD outcomes include suppression of the renin-aldosterone system, effects on the vasculature, improved glycemic control, and the reduction of inflammatory cytokines.[26] An increase in systolic BP was associated with low vitamin D levels.[28]

The association between vascular function, vitamin D deficiency, and CVD risk was evaluated in a cross-sectional, observational study. The 554 community-based subjects (ages 20 to 79 years) free from acute illness were recruited and underwent lab testing, including serum 25(OH)D testing and vascular testing. Serum 25(OH)D levels were noted to be lower in Black or Hispanic individuals, and those with diabetes and/or hypertension. The research suggests that improvement in vitamin D status improves vascular function.[29]

Symptoms of osteomalacia may be mistaken for diseases such as fibromyalgia, dysthymia, arthritis, and chronic fatigue syndrome.

Fifty newly diagnosed hypertensive patients (with a mean age of 49 years) were divided into three groups according to their BMI. Lab measurements of vitamin D, plasma renin, and aldosterone levels were assessed. These lab findings were correlated with BMIs and BP readings. The group with vitamin D levels greater than 30 ng/mL had lower BP measures as well as lower measures of renin and aldosterone. The active vitamin D metabolite appears to downregulate renin. The association between vitamin D deficiency, hypertension, obesity, and RAS activation requires further delineation.[30]

Mortality and cancer

Supplementation with vitamin D appears to be associated with decreased cancer mortalities. Insufficient vitamin D levels are associated with increased mortality for patients with breast and colon cancer.[31,32] A meta-analysis reviewed randomized control trials regarding cancer incidence, mortality, and the effects of vitamin D supplementation. The researchers noted a lack of trials with cancer incidence or mortality as the primary end points.

Vitamin D in doses of 400 to 1,100 IU had negligible effects on the incidence of cancer over 2 to 7 years. However, the effect of vitamin D on cancer mortality was statistically significant at a 12% decrease.[33,34] A higher vitamin D level is associated with a lower death rate in patients with colorectal and breast cancer.[31,32]

Respiratory infection and asthma

Patients with vitamin D deficiency are more susceptible to respiratory infections. Vitamin D has a protective effect against respiratory tract infection. There appears to be a beneficial effect of vitamin D and respiratory disease prevention.[35,36] Reduced risk of asthma exacerbation is associated with higher 25(OH)D levels. A meta-analysis reviewed vitamin D daily doses of 500 to 2,000 IU administered to pediatric patients with asthma and found vitamin D therapy reduced asthma exacerbation. This may be due to the association of vitamin D with a decrease in respiratory infections.[37]

IBD

A high incidence of vitamin D deficiency is seen in patients with IBD. Patients with ulcerative colitis and Crohn disease who are vitamin D deficient have worse outcomes. An increased risk of hospitalization and surgery was found in patients with IBD who were vitamin D deficient.[38]

A study of vitamin D and Crohn disease failed to reach statistical significance until the 25(OH)D levels reached 40 ng/mL. This required doses up to 5,000 IU of vitamin D daily. A significant improvement in quality of life and disease activity was noted.[39]

Older adults, physical performance, and falls

Older adults have an increased risk of vitamin D deficiency due to age-related decreases in kidney function. The skin is not as efficient in producing vitamin D3, and nutritional status is often not optimal. Vitamin D deficiency causes low bone mass and predisposes older adults to fragility fractures and osteoporosis.

Older adults are at a higher risk for falls due to visual impairment, decreased muscle strength, disturbed gait and balance, and medication adverse reactions. An individual who is vitamin D deficient is at higher risk for falling. Beneficial effects on strength and balance were found with vitamin D daily doses of 800 to 1,000 IU.[40]

The vitamin D (800 IU daily) reduced hip fracture risk by 30% and showed a 14% reduction in nonvertebral fracture risk.[41] It was unclear what role calcium supplementation played to reduce fractures. Fracture prevention was not shown consistently in patients taking vitamin D alone.

A decrease in fractures was seen with sufficient serum 25(OH)D levels in older men. Muscle strength of the lower legs show positive effects of vitamin D supplementation.[42] Serum 25(OH)D levels were correlated with physical performance levels in older adults over a 3-year period. Physical performance was measured with a walking test, sit-to-stand tests, and the ability to stand with one foot in front of the other.

The findings of the physical performance tests were correlated with vitamin D levels. The subjects who had low levels of vitamin D were at higher risk for physical decline and falls. Vitamin D levels of 20 ng/mL or higher was protective against falls.[42] The American Geriatrics Society recommends a serum 25(OH)D level of 30 ng/mL should be the minimum goal to achieve in older adults especially those at increased risk for falls.[9] The USPSTF recommends vitamin D supplementation for any patient at risk for falls.[10]

Implications for NP practice

Vitamin D deficiency is a widespread problem affecting all age groups. Patients with risk factors for vitamin D deficiency should have serum 25(OH) D levels done as part of annual preventive health maintenance. If testing is not available, prescribing doses from the IOM's RDI is a safe approach.

Due to low risk of toxicity in standard doses, follow-up testing in 4 to 6 months will evaluate dosage efficacy. Certain drugs can interfere with vitamin D absorption, such as corticosteroids, orlistat, cholestyramine, antiepileptic drugs, and antituberculosis drugs. Patients with certain comorbidities such as IBD may need doses up to 5,000 IU daily. Some patients may need multiple dosage adjustments and testing to achieve sufficiency. Specific dose levels are variable and should be assessed before prescribing.

Vitamin D2 and D3 are both indicated to treat vitamin D deficiency. Treatment doses should be individualized according to risk factors and response. NP

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The authors and planners have disclosed no financial relationships related to this article.

DOI-10.1097/01.NPR.0000531916.07387.d4

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