Anticancer Effects of Vitamins

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Abstract

Vitamin D is a precursor to the potent steroid hormone calcitriol, which mediates numerous actions in the body. Vitamin D can be synthesized in adequate amounts in the skin using the energy of ultraviolet radiation in sunlight. There are few dietary sources of vitamin D unless they are fortified; therefore, humans are dependent on sunlight to maintain adequate vitamin D stores. Unfortunately, many people do not receive adequate sunlight. High serum vitamin D levels among adult populations are associated with a substantial decrease in cardiovascular disease, cancer, type 2 diabetes, and metabolic syndrome. This article reviews the relationship between vitamin D and cancer, as well as current clinical guidelines for the diagnosis and management of vitamin D deficiency.

Keywords: Falls, fractures, bone, immunity, sarcopenia, gait, outcomes, mortality, survival, neoplasia, breast, colorectal, prostate, leukemia, muscle, neuromuscular, vitamin D receptor, disease-free survival.

Introduction

Vitamin D status has become a public health concern in the United States over the past several years due to an increasing number of reports of vitamin D deficiency.[1,2] Although vitamin D could be synthesized in adequate amounts in the skin using the energy of ultraviolet radiation, limited exposure and northern latitudes result in inadequate synthesis.[3] The identification of vitamin D receptors (VDRs) in most tissues indicates an expanded role of vitamin D beyond the classic actions of maintaining bone health.

Vitamin D is a precursor to the potent steroid hormone calcitriol, which mediates numerous actions in the body. Vitamin D can be synthesized in adequate amounts in the skin using the energy of ultraviolet (UV) radiation in sunlight. There are few dietary sources of vitamin D unless they are fortified; therefore, humans are dependent on sunlight to maintain adequate vitamin D stores.[1] Unfortunately, many people do not receive adequate sunlight due to indoor occupations; avoidance of sunlight; use of sunscreen; northern latitudes with low levels of sunlight, especially in winter; and having dark skin that blocks the rays of the sun.

High serum vitamin D levels among adult populations are associated with a substantial decrease in cardiovascular disease, cancer, type 2 diabetes, and metabolic syndrome.[4-6] Although an association between low vitamin D levels and these diseases has been established, there are no prospective studies. In addition, vitamin D levels may reflect polymorphisms in vitamin D transport and VDRs, so it may not be that straightforward to infer that vitamin D replacement will improve clinical outcomes or survival.

Herein, we review the relationship between vitamin D and cancer, as well as current clinical guidelines for the diagnosis and management of vitamin D deficiency.

Vitamin D Metabolism

Cholecalciferol or vitamin D_3, is the precursor to the steroid hormone calcitriol. Ultraviolet rays convert the substrate 7dehydrocholesterol to vitamin D_3 in the skin.[2] Hydroxylation in cytochrome P450 converts vitamin D_3 to its hormonal form, calcitriol (1,25 dihydroxyvitamin D_3 = $1,25(OH)_2D$).[7] The first hydroxylation step occurs in the liver to yield 25hydroxyvitamin D_3 (25(OH)D), which is catalyzed by the enzyme vitamin D-25hydroxylase (predominantly CYP2R1).[8] Hydroxyvitamin D is measured in the blood and clinically used to determine vitamin D status. The second hydroxylation occurs at the kidney, where circulating $25(OH)D_3$ is hydroxylated at the C1α position by the cytochrome P450 enzyme CYP27B1 (1αhydroxylase) to produce calcitriol (1,25 (OH)2 D3)[7] (**Figure 1**).

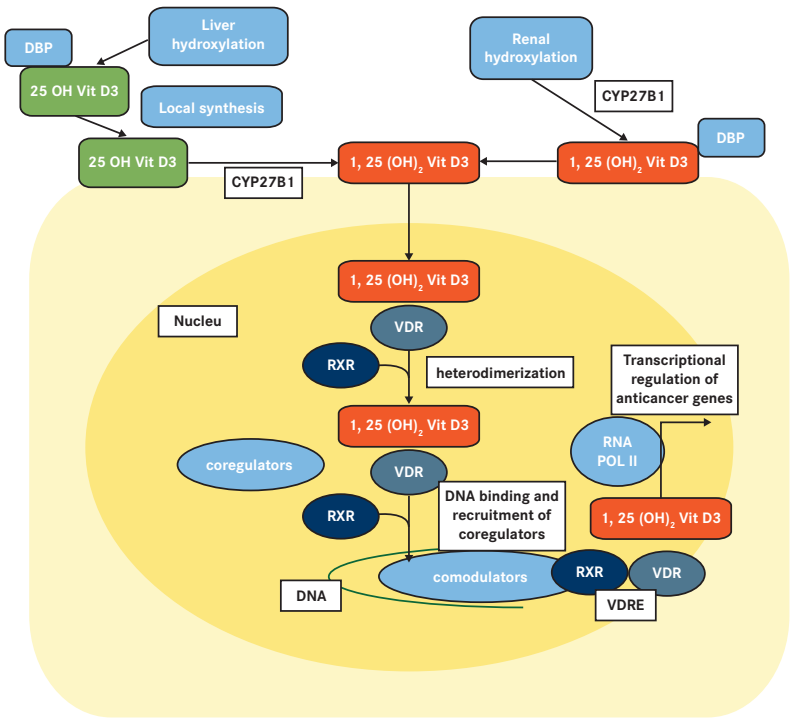
Calcitriol functions by binding to and activating the nuclear VDR, which is a member of the steroid–thyroid–retinoid receptor superfamily of ligand-activated transcription factors. Vitamin D receptor is present in most cells in the body,[9] and calcitriol directly or indirectly regulates as much as 3% to 5% of the human genome. Vitamin D activity is widespread, and it exerts actions that can alter the defenses of the body.[9-11] Vitamin D activity can limit the development of multiple diseases, including cancer.[1,12-21] The 24-hydroxylase, or CYP24A1, is induced by calcitriol and is of particular importance; it encodes the enzyme that catalyzes the degradation of $1,25(OH)_2D$ and $25(OH)D$.[21] The activity of the hormone is self-regulated because it concurrently induces its

own inactivation. The administration of supraphysiologic concentrations of calcitriol results in the development of hypercalcemia, mainly due to the actions of calcitriol stimulating intestinal calcium absorption. Current research efforts strive to develop a calcitriol analog with anticancer effect but less hypercalcemia.[3]

Regulation of Vitamin D

Three calcitriopic hormones regulate renal CYP27B1 and CYP24A1—calcitriol, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23)—which are involved in mineral and skeletal homeostasis.[22,23] Although the kidney is the major source of circulating calcitriol, CYP27B1 is also expressed in multiple extrarenal sites, including cancer cells, where it can exert anticancer actions.[24] Calcitriol can function in an endocrine manner, or in an intracrine, autocrine, or paracrine manner when it is synthesized locally. In contrast to the renal enzyme, extrarenal CYP27B1 is not regulated by the calciotropic hormones but by other factors.[23-26] The presence of CYP27B1 in cancer cells suggest that dietary vitamin D might be used in cancer therapy and exert anticancer effects. Dietary vitamin D is ultimately converted to 1,25(OH)2D, resulting in high local concentrations without the concern about developing hypercalcemia.

FIGURE 1. Calcitriol Action Through VDR and Its Antineoplastic Actions



Calcitriol and 25 hydroxyvitamin D3 (25(OH)D3) circulate bound to vitamin D binding protein (DBP). The biologically available molecules enter the target cells. Calcitriol is derived by cellular conversion from 25(OH)D3 by the P450 enzyme CYP27B1 and by renal synthesis. Actions of calcitriol are mediated by the vitamin D receptor (VDR). Calcitriol bound to VDR causes dimerization with the retinoid X receptor (RXR) and translocates to the nucleus. The VDR-RXR complex binds to vitamin D response elements (VDREs) in multiple regulatory regions located in promoters of target genes or at distal sites. The recruitment of co-activators or co-repressors leads to positive or negative transcriptional regulation of gene expression.
Source: Jones G, Prosser DE, Kaufmann M. Cytochrome P450-mediated metabolism of vitamin D. *J Lipid Res.* 2014;55(1):13-31.

CYP24A1 and CYP27B1 Expression in Cancer

A high basal expression level of the enzyme CYP24A1 occurs in several cancer cells, thereby making them resistant to calcitriol action.[27,28] Spontaneous upregulation of CYP24A1 is seen in some cancers, which correlates with poor clinical outcome.[27] Inhibition of CYP24A1 function amplifies the biological activity of calcitriol; indeed, the use of cytochrome P450 inhibitors, such as ketoconazole,[29] liarazole,[30] and genistein,[31] increases the biological actions of calcitriol, and can cause calcitriol-resistant cells to revert to sensitive cells.[30,31] Genistein is present in currants (2167 mg), raisins (1458 mg), prunes (661 mg), plums (550 mg), strawberries (457 mg), passion fruit (403 mg), mango (212 mg), and soy products (100 mg).[32] However, the combination with CYP24A1 inhibitors not only increases the anticancer actions of calcitriol, but also augments its hypercalcemic effects, increasing the risk of hypercalcemia.[33] Thus, a cautious approach is necessary when using these combinations.

Data on CYP27B1 expression and activity in cancer are more varied.[3] The regulation of CYP27B1 in cancer cells might depend on the tissue and the tumor stage. The expression of CYP27B1 expression is dependent on the degree of cellular differentiation, being greatest in well differentiated tumors than in poorly differentiated tumours.[34] Thus, the reduction in CYP27B1 expression that is seen in some cancer cells[35,36] or that is experimentally induced might endow these cells with a growth advantage because of the decrease in the local production of calcitriol, thereby decreasing an inhibitor of proliferation.[35]

Epidemiology

In 1980, an epidemiologic study suggested a relationship between vitamin D and cancer. It was recognized that death rates for colon cancer were higher with increasing latitude and decreasing

TABLE 1. Mechanisms of Calcitriol Anticancer Effects

Proliferation	Increase in p21 and p27 expression[116]
	Decrease in CDKs, cyclins, MYC and RB expression[117]
Apoptosis	Increase in BAX[118]
	Decrease in BCL-2[119]
	Increased sensitivity to radiation and chemotherapy[120]
Differentiation	Myeloid leukemia cells differentiate into monocytes[121]
	Increased expression of differentiation factors such as casein, lipids, PSA, E-cadherin[82,83]
Inflammation	Inhibition of expression of COX2, PG receptors, stress kinase, and NF-κB signaling[12,122]
	Increased TIMP 1 and E-cadherin response[123]
Invasion and metastasis	Decreased expression of MMP9, α6 integrin, ·4 integrin, plasminogen activator[123]
Angiogenesis	Decreased HIF1 α, VEGF, IL-8, tenascin C, PGE2 levels[124]

CDK indicates cyclin-dependent kinase; COX2, cyclooxygenase 2; HIF1 α, hypoxia inducible factor 1alpha; IL-8, interleukin 8; MAPKP5, mitogen activated protein kinase phosphatase 5; MMP9, metalloproteinase 9 ; NF-κB, nuclear factor κB; PG, prostaglandin; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PGE, prostaglandin E; POL II, polymerase II; PSA, prostate-specific antigen; TIMP1, tissue inhibitor of metalloproteinase 1; VEGF, vascular endothelial growth factor.
Adapted from Feldman D, Krishnan AV, Swami S, et al. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer.* 2014;14(5):342-357.

sunlight.[37] Later, an inverse relationship between 25 (OH)D_3 levels and the incidence of colon cancer was ascertained.[38] A similar relationship between vitamin D levels and fatal breast and prostate cancer has been suggested.[39,40] Genetic variants of VDR may modify the associations between vitamin D exposure and breast cancer risk.[41]

Association studies have mostly been observed for colorectal cancer.[42] Meta-analyses show a 30% to 40% reduction in colorectal cancer risk in those with high 25(OH)D levels as compared with those with low 25(OH)D_3 levels, after adjustment for known risk factors.[43] A meta-analysis of 11 prospective studies evaluating vitamin D intake or vitamin D levels, conducted in the United States, Europe, and Asia, demonstrated that vitamin D intake and blood 25(OH)D levels are both inversely associated with risk of colorectal cancer, with a pooled relative risk of 0.88 and 0.67, respectively.

In breast cancer, controversy exists with a dose–response meta-analysis of plasma 25(OH)D levels that identified an inverse association beyond a threshold of 27 ng/mL, flattening beyond 35 ng/mL, and only seen in postmenopausal women.[45] In a recent meta-analysis, women with the highest quartile of circulating 25(OH)D level at diagnosis showed a 37% reduced risk for all causes of death compared with those who had the lowest quartile. Patients with breast cancer with the highest quartile of circulating 25(OH)D level had a 35% reduced risk for cancer-specific mortality, and 58% had better disease-free survival (DFS) compared with those with the lowest quartile of 25(OH)D level.[46] More recent consortium studies confirm the association with higher breast cancer risk, but not with prostate cancer.[47-50]

Vitamin D polymorphisms have been identified in men with more advanced prostate cancer at diagnosis; BsmI, Apa I, and Taq I are associated with high Gleason score with an overall summary odds ratios of 1.12.[51] Zhang et al[52] assessed 40 studies and identified that polymorphisms of VDR such as the FF genotype illustrated a protective effect on prostate cancer in the Caucasian subgroup (odds ratio [OR] = 0.905); conversely, the bb and the TT genotypes were associated with increased risk of prostate cancer (OR = 1.127).

Primary prevention clinical trials currently under way include the VITamin D and omega-A3 triaL (VITAL) study, which is investigating whether daily dietary supplements of vitamin D (2000 IU/day) or omega-3-fatty acids reduce the risk of developing cancer, heart disease, or stroke (ClinicalTrials.gov Identifier: NCT01169259).[4]

Anticancer Effect of Vitamin D

Some of the common mechanisms underlying anticancer effects of calcitriol include antiproliferative effects by calcitriol inhibiting the mitogenic signaling by growth factors, such as IGF-1, by increasing the expression of IGF-1 binding protein, epidermal growth factor, and an increase in growth inhibitors such as TGF-β. Calcitriol increases the expression of cyclin-dependent kinase (CDK) inhibitors p21 and p27, decreasing CDK activity and arresting the cell cycle.[53] Calcitriol induces apoptosis by activating of intrinsic pathways of apoptosis through suppression of apoptosis-specific genes such as BCL-2.[54] Calcitriol induces cell-specific pro-differentiation mechanisms such as regulation of β catenin, JUN N-terminal kinase, and NFκB signaling pathways.[10] Calcitriol inhibits angiogenesis by suppression of the expression of vascular endothelial growth factor (VEGF) through transcriptional repression of hypoxia-inducible factor 1 alpha and IL-8 in an NF-κB–dependent manner.[55] VDR null mice have increased expression of pro-angiogenic factors such as HIF1α, VEGF, angiopoietin 1, and platelet-derived growth factor (PDGF) in tumors.[56] Calcitriol has a direct antiproliferative action on tumor-derived endothelial cells.[56] Calcitriol has anti-inflammatory effects suppressing cyclooxygenase 2 (COX-2) and prostaglandin,[12] and NF- κB signaling[55] (**Table 1**).

Vitamin D acts as an antiproliferative agent in cancer. The antiproliferative effect of 1,25 $(OH)_2D$ was first demonstrated in hu-

TABLE 2. Association Between Vitamin D and Overall and Cancer-Specific Mortality

Type of Study	Overall Mortality	Cancer-Specific Mortality	Disease-Free Survival	BC Recurrence
Meta-analysis in BC	HR, 1.52; 95% CI, 1.22-1.88.[125]	HR, 1.74; 95% CI, 1.23- .40.[125]		
Prospective cohort study in BC	HR, 1.58; 95% CI, 1.00-2.39[126]		HR, 2.05; 95% CI, 1.29-3.41[126]	HR, 1.14; 95% CI, 1.05-1.24[126]
Cohort study in BC, CC, LC, and lymphoma:	Comparing highest 25(OH)D quartiles with lowest quartiles: BC: HR, 0.42; 95% CI, 0.21-0.82 CC: HR, 0.37; 95% CI, 0.08-1.81 LC: HR, 0.18; 95% CI, 0.11- 0.29 Lymphoma: HR, 0.39; 95% CI, 0.18-0.83[127]	Comparing highest 25(OH)D quartiles with lowest quartiles: BC: HR, 0.41; 95% CI, 0.32-0.72 CC: HR, 0.20; 95% CI, 0.20 95% CI 0.04-1.10 LC: HR, 0.20; 95% CI, 0.11-0.29 Lymphoma: HR, 0.3;9 95% CI, 0.18- 0.83[127]		
Meta-analysis in BC		Comparing highest 25(OH)D quartile with lowest quartile: BC: Pooled OR=0.56; P <.0001[64]		
Meta-analysis in CC		Comparing highest quintile to lowest quintile: pooled OR=0.63; P<.0001[84]		
Meta-analysis in BC and CC	Comparing highest quartiles with lowest quartiles: CC: pooled OR=0.71; 95% CI, 0.55-0.9. BC: pooled OR=0.62; 95% CI, 0.49-0.78[128]	Comparing highest quartiles with lowest quartiles: CC: pooled OR=0.65; 95% CI, 0.49-0.85 BC: pooled OR=0.58; 95% CI, 0.38-0.84[128]		
Large prospective study in BC		BC: Mortality highest in lowest and highest tertile of 25(OH)D T1: HR, 2.46; 95% CI, 1.38-4.37 T3: HR, 1.99; 95% CI, 1.14-3.49[129]		

BC indicates breast cancer; CC, colon cancer; CI, confidence interval; HR, hazard ratio; LC, lung cancer; OR, odds ratio; PC, prostate cancer.

man cancer cells in 1981. Breast cancer cells can be inhibited by 1,25 $(OH)_2D$. Growth of MCF-7 cells was significantly inhibited by $1,25(OH)_2D$ and 4 vitamin D analogs—Ro 23-7553, Ro 24-5531, Ro 25-5317, and Ro 24-5583—at 10^{-8} M ($P < .05$).[57] The presence of extra-renal 1alpha-hydroxylase has been reported in several cell types, including prostate and colon cancer cells. The mRNA for 1alpha-hydroxylase has been detected in breast cancer tissue and in MCF-7 breast cancer cells. Interestingly, the mRNA levels for 1alpha-hydroxylase were significantly increased in breast cancer compared with normal breast tissue. When the MCF-7 cells were treated with $1\text{-}25(OH)_2D$, cell proliferation was inhibited in a dose-dependent manner. Incubation of the MCF-7 cells with [3H]-25(OH)D resulted in its conversion to $[3H]\text{-}1,25(OH)_2D$. Breast cancer cells expressed 1alpha-hydroxylase mRNA, and, therefore, might have the ability to synthesize $1,25(OH)_2D$ within the cells. The local production of $1,25(OH)_2D$ has been shown to regulate the proliferation and differentiation of breast cells. Alterations in the local production of $1,25(OH)_2D$ plays a role in the tumorigenesis of breast cancer.[58]

Vitamin D analogs have cytotoxic effects on cancer cells. Pretreatment of MCF-7 and Hs578T cells with the vitamin D analogs substantially potentiated the cytotoxic effects of TNF α. Potentiation by CB1093 of TNF α-induced apoptosis in MCF-7 cells was accompanied by increased activation of cytosolic phospholipase A2 and arachidonic acid release, which was partially

TABLE 3. Causes of High Risk for Vitamin D Deficiency in Individuals

Rickets	Some lymphomas
Osteomalacia	Medications
Osteoporosis	Anticonvulsant medications
Chronic kidney disease	Glucocorticoids
Hepatic failure	Antifungals
Malabsorption syndromes	AIDS medications
Radiation enteritis	Older adults with history of falls
Inflammatory bowel disease	Older adults with history of fractures
Bariatric surgery	Granuloma-forming disorders
Hyperparathyroidism	Tuberculosis
African-American and Latino children and adults	Sarcoidosis
Obese children and adults	Histoplasmosis

Source: Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health in Cancer Care. *J Natl Compr Canc Netw.* 2009;7 Suppl 3:S1-32; quiz S33-35.

inhibited by a specific cPLA2 inhibitor. The broad-spectrum caspase inhibitor z-VAD-fmk prevented TNF α, but not CB1093 mediated cell death and activation of cPLA2. Serum starvation-induced apoptosis was accompanied by cPLA2 activation, which was inhibited by IGF-I and by z-VAD-fmk. However, the ability of these agents to suppress cPLA2 activation was abrogated by co-treatment with CB1093, suggesting a role for arachidonic acid release in the caspase-independent mechanism by which vitamin D analogs prevent the protective effects of IGF-I on breast cancer cell survival.[59]

Calcitriol Effect on Outcomes in Breast, Prostate, and Colon Cancer

Calcitriol effect on breast cancer. The combinations of gefitinib with calcitriol or its analogs were more effective to inhibit cell growth than each compound alone in all breast cancer cells studied.[60] The gene expression of *EGFR* and *HER2* was downregulated and not affected, respectively, by the combined treatment. Furthermore, phosphorylation of ERK 1/2 was inhibited to a greater extent in co-treated cells than in the cells treated with alone compounds. The combination of gefitinib with calcitriol or their synthetic analogs resulted in a greater antiproliferative effect than with either of the agents alone in *EGFR*- and *HER2*-positive breast cancer cells.[60] Calcitriol was able to induce the expression of a functional ERα in estrogen receptor negative breast cancer cells. This effect was mediated through the VDR, since it was abrogated by a VDR antagonist. Interestingly, the calcitriol-induced ERα restored the response to antiestrogens by inhibiting cell proliferation. In addition, calcitriol-treated cells in the presence of ICI-182,780 resulted in a significant reduction of two important cell proliferation regulators CCND1 and EAG. Calcitriol decreased PGE2, a major stimulator of aromatase transcription in breast cancer cells.[61]

The combination of calcitriol and an estrogen antagonist may be a novel combination for treatment of breast cancer.[62] A meta-analysis of 26 studies suggests that circulating 25-OH(D) levels may be associated with better prognosis in patients with breast and colorectal cancer, but there is a paucity of information on its association with prognosis in other cancers.[63] A meta-analysis of 6 studies revealed that high serum 25(OH)D was associated with lower mortality from breast cancer. Recommendations were that serum 25(OH)D in all patients with breast cancer should be restored to the normal range (30 ng/mL-80 ng/mL), with appropriate monitoring.[64]

Calcitriol Actions on Prostate Cancer

Gonadal action on prostate cancer cells is mediated through androgen receptor (AR)-mediated events. There is cross-talk between calcitriol and androgen signaling in some cancer cells. Actions of calcitriol include upregulation of the AR, and other androgen-responsive genes.[65-68] Conversely, VDR is regulated by androgens, and there is induction of a gene expression pattern consistent with differentiation, and growth inhibition and the regulation of genes involved in androgen catabolism. Calcitriol induces an increase in androgen-stimulated prostate-specific antigen (PSA) expression,[69] as well as an increase in androgen-inducible growth inhibitor AS3 (APRIN).[70] Calcitriol induces the differentiation of prostate cell progenitor into AR+ luminal epithelial cells.[71] In castration-sensitive cells, a vitamin D analog may prolong the effectiveness of androgen-deprivation therapy.

Calcitriol Action on Colon Cancer

One of the key pathways disrupted in colon cancer is the wnt/β-catenin signaling pathway, often regarded as part of the initial event leading to colon cancer.[73] In colon cancer, the wnt/β-catenin pathway is disrupted due to mutations in β-catenin or APC.[74] These mutations prevent the phosphorylation of β-catenin and contribute to its accumulation in the cytosol of the cells; unphosphorylated β-catenin is then able to migrate and accumulate in the nucleus.[75] In the nucleus, β-catenin dimerizes with DNA-bound T-cell factor (TCF) 1–4, which leads to the expression of genes (eg, *c-myc*, *cyclin D1*) capable of inducing the transformation of normal cells into an oncogenic phenotype.[76-78] Recent research has suggested that components of the vitamin D pathway can modulate the unregulated wnt/β-catenin signaling.[79] Calcitriol inhibits β catenin pathway, VDR binding to β-catenin inhibits β-catenin nuclear translocation, and increases levels of extracellular wnt inhibitors DICKKOPF1 and DICKKOPF4.[80,81] Calcitriol regulates RHOA-ROCK-p38

MAPK-MSK pathway resulting in an increase in E-cadherin.[82] Calcitriol increases E-cadherin and sequestration of β catenin at the membrane.[83]

Data suggest that higher 25(OH)D levels at the time of diagnosis and treatment may improve survival from multiple cancers,[84,85] and conversely, low 25(OH)D levels are associated with higher risk of death in some studies.[86] Dietary and supplemental vitamin D may have beneficial effects on patients with cancer (**Table 2**), so we will review clinical guidelines regarding vitamin D supplementation

Vitamin D Guidelines

Guidelines for the management of postmenopausal osteoporosis were published in 2010 by the American Academy of Clinical Endocrinology.[87] Its recommendations included ensuring sufficiency of vitamin D among children and adults. Most individuals being treated for osteoporosis have serum 25(OH)D levels that are lower than desirable.[88] Vitamin D is not widely available in natural food sources.[87] For adults age 50 years or older, the National Osteoporosis Foundation recommends 800 IU to 1000 IU of vitamin D per day.[89] A review of studies assessed diverse outcomes such as bone mineral density (BMD), lower extremity function, dental health, risk of falls, fractures, cancer prevention, incident hypertension, and mortality.[90] For all endpoints, levels in the deficient range (<50 nmol/L; <20 ng/mL) are associated with no benefit or adverse effects, while the most advantageous serum levels for 25(OH)D appeared to be close to 75 nmol/L (30 ng/mL). An intake of 800 IU (20 mcg) of vitamin D_3 (cholecalciferol) per day for all adults may bring 97% of the population to a level of at least 50 nmol/L and about 50% up to 75 nmol/L.[90] Many authorities recommend 1000 IU to 2000 IU per day (4000 IU/day is the "safe upper limit"[91]), and some patients require higher supplementation to achieve desirable levels.

It is advisable to assess vitamin D levels in individuals with cancer treatment-induced bone loss (CTIBL) with breast and prostate cancer. Additionally, patients with cancer who will receive antiresorptives (bisphosphonates and RANKL binders) for treatment of skeletal metastasis will benefit from having 25(OH) D levels above between 30 mL and 80 ng/mL.

Home-bound individuals with limited mobility, patients who have intestinal malabsorption, or those who are receiving long-term anticonvulsant or glucocorticoid therapy are particularly at risk for vitamin D deficiency. The currently accepted minimal level for 25(OH)D adequacy is 30 ng/mL to 32 ng/mL, on the basis of a growing body of evidence indicating that secondary hyperparathyroidism is increasingly common as 25(OH)D levels decline below
30 ng/mL,[92] and that fractional calcium absorption improves with vitamin D supplementation in patients with levels below 30 ng/mL, but not in patients with levels above 30 ng/mL. A reasonable upper limit, based on levels in sun-exposed healthy young adults, is 60 ng/mL.[93]

A meta-analysis of studies in postmenopausal women found a significant reduction in hip and nonvertebral fractures with vitamin D supplementation at dosages of 700 IU to 800 IU per day or more.[94] In addition to the skeletal effects of vitamin D, studies have shown a decreased risk of falling,[95-97] as well as improvement in survival.[98]

Vitamin D supplements are available as ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) in strengths up to 50,000 IU per tablet. With daily dosing, vitamins D_2 and D_3 appear to be equally potent,[99] but with intermittent (weekly or monthly) dosing, vitamin D_3 appears to be about 3 times more potent than vitamin D_2.[100] Blood levels of 25(OH)D provide the best index of vitamin D stores. A desirable range is between 30 ng/mL and 60 ng/mL. Some individuals may require vitamin D supplements of 2000 IU per day or more to achieve desirable levels. (Vitamin D_3 1000 IU daily will raise blood levels, on average, by approximately 10 ng/mL.)

The Endocrine Society published guidelines for the management of vitamin D deficiency in 2011.[101] The diagnostic recommendation included: (1) screening for vitamin D deficiency in patients at high risk (**Table 3**); and (2) 25(OH)D should be used to evaluate vitamin D status in patients at risk. Vitamin D *deficiency* is defined as a 25(OH)D below 20 ng/mL (50 nmol/L), and vitamin D *insufficiency* as a 25(OH)D of 21 ng/mL to 29 ng/mL (525 nmol/L-725 nmol/L). Serum $1,25(OH)_2D$ should not be used for this purpose. However, widespread screening has not been advocated. Discrepancy occurs regarding vitamin D deficiency cutpoints, with the Institute of Medicine setting it at 20 ng per mL (50 nmol/L)[91] and the Endocrine Society, at 30 ng per mL (75 nmol/L).[91,101]

Recommended Dietary Intakes of Vitamin D for Patients at Risk for Vitamin D Deficiency

The intake of vitamin D in adults age 19 years and older at risk of deficiency is recommended to be above 600 IU to 800 IU daily. The National Comprehensive Cancer Network (NCCN) bone health guidelines note that expert opinion on supplementation for adults older than age 50 years is 1200 mg of calcium (from all sources) and 800 IU to 1000 IU of vitamin D daily, and recommends these ranges for younger patients at risk for CTABL.[102] In individuals ages 50 to 70 years and age 70+ years, the recommendations are that they consume 600 IU to 800 IU of vitamin D daily in order to maximize bone and muscle health. Among those age 65 years and older, 800 IU daily is recommended in order to prevent falls and fractures. However, to raise the level above 30 ng/mL may require at least 1500 IU to 2000 IU per day.[101]

Obese adults (body mass index >30 kg/m^2) are at high risk for vitamin D deficiency because the body fat sequesters the fat-soluble vitamin. When obese and nonobese adults were exposed to simulated sunlight or received an oral dosage of 50,000 IU of vitamin D_2, they were able to raise their blood levels of vitamin D by no more than 50% compared with nonobese adults.

Patients taking anticonvulsant medications, glucocorticoids, or AIDS treatment are at increased risk for vitamin D deficiency because these medications increase the catabolism of 25(OH)D.[2,103,104]; they should receive at least 2 to 3 times more vitamin D for their age group to satisfy their body's vitamin D requirement. The maintenance tolerable upper limit (UL) of vitamin D that should not be exceeded without a physician's supervision should be 4000 IU per day for individuals older than age 8 years.[101]

Treatment of vitamin D deficiency should involve vitamin D_2 or vitamin D_3 for the treatment and prevention of vitamin D deficiency. In adults who are vitamin D-deficient, treatment should include 50,000 IU of vitamin D_2 or vitamin D_3 once weekly for 8 weeks or its equivalent of 6000 IU of vitamin D_2 or vitamin D_3 daily to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 1500 IU to 2000 IU daily. 25(OH)D levels should be checked no earlier than 3 months after initiating therapy. In obese patients, patients with malabsorption syndromes, and patients taking medications affecting vitamin D metabolism (eg, corticosteroids), a higher dosage was advocated (2-3 times higher; at least 6000 IU to 10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a $25(OH)D_3$ level above 30 ng/mL, followed by maintenance therapy of 3000 IU to 6000 IU daily.[101] Vitamin D_2 is a form of vitamin D that is of plant origin, is derived from ergosterol, and functions much like vitamin D_3 but is less active. Assays measuring circulating blood vitamin D metabolites 25(OH)D and $25(OH)D_2$ do not distinguish the 2 forms, or they report the total.[3]

Vitamin D and Muscle Function

VDR has been identified in muscle cells.[105] Vitamin D deficiency may result in muscle weakness and an important loss of muscle mass.[106] Several studies have shown that vitamin D metabolites affect muscle cell metabolism through gene transcription, variation in the VDR allele, and rapid pathways not involving DNA synthesis.[105] Vitamin D exerts functions mediated by specific receptors in processes that range from protein synthesis to the kinetics of muscle contraction, with direct repercussions on the functional capacity of postmenopausal women. Vitamin D deficiency (< 20 ng/mL [50 nmol/L]) has been associated with increased body sway, and a level below 10 ng/mL (30 nmol/L) with decreased muscle strength.[107-111] Changes in gait, difficulties in rising from a chair, inability to ascend stairs, and diffuse muscle pain are the main clinical symptoms in osteomalacic myopathy. [107-111] Additionally, vitamin D supplements of 800 IU and 1000 IU daily resulted in a up to a 25% increase in lower extremity strength or function,[90,97] and up to a 28% improvement in body sway,[97,112,113] and a decrease in the rate of falls in vitamin-deficient older adults.[105,114]

Vitamin D and Chronic Kidney Disease

In chronic kidney disease (CKD) stages 3-5, the 1 α-hydroxylase enzyme is located primarily in the kidney, and nephrectomy or reduced kidney function equate with marked reduction in conversion of 25(OH)D to $1,25(OH)_2D$. However, the discovery of 1 α hydroxylase in the placenta, gastrointestinal tract, skin, blood vessels, and granulomatous tissue demonstrated that $1,25(OH)_2D$ production is not limited to the kidney. Although knowledge of the biological mechanisms of vitamin D for bone maintenance in individuals with all stages of CKD has expanded, no consensus currently exists within the medical community regarding methods for 25(OH)D supplementation or optimal 25(OH)D levels in individuals with CKD.[115]

Vitamin D Toxicity

As a lipid soluble vitamin, vitamin D can be stored in adipose tissue. Thus, there is concern about potential toxicity of vitamin D. The Endocrine Society guidelines comment that based on the available literature, vitamin D toxicity is rare, and may be caused by inadvertent or intentional ingestion of unusually high amounts of vitamin D. Therefore, vitamin D toxicity with supplementation within the levels recommended by guidelines should not be a major concern, except in certain populations who may be more sensitive. Patients with chronic granulomatous diseases such as sarcoidosis or tuberculosis, chronic fungal infections, or lymphoma may be at higher risk for this complication. Lymphoma may have activated macrophages that produce $1,25(OH)_2D$ in an unregulated fashion. The effect of elevated $1,25(OH)_2D$ is enhanced intestinal calcium absorption as well as increased mobilization of skeletal calcium. Thus, careful monitoring of such patients is generally recommended.[87]

In summary, calcitriol is associated with beneficial anticancer effects. It may be advisable to screen patients with cancer who are at high risk for vitamin D deficiency, and clinicians should identify and treat those patients with vitamin D deficiency.

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