

## Vitamin D

### Introduction

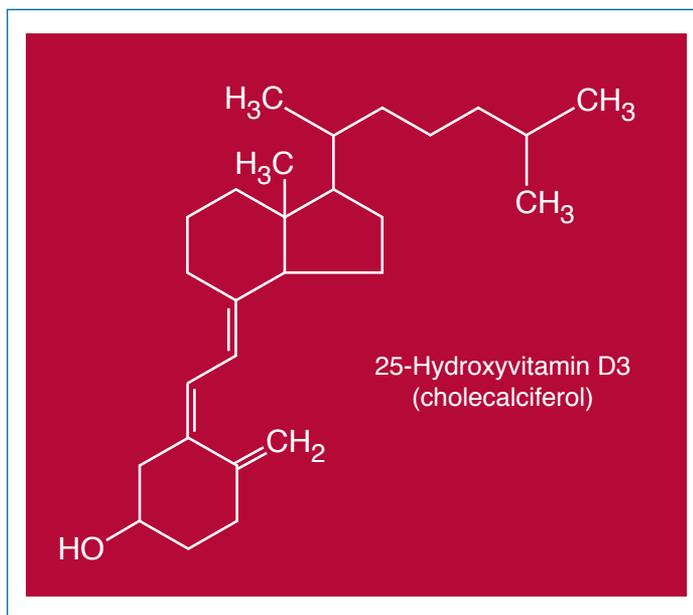
Vitamin D is a secosteroid molecule which, in its active 1,25 di-hydroxylated form, has hormone activities in humans. Most cells and tissues in the body have vitamin D receptors (VDRs) that stimulate the nuclear transcription of various genes to alter cellular function or provide a rapid response in cellular membranes. Vitamin D appears to have an effect on numerous disease states and disorders, including chronic musculoskeletal pain, diabetes (types 1 and 2), multiple sclerosis, cardiovascular disease, osteoporosis, and cancers of the breast, prostate, and colon.

According to many researchers there is currently a worldwide vitamin D deficiency in various populations, including infants, pregnant and lactating women, the elderly, individuals living in latitudes far from the equator, persons who avoid the sun or ultraviolet radiation in the blue spectrum (UVB), and populations with dark skin pigmentation. Vitamin D in the food supply is limited and most often inadequate to prevent deficiencies. Supplemental vitamin D is likely necessary to avoid deficiency in winter months; however, all forms of vitamin D supplementation may not be equal in efficacy for maintaining optimal blood levels.

### Biochemistry

Vitamin D's chemical structure is almost identical to cholesterol, except vitamin D has double bonds between C-7 and C-8, and C-10 and C-19, and an open B ring structure. The two forms of vitamin D utilized in the human body, D<sub>2</sub> and D<sub>3</sub>, begin with four intact rings. UVB, when at an adequate strength (18 mc/cm<sup>2</sup>) and particular wavelength (290-315 nm),<sup>1</sup> can alter the cholesterol-based precursor 7-dehydrocholesterol in human skin by breaking the bond between C-9 and C-10 of the B ring. Consequently, a double bond is formed between C-10 and C-19, making pre-vitamin D<sub>3</sub>. With naturally occurring thermogenic isomerization, a more open configured molecule is formed, termed D<sub>3</sub> (cholecalciferol). In a similar manner, lanolin is irradiated to form supplemental D<sub>3</sub>, while ergosterol from plant sterols or yeast can be irradiated to form supplemental D<sub>2</sub> (ergocalciferol).

Endogenously produced D<sub>3</sub> can travel to the liver via D-binding protein (DBP), while supplemented D<sub>2</sub> or D<sub>3</sub> is incorporated into micelles with dietary fats and the assistance of bile salts and primarily absorbed in the duodenum. D<sub>2</sub> and D<sub>3</sub> are transported in lymph via chylomicrons to the liver. Within the liver, the monooxygenase enzymes of the cytochrome P450 (CYP) family, and particularly CP27A1, add a hydroxyl group to C-25. This 25-hydroxyvitamin D<sub>3</sub> or D<sub>2</sub> (25(OH)D) can be further metabolized to the "active" or "hormonal" form of vitamin D with the hydroxylation of C-1 by CYP27B1 in the kidney to produce 1alpha25-dihydroxyvitamin D<sub>3</sub> or D<sub>2</sub> (1,25(OH)<sub>2</sub>D), also known as calcitriol. The conversion of D to 25(OH)D is not well regulated; however, the conversion to the active 1,25(OH)<sub>2</sub>D form is tightly regulated by parathyroid hormone (PTH) and low levels of calcium and phosphorus. PTH is released from the parathyroid gland in response to decreased calcium and/or elevated phosphorus levels. PTH stimulates the kidneys to increase calcium resorption and activate CYP27B1 to synthesize more 1,25(OH)<sub>2</sub>D.<sup>2</sup>



PTH also activates osteoblasts that facilitate the conversion of preosteoclasts to osteoclasts. Osteoclasts dissolve bone to free up calcium to negate the deficiency that originally activated the parathyroid gland to secrete PTH. Over-production of active vitamin D is inhibited by a negative feedback loop;  $1,25(\text{OH})_2\text{D}$  inhibits PTH, stimulates the release of fibroblast growth factor 23 (FGF23) from osteoblasts, and induces the enzyme CYP24A1. FGF23 reduces circulating phosphorus by altering kidney production of a sodium phosphorus co-transporter and inhibits the vitamin-D activating enzyme CYP27B1. CYP24A1 places a hydroxyl group on C-24 of  $1,25(\text{OH})_2\text{D}$ , allowing for its metabolism into calcitriol and excretion in the bile.<sup>2,3</sup>

### Pharmacokinetics

Due to its metabolism into many inactive and excretable forms, less than 25 percent of vitamin D becomes  $25(\text{OH})\text{D}$ .<sup>4</sup> Vitamin D is stored in both muscle and fat tissue, with vitamin  $\text{D}_3$  levels in the serum correlated to the amount of  $\text{D}_3$  in fat tissue.<sup>5</sup> Studies of radioactively labeled  $\text{D}_3$  find the whole body half-life of vitamin  $\text{D}_3$  molecules to be approximately 62 days.<sup>6</sup>

The potency of  $\text{D}_3$  or  $\text{D}_2$  is determined by the molecule's ability to raise  $25(\text{OH})\text{D}$  levels. Because of differences in chemical structure ( $\text{D}_2$  differs from  $\text{D}_3$  by having a methyl group attached to C-24 and a double bond between C-22 and C-23), vitamins  $\text{D}_2$  and  $\text{D}_3$  have similar but variable metabolism. In one study, 20 healthy males were given single 50,000-IU doses of either  $\text{D}_2$  or  $\text{D}_3$ , and serum levels of  $\text{D}_2$ ,  $\text{D}_3$ , as well as 25-hydroxylated versions of vitamins  $\text{D}_2$  and  $\text{D}_3$  were measured over a 28-day period. Although the two forms demonstrated similar rises in serum  $25(\text{OH})\text{D}$  levels over three days, the  $\text{D}_2$ -treated group experienced a rapid decline to baseline levels at day 14 and were well below baseline by day 28. By contrast,  $25(\text{OH})\text{D}$  levels in the  $\text{D}_3$ -treated group peaked at day 14 and remained significantly elevated throughout the study. As a result, the authors concluded, "The data presented in this paper indicate that the 50,000-IU dosage form of vitamin  $\text{D}_2$  should be considered to be equivalent to no more than 15,000 IU of vitamin  $\text{D}_3$  and perhaps closer to only 5,000 IU. In any event, the tolerable upper intake level, 2,000 IU/d published for vitamin  $\text{D}_3$ , and already judged to be set too low, ought not be applied to vitamin  $\text{D}_2$ ."<sup>7</sup>

According to a 2006 commentary in *American Journal of Clinical Nutrition*, studies have indicated vitamin  $\text{D}_2$  supplementation results in inferior elevation of  $25(\text{OH})\text{D}$  levels, decreased binding affinity to DBP in plasma, and a shorter shelf life. The authors Houghton and Vieth conclude by stating, "Vitamin  $\text{D}_2$ , or ergocalciferol, should not be regarded as a nutrient suitable for supplementation or fortification."<sup>8</sup>

### Mechanism of Action

Active  $1,25(\text{OH})_2\text{D}$  has both endocrine and autocrine hormone activity. It binds to vitamin D receptors in the nucleus of cells and, with a retinoid X receptor (RXR) partner, binds specific regions of DNA named vitamin D response elements (VDRE) located in the promoter region of genes. The heterodimeric group then allows the binding of co-activator protein complexes that link the RXR-VDR group to transcription start sites. With most human cells expressing VDRs,  $1,25(\text{OH})_2\text{D}$  has the potential to alter the function of most tissues in the body. The enzyme responsible for the rate-limiting step for the formation of  $1,25\text{D}$ , 1-alpha hydroxylase (CYP27B1), has been found in the pancreas, prostate, breast, macrophages, epidermis, parathyroid gland, and intestines. Other non-VDRE related interactions are being investigated.<sup>9</sup>

### Deficiency

Vitamin D status is determined by measuring serum  $25(\text{OH})\text{D}$ . Holick,<sup>10</sup> Vieth,<sup>11</sup> and Bischoff-Ferrari et al<sup>12</sup> agree a minimum  $25(\text{OH})\text{D}$  serum concentration of 30 ng/mL (75 nmol/L) appears necessary to experience the multitude of beneficial health effects of vitamin D. Cannell and Hollis<sup>13</sup> argue higher levels of >40 ng/mL may be needed, and persons with heart disease, MS, autism, diabetes, and cancer may benefit from >55 ng/mL serum  $25(\text{OH})\text{D}$  levels year round. Garland et al<sup>14</sup> estimates the risk for two common cancers could be reduced by 50 percent when levels of  $25(\text{OH})\text{D}$  are maintained at or above 34 ng/mL for colon cancer and 52 ng/mL for breast cancer.

Many researchers have concluded there is a worldwide epidemic of vitamin D deficiency. Of 28 studies assessing worldwide vitamin D status, Thailand was the only country that demonstrated a study population with mean serum values above 33 ng/mL.<sup>15</sup> As an

important hormone in the human body with receptors in a multitude of tissues, a lack of vitamin D can initiate, precipitate, and exacerbate a host of health disorders. Symptoms may manifest as inflammatory diseases, bone metabolism disorders, infectious diseases, and immunological imbalances. Dietary sources of vitamin D are inadequate to meet daily requirements. Therefore, the majority of the world's population relies on unimpeded skin exposure to UVB radiation to allow for endogenous production of vitamin D or vitamin D supplementation. Any factor that impedes the endogenous or exogenous absorption, formation, or transformation of this nutrient may contribute to deficiency.<sup>10,13</sup>

There are many potential barriers to UVB radiation reaching the skin in adequate amounts for photolysis to occur. Clothing,<sup>16</sup> dark skin pigmentation,<sup>17</sup> sunscreen,<sup>18</sup> air pollution, cloud cover, time of day, distance from the equator, and atmospheric ozone content can limit UVB photon strength or passage through the skin.<sup>19</sup> Elderly populations have lower levels of 7-dehydrocholesterol and many have limited exposure to adequate UVB radiation.<sup>20,21</sup>

Vitamin D is a fat-soluble nutrient absorbed primarily in the duodenum. Individuals with malabsorptive disorders of the small intestine, such as those with celiac disease,<sup>22</sup> cystic fibrosis,<sup>23,24</sup> and Crohn's disease,<sup>25</sup> or populations that have undergone gastric bypass surgery<sup>26,27</sup> may be at increased risk for vitamin D deficiency.<sup>28</sup> Obesity is also a risk factor for deficiency due to the inability of fat tissue to sequester vitamin D.<sup>29</sup> Vitamin D needs increase during pregnancy and lactation. Limited vitamin D passes through the breast milk. As a result, many pregnant women and their offspring are vitamin D deficient.<sup>30</sup>

The liver and kidneys play direct and indirect roles in vitamin D physiology; therefore, diseases of either organ can adversely affect vitamin D status.<sup>10</sup>

## Clinical Indications

### Osteoporosis/Fracture

Suboptimal calcium absorption, secondary hyperparathyroidism, increased bone resorption, decreased muscle strength, and increased risk of falling can be related to vitamin D deficiency/insufficiency, which in the elderly increases fracture risk.<sup>31</sup>

The number of falls experienced by elderly women in geriatric care was reduced 49 percent when they were given 800 IU vitamin D<sub>3</sub> and 1,200 mg calcium (as carbonate) for 12 weeks, compared to a control group receiving the same amount of calcium and no vitamin D.<sup>32</sup>

Vitamin D deficiency is common in patients with osteoporotic fractures, with two studies showing 95-97 percent of fracture patients being classified as vitamin D deficient.<sup>33,34</sup>

When 100,000 IU vitamin D<sub>3</sub> was given every four months to 2,686 community-living 65- to 85-year-old men and women, a 33-percent reduction in fractures was seen at the most common osteoporotic sites including hip, spine, wrist, and forearm over a five-year period.<sup>35</sup>

A meta-analysis of prospective cohorts and randomized trials found an average 25-percent risk reduction for non-vertebral and hip fractures when study subjects were given 700-800 IU of supplemental vitamin D per day. Results were consistent in the presence or absence of calcium supplementation beyond adequate dietary calcium intake. The authors concluded: "Thus, calcium additional supplementation may not be critical for non-vertebral fracture prevention once 700-800 IU of vitamin D are provided."<sup>36</sup>

Researchers in Iceland confirmed the importance of vitamin D in calcium homeostasis via its effect on PTH by saying: "Vitamin D may have a calcium sparing effect and as long as vitamin D status is ensured, calcium intake levels of more than 800 mg/day may be unnecessary for maintaining calcium metabolism."<sup>37</sup>

Vitamin D can have profound effects on osteoporosis; however, researchers were surprised to find that of 1,246 postmenopausal women taking pharmacological medication for osteoporosis therapy, 52 percent had serum 25(OH)D levels below 30 ng/mL, and 16.5 percent showed biochemical signs of secondary hyperparathyroidism.<sup>38</sup>

### Longevity/Anti-Aging

A recent meta-analysis of 18 randomized controlled trials examining data from 57,311 participants over a mean follow-up period of 5.7 years revealed a relative risk of mortality from any cause to be 0.93 (95% CI: 0.87-0.99) in the study groups that took supplemental vitamin D (mean daily dose was 528 IU) compared to groups without supplementation.<sup>39</sup>

Researchers studying serum values of vitamin D in 2,160 twins found higher vitamin D levels may alter telomere length of leukocytes. "The difference between the highest and lowest tertiles of vitamin D was 107 base pairs ( $p=0.0009$ ), which is equivalent to 5.0 y of telomeric aging." The authors go on to state that this finding "...underscores the potentially beneficial effects of this hormone on aging and age-related diseases."<sup>40</sup>

### Cardiovascular Disease

Hypertension, diabetes mellitus, obesity, and hyperlipidemia can lead to atherosclerosis and consequently fatal myocardial infarctions. Along with cerebrovascular disease, these health disorders are considered to be the most common contributing factors to death worldwide in both adult males and postmenopausal females. Secondary analysis of the Third National Health and Nutrition Examination Survey (NHANES III) found that participants with a serum 25(OH)D level of <21 ng/mL had a higher prevalence of diabetes mellitus (OR: 1.98), obesity (OR: 2.29), high serum triglycerides (OR: 1.47), and hypertension (OR: 1.30) compared with participants with a serum 25(OH)D level  $\geq 37$  ng/mL.<sup>41</sup>

The relative risk for myocardial infarction was found to be 57-percent less in patients with a 25(OH)D level  $\geq 12.82$  ng/mL compared with age- and gender-matched controls.<sup>42</sup>

Compared to healthy age-matched controls, 77 percent of acute stroke patients in the United Kingdom were found to have vitamin D levels in the insufficient range (25(OH)D <20.0 ng/mL).<sup>43</sup>

The enzymatic conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D, as well as other regulating factors of vitamin D metabolism, occurs in the kidney. Evidence that vitamin D plays a role in the pathogenesis of cardiovascular disease comes from research on end-stage renal disease (ESRD). When undergoing peritoneal dialysis or hemodialysis, the adjusted cardiovascular mortality of ESRD patients is 10-20 times higher than the average population.<sup>44</sup> However, when the active hormone 1,25(OH)<sub>2</sub>D or the vitamin D analogue paricalcitol is given to ESRD patients, the risk of death from cardiovascular disease decreases.<sup>45,46</sup>

Most steps in the initiation and progression of cardiovascular disorders have an inflammatory component.<sup>47</sup> Vitamin D (1,25(OH)<sub>2</sub>D) has proven to be an important modulator of immune function, showing effects on numerous components of the inflammatory cascade, including antigen presenting cells, B-cells, T-cells, interleukin-1, -4, and -10 (IL-1; IL-4; IL-10), interferon-gamma (IFN- $\gamma$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and nuclear factor kappa-B (NF $\kappa$ B).<sup>48-50</sup>

Low-density lipoprotein receptor-related protein 5 (Lrp5) has been associated with normal cholesterol metabolism, glucose-induced insulin secretion,<sup>51</sup> and hypercholesterolemia-induced calcification of the aortic valves in animal models.<sup>52,53</sup> It was recently found that 1,25(OH)<sub>2</sub>D<sub>3</sub> regulates the expression of Lrp5, identifying a potential mechanism for clinical outcomes in these parameters.<sup>54</sup>

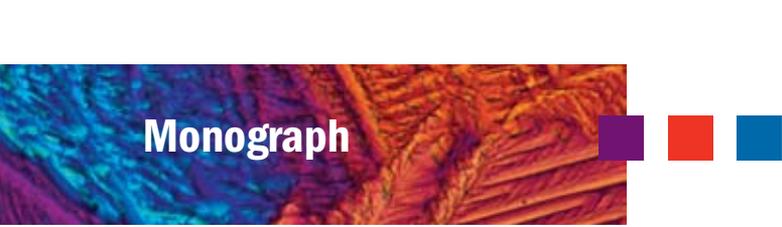
### Hypertension

Key aspects of hypertension, including endothelial cell function,<sup>55</sup> proliferation of vascular smooth muscle cells,<sup>56,57</sup> and regulation of the renin-angiotensin pathway<sup>58</sup> are affected by vitamin D.

In 613 men from the Health Professionals Follow-Up Study and 1,198 women from the Nurses' Health Study, researchers found lower serum 25(OH)D levels (<15 ng/mL compared to 30 ng/mL) increased the relative risk for hypertension in the men to 6.13 (95% CI: 1.00-37.8) and the women to 2.67 (95% CI: 1.05-6.79).<sup>59</sup>

An eight-week randomized, double-blind, parallel group study examined the effects of a single 100,000-IU dose of vitamin D<sub>2</sub> on endothelial function and blood pressure in type 2 diabetics. Flow-mediated dilation improved 2.3 percent and systolic blood pressure decreased 14 mm/Hg compared with placebo when average baseline 25(OH)D level of 15.3 ng/mL was raised to an average of 21.4 ng/mL.<sup>60</sup>

When compared to taking a 1,200-mg calcium supplement daily, 145 women age 70 or older taking an additional 800 IU vitamin D<sub>3</sub> along with the calcium supplement showed a 72-percent increase in 25(OH)D, a 17-percent decrease in serum PTH, a 9.3-percent decrease in systolic blood pressure, and a 5.4-percent decrease in heart rate. In the eight weeks of the study, 25(OH)D levels in the subjects increased (on average) from 10.3 ng/mL to 26 ng/mL.<sup>61</sup>



## Monograph

### Preeclampsia

Preeclampsia, a potentially serious complication of late second and third trimester of pregnancy, includes hypertension, edema, proteinuria, and sudden weight gain. A nested, case-control study investigated 25(OH)D levels in early pregnancy and the risk of preeclampsia, as well as the 25(OH)D status of newborns of preeclamptic mothers. In women who developed preeclampsia, 25(OH)D levels were lower in early pregnancy compared to controls (18.2 ng/mL vs. 21.3 ng/mL). After adjusting for season, gestational age, prepregnancy body mass index, education, and race/ethnicity, the researchers found a five-fold increase in the odds of preeclampsia (95% CI: 1.7-14.1) for those with 25(OH)D <15 ng/mL at less than 22 weeks gestation. The newborns of preeclamptic mothers, after controlling for confounders and compared to newborns of non-preeclamptic mothers, were twice as likely to have a 25(OH)D level <15 ng/mL.<sup>62</sup>

Using data from the Northern Finland Birth Cohort, Hypponen et al found women given vitamin D supplementation during the first year of life (2,000 IU daily) had a 50-percent reduced risk (OR: 0.49; 95% CI: 0.26-0.92) of preeclampsia in their first pregnancy compared to women who had irregular vitamin D supplementation or no supplementation.<sup>63</sup>

### Congestive Heart Failure

A randomized, double-blind, placebo-controlled trial in Germany examined supplementation of 500 mg calcium daily with or without 2,000 IU vitamin D<sub>3</sub> in a population of 93 congestive heart failure (CHF) patients (mean age 55). After nine months the vitamin D group demonstrated lower levels of PTH (3%) and the pro-inflammatory TNF- $\alpha$  (12%), and higher levels of the anti-inflammatory cytokine IL-10 (43%), compared to the non-vitamin D supplemented group. Objective clinical parameters did not change with vitamin D supplementation.<sup>64</sup>

In a case study, a 71-year-old man with CHF who was severely hypocalcemic (5.5 mg/dL) demonstrated a 58-percent improvement of symptoms and ejection fraction when hypocalcemia was corrected with IV calcium and calcitriol.<sup>65</sup>

One study comparing CHF patients with healthy gender- and age-matched controls found CHF patients had 34-percent lower 25(OH)D levels than controls.<sup>66</sup>

### Type 2 Diabetes Mellitus

The pathogenic mechanisms involved in type 2 diabetes and glucose intolerance include increased systemic inflammation, decreased pancreatic beta-cell function, and dysfunctional insulin sensitivity. Multiple studies demonstrate vitamin D has an influence on these mechanisms.<sup>67</sup>

In a review article by Palomer et al, 17 separate studies showed associations between the pathogenesis of type 2 diabetes and the prevalence of various genes associated with vitamin D status, including VDR, DBP, and CYP1alpha genes.<sup>68</sup>

### Type 1 Diabetes

Hemoglobin A1C (HbA1C) is used to monitor long-term blood sugar regulation. Evaluating data from 285,705 diabetic veterans in the United States, Tseng et al found a seasonal variation in HbA1C levels, with higher values in the winter compared to summer, implying UVB exposure may have a role in modulating blood sugar.<sup>69</sup>

Use of cod liver oil or vitamin D supplementation in early life has been associated with a reduced risk of childhood-onset type 1 diabetes.<sup>70</sup> A 2001 study in *Lancet* showed an 80-percent decrease in type 1 diabetes incidence in individuals who took 2,000 IU vitamin D daily during the first year of life. In contrast, the same group found more than a three-fold increased risk for developing type 1 diabetes in children with suspected rickets.<sup>71</sup> The effect vitamin D has on type 1 diabetes pathogenesis is thought by some to be due to its function as a potent modulator of inflammatory cytokines that damage pancreatic beta cells.<sup>72</sup>

### Multiple Sclerosis

Multiple sclerosis (MS) is a CD4+ T-cell mediated autoimmune disease that leads to an increase of inflammatory cytokines in the central nervous system, axonal degeneration, oligodendrocyte loss, and demyelination.<sup>73,74</sup> A recent review summarizing neuroimmunology in MS explains the role of cholecalciferol as

follows. By binding with various VDRs,  $1,25(\text{OH})_2\text{D}$  causes gene transcription that inhibits CD4 T-cells from expressing a T-helper 1 dominant cytokine profile including IFN- $\gamma$  and TNF- $\alpha$ , and promotes a T-helper 2 cytokine profile including increased expression of IL-4, IL-5, and IL-13. Active  $1,25(\text{OH})_2\text{D}$  also helps promote the growth and differentiation of CD4 T-cells to T-regulatory cells associated with the less inflammatory cytokines IL-10 and transforming growth factor-beta.<sup>75</sup>

In a 2006 prospective, nested case-control study in a cohort of more than seven million U.S. military personnel, blood samples and serum levels of 25(OH)D were analyzed to determine a correlation between the risk of MS and levels of 25(OH)D. The risk of MS decreased 40 percent in Caucasian men and women with every 20-ng/mL increase in circulating 25(OH)D. Between the highest quintile of 25(OH)D concentration (>39.7 ng/mL) and lowest (<25.2 ng/mL), there was a significant 62-percent relative reduction in risk of MS. The reduction of risk was strongest in late adolescence. In this subgroup, a 91-percent reduction was seen when serum 25(OH)D levels were 40 ng/mL before age 20, compared to those with lower values.<sup>76</sup>

In an earlier study using data from the Nurses' Health Study (both I and II), Munger et al documented an inverse relationship between vitamin D supplementation and risk of MS. They found a 41-percent risk reduction in women taking 400 IU/day compared to women taking no supplemental vitamin D.<sup>77</sup>

A longitudinal study published in the *Journal of Neurology, Neurosurgery, and Psychiatry* found serum 25(OH)D and intact parathyroid hormone, two indicators of vitamin D status, were significantly associated with incidence of MS relapse and remission. Mean 25(OH)D levels were 19 ng/mL during relapse and 24 ng/mL during remission.<sup>78</sup>

In a study of high-dose vitamin D supplementation in 12 MS patients, at the end of 28 weeks of progressively increasing doses of vitamin D<sub>3</sub> ending at 280,000 IU per week, four patients had complete resolution of gadolinium-enhancing lesions, and eight patients experienced a decline in the number of lesions compared to baseline.<sup>79</sup>

## Cancer

More than 200 human genes that contain a vitamin D response element have been identified. Beyond mineral homeostasis, it is known that vitamin D regulates gene expression in many cell processes including apoptosis, proliferation, differentiation, and a host of immune-modulating effects that may be directly or indirectly associated with cancer.<sup>80-82</sup>

As early as 1940, Apperly et al observed an association between the prevalence of skin cancer and a decrease in other cancers. A December 1940 article published in *Cancer Research* states, "It is suggested that we may be able to reduce our cancer deaths by inducing a partial or complete immunity by exposure of suitable skin areas to sunlight or the proper artificial light rays of intensity and duration insufficient to produce an actual skin cancer. A closer study of the action of solar radiation on the body might well reveal the nature of cancer immunity."<sup>83</sup>

Investigators publishing in *Breast Journal*, March 2008, confirmed the 1940 hypothesis by demonstrating a decrease in breast cancer risk in 107 countries with increased UVB irradiance and higher 25(OH)D levels.<sup>15</sup>

Observational studies highlight an inverse association between serum 25(OH)D levels and the risk of breast and colorectal cancers. In a recent review article, Garland et al looked at the dose-response gradient between the risk of these two common cancers and serum levels of 25(OH)D. The authors estimated a 50-percent decreased incidence of colorectal and breast cancer with a maintenance of serum 25(OH)D levels at  $\geq 34$  ng/mL (colorectal cancer) and  $\geq 52$  ng/mL (breast cancer).<sup>14</sup>

Many other cancer types have been associated with decreased UVB exposure and/or serum 25(OH)D levels, including recent studies examining Hodgkins lymphoma and lung and prostate cancer.<sup>84-86</sup>

## Chronic Pain

The active  $1,25(\text{OH})_2\text{D}$  form of vitamin D is a potent modulator of inflammation, and may play a role in shutting off chronic inflammatory responses.<sup>87</sup> A 1991 article found an association with an unusual pain that occurred in five patients with low vitamin D status; the pain resolved within 5-7 days after supplementation with ergocalciferol.<sup>88</sup>



## Monograph

A cross-sectional study of 150 patients presenting to the health clinic at the University of Minnesota with nonspecific musculoskeletal pain found 140 (93%) were vitamin D deficient (mean 25(OH)D level of 12.08 ng/mL; 95% CI: 11.18-12.99).<sup>89</sup>

German researchers found a “strong correlation between low 25(OH)D levels and higher rates and longer duration of generalized bone and/or muscle pain.”<sup>90</sup>

Older women, but not men, with vitamin D deficiency (<10 ng/mL) were two times as likely to have moderate back pain in a group of subjects in Tuscany, Italy.<sup>91</sup>

In an Egyptian study, 81 percent of women of childbearing age with a 25(OH)D level <40 ng/mL were significantly more likely to have chronic low back pain than controls who had levels >40 ng/mL.<sup>92</sup>

Of 360 patients ages 15-52 presenting to spinal and internal medicine clinics in Saudi Arabia with unexplained chronic low back pain, 83 percent had abnormally low 25(OH)D levels. After supplementation of either 5,000 IU or 10,000 IU vitamin D<sub>3</sub> daily for three months, 95 percent (341) had low back pain resolution.<sup>93</sup>

Observations from a pilot study at a pain rehabilitation center compared opioid use in patients with either adequate (20 ng/mL) or inadequate (20 ng/mL) 25(OH)D levels. The inadequate group required 1.9 times the amount of pain medication and needed opioids 1.6 times longer. This group also reported worse physical functioning and health perception compared to vitamin D-adequate counterparts. The authors concluded, “...vitamin D inadequacy may represent an under-recognized source of nociception and impaired neuromuscular functioning among patients with chronic pain.”<sup>94</sup>

### Drug-Nutrient Interactions

The cytochrome P450 family of enzymes is needed for hydroxylation of carbon 25 that provides the 25-hydroxy or “storage” form of vitamin D and carbon 1 that provides the 1,25 dihydroxy or “active hormone” product. Other CYP-dependent reactions may include the hydroxylation of other carbons including 23 and/or 24 that can lead to an “inactive” form of vitamin D

that may be excreted from the body. Medications that directly or indirectly alter the function of particular CYP enzymes responsible for these reactions may alter the biotransformation and thus physiological effects of vitamin D. These include anti-seizure medications such as gabapentin and phenobarbital, glucocorticoids, rifampin (potent CYP3A4 inducer), and drugs used in highly active antiretroviral therapy (HAART).<sup>95-102</sup>

### Side Effects and Toxicity

The current upper tolerable level (UL) for vitamin D in North America and Europe is 2,000 IU/day. Unimpeded mid-day sun exposure can lead to the endogenous production of the equivalent of ingesting 10,000 IU vitamin D. This observation and the results of numerous safety trials have led to the recommendation of experts to raise the UL for vitamin D to 10,000 IU.<sup>103</sup>

Studies show vitamin D toxicity with hypercalcemia occurs in amounts multiple folds higher:

- ➔ Two individuals with vitamin D-poisoned sugar (>56,667 IU/day for seven months)<sup>104</sup>
- ➔ Fourteen people with oil-based vitamin D supplements accidentally used for cooking oil (2 million IU/g for 11 subjects and 5 million IU/mL for three subjects)<sup>105,106</sup>
- ➔ Two individuals with undiluted vitamin supplements (both >155,000 IU/day up to 2,000,000 IU)<sup>107,108</sup>
- ➔ One child with accidental overdose by mother administering imported concentrated liquid supplement (60,000 IU/day for a two-year-old)<sup>109</sup>

Some define vitamin D toxicity as the presence of hypercalcemia (>2.75 mmol/L on one occasion) and an elevated 25(OH)D level (>150 ng/mL). Urinary calcium:creatinine ratios >1 often precede hypercalcemia.<sup>6,79,103</sup>

Common symptoms of hypervitaminosis D and hypercalcemia are anorexia, weight loss, weakness, fatigue, disorientation, vomiting, dehydration, polyuria, constipation, fever, chills, abdominal pain, and renal dysfunction.<sup>110,111</sup>

In granulomatous disorders such as sarcoidosis, tuberculosis, silicosis, chronic or active fungal infections, and lymphoma, there is an increased risk of elevated levels of  $1,25(\text{OH})_2\text{D}$  and consequently hypercalcemia due to excessive production of this metabolite by activated macrophages.<sup>112,113</sup>

## Dosage

If sun exposure is used as a vitamin D source, more skin exposure allows for more photolytic conversion in the skin, with six-percent of whole body area in mid-day providing the equivalent of 600 IU with a light pinking of Caucasian skin, and whole body exposure allowing for a 10,000 IU equivalent. Those living above or below the 35th parallel may not be able to rely on sun exposure from late fall through early spring, with narrowing time frames the farther the distance from the equator.<sup>1</sup>

When adequate UVB exposure is lacking, dosing of 1,000 IU vitamin  $\text{D}_3$  per day is required to bring serum  $25(\text{OH})\text{D}$  to 30 ng/mL in 50 percent of the general population.<sup>12</sup>

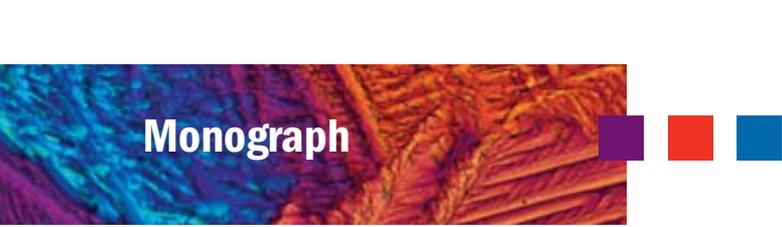
Cannell and Hollis recommend: "Treatment of vitamin D deficiency in otherwise healthy patients with 2,000-7,000 IU vitamin  $\text{D}_3$  per day should be sufficient to maintain year round  $25(\text{OH})\text{D}$  levels between 40-70 ng/mL. In those with serious illnesses associated with vitamin D deficiency such as cancer, heart disease, multiple sclerosis, diabetes, autism, and a host of other illnesses, doses should be sufficient to maintain year-round  $25(\text{OH})\text{D}$  levels between 55-70 ng/mL."<sup>13</sup>

Some researchers have extrapolated dosing equations via study results. With 800 IU vitamin D daily for three months, 208 healthy postmenopausal black women only attained an average  $25(\text{OH})\text{D}$  level of 28.6 ng/mL. Upon raising supplementation to 2,000 IU/day for three months, levels increased to a mean serum concentration of 35 ng/mL or 87.3 nmol/L. However, only 60 percent of participants achieved a concentration >30 ng/mL. The authors suggest a dose of 2,800 IU/day for those with a concentration >18 ng/mL and a dose of 4,000 IU/day for those with a concentration <18 ng/mL.<sup>114</sup>

Heaney et al suggest an elevation of 0.04 ng/mL  $25(\text{OH})\text{D}$  for every 40 IU of supplemental vitamin  $\text{D}_3$  ingested.<sup>115</sup>

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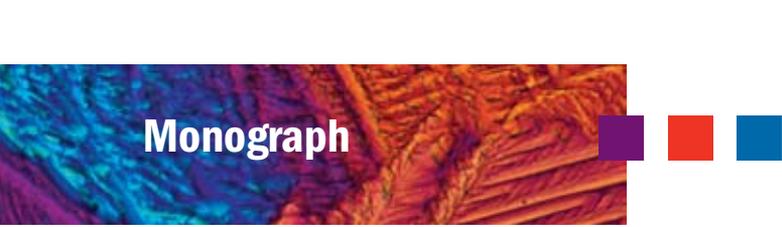
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