The Linus Pauling Institute

Micronutrient Research Center

Vitamin D

Vitamin D is a fat-soluble vitamin that is essential for maintaining normal calcium metabolism (1). Vitamin D_3 (cholecalciferol) can be synthesized by humans in the skin upon exposure to ultraviolet-B (UVB) radiation from sunlight, or it can be obtained from the diet. Plants synthesize ergosterol, which is converted to vitamin D_2 (ergocalciferol) by ultraviolet light. Vitamin D_2 is less active in birds than vitamin D_3 and may also be less active in humans (2). When exposure to UVB radiation is insufficient for the synthesis of adequate amounts of vitamin D_3 in the skin, adequate intake of vitamin D from the diet is essential for health.

Function

Activation of Vitamin D

Vitamin D itself is biologically inactive, and it must be metabolized to its biologically active forms. After it is consumed in the diet or synthesized in the epidermis of skin, vitamin D enters the circulation and is transported to the liver. In the liver, vitamin D is hydroxylated to form 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D. Increased exposure to sunlight or increased dietary intake of vitamin D increases serum levels of 25(OH)D, making the serum 25(OH)D concentration a useful indicator of vitamin D nutritional status. In the kidney, the 25(OH)D_3-1-hydroxylase enzyme catalyzes a second hydroxylation of 25(OH)D, resulting in the formation of 1alpha,25-dihydroxyvitamin D [1,25$(OH)_2$D]—the most potent form of vitamin D. Most of the physiological effects of vitamin D in the body are related to the activity of 1,25$(OH)_2$D (3).

Mechanisms of Action

Many of the biological effects of 1,25$(OH)_2$D are mediated through a nuclear transcription factor known as the vitamin D receptor (VDR) (4). Upon entering the nucleus of a cell, 1,25$(OH)_2$D associates with the VDR and promotes its association with the retinoic acid X receptor (RXR). In the presence of 1,25$(OH)_2$D the VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of specific genes. More than 50 genes in tissues throughout the body are known to be regulated by 1,25$(OH)_2$D (5).

Calcium Balance

Maintenance of serum calcium levels within a narrow range is vital for normal functioning of the nervous system, as well as for bone growth and maintenance of bone density. Vitamin D is essential for the efficient utilization of calcium by the body (1). The parathyroid glands sense serum calcium levels and secrete parathyroid hormone (PTH) if calcium levels drop too low (**diagram**). Elevations in PTH increase the activity of the 25(OH)D_3-1-hydroxylase enzyme in the kidney, resulting in increased production of 1,25$(OH)_2$D. Increasing 1,25$(OH)_2$D production results in changes in gene expression that normalize serum calcium by 1) increasing the intestinal absorption of dietary calcium, 2) increasing the reabsorption of calcium filtered by the kidneys, and 3) mobilizing calcium from bone when there is insufficient dietary calcium to maintain normal serum calcium levels. Parathyroid hormone and 1,25$(OH)_2$D are required for these latter two effects (6).

Cell Differentiation

Cells that are dividing rapidly are said to be proliferating. Differentiation results in the specialization of cells for specific functions. In general, differentiation of cells leads to a decrease in proliferation. While cellular proliferation is essential for growth and wound healing, uncontrolled proliferation of cells with certain mutations may lead to diseases like cancer. The active form of vitamin D, 1,25$(OH)_2$D, inhibits proliferation and stimulates the differentiation of cells (1).

Immunity

Vitamin D in the form of 1,25$(OH)_2$D is a potent immune system modulator. The vitamin D receptor (VDR) is expressed by most cells of the immune system, including T cells and antigen-presenting cells, such as dendritic cells and macrophages (7). Under some circumstances, macrophages also produce the 25$(OH)D_3$-1-hydroxylase enzyme that converts 25(OH)D to 1,25$(OH)_2$D (8). There is considerable scientific evidence that 1,25$(OH)_2$D has a variety of effects on immune system function, which may enhance innate immunity and inhibit the development of autoimmunity (9).

Insulin Secretion

The VDR is expressed by insulin-secreting cells of the pancreas, and the results of animal studies suggest that 1,25$(OH)_2$D plays a role in insulin secretion under conditions of increased insulin demand (10). Limited data in humans suggest that insufficient vitamin D levels may have an adverse effect on insulin secretion and glucose tolerance in type 2 diabetes (noninsulin-dependent diabetes mellitus; NIDDM) (11-13).

Blood Pressure Regulation

The renin-angiotensin system plays an important role in the regulation of blood pressure (14). Renin is an enzyme that catalyzes the cleavage (splitting) of a small peptide (Angiotensin I) from a larger protein (angiotensinogen) produced in the liver. Angiotensin converting enzyme (ACE) catalyzes the cleavage of angiotensin I to form angiotensin II, a peptide that can increase blood pressure by inducing the constriction of small arteries and by increasing sodium and water retention. The rate of angiotensin II synthesis is dependent on renin (15). Research in mice lacking the gene encoding the VDR indicates that 1,25$(OH)_2$D decreases the expression of the gene encoding renin through its interaction with the VDR (16). Since inappropriate activation of the renin-angiotensin system is thought to play a role in some forms of human hypertension, adequate vitamin D levels may be important for decreasing the risk of high blood pressure.

Deficiency

In vitamin D deficiency, calcium absorption cannot be increased enough to satisfy the body's calcium needs (3). Consequently, PTH production by the parathyroid glands is increased and calcium is mobilized from the skeleton to maintain normal serum calcium levels—a condition known as secondary hyperparathyroidism. Although it has long been known that severe vitamin D deficiency has serious consequences for bone health, recent research suggests that less obvious states of vitamin D deficiency are common and increase the risk of osteoporosis and other health problems (17, 18).

Severe Vitamin D Deficiency

Rickets

In infants and children, severe vitamin D deficiency results in the failure of bone to mineralize. Rapidly growing bones are most severely affected by rickets. The growth plates of bones continue to enlarge, but in the absence of adequate mineralization, weight-bearing limbs (arms and legs) become bowed. In infants, rickets may result in delayed closure of the fontanels (soft spots) in the skull, and the rib cage may become deformed due to the pulling action of the diaphragm. In severe cases, low serum calcium levels (hypocalcemia) may cause seizures. Although fortification of foods has led to complacency regarding vitamin D deficiency, nutritional rickets is still being reported in cities throughout the world (19, 20).

Osteomalacia

Although adult bones are no longer growing, they are in a constant state of turnover, or "remodeling." In adults with severe vitamin D deficiency, the collagenous bone matrix is preserved but bone mineral is progressively lost, resulting in bone pain and osteomalacia (soft bones).

Muscle Weakness and Pain

Vitamin D deficiency causes muscle weakness and pain in children and adults. Muscle pain and weakness were a prominent symptoms of vitamin D deficiency in a study of Arab and Danish Moslem women living in Denmark (21). In a cross-sectional study of 150 consecutive patients referred to a clinic in Minnesota for the evaluation of persistent, nonspecific musculoskeletal pain, 93% had serum 25(OH)D levels indicative of vitamin D deficiency (22). A randomized controlled trial found that supplementation of elderly women with 800 IU/day of vitamin D and 1,200 mg/day of calcium for three months increased muscle strength and decreased the risk of falling by almost 50% compared to supplementation with calcium alone (23). More recently, a randomized controlled trial in 124 nursing home residents (average age, 89 years) found that those taking 800 IU/day of supplemental vitamin D had a 72% lower fall rate than those taking a placebo (24).

Risk Factors for Vitamin D Deficiency

- **Exclusively breast-fed infants:** Infants who are exclusively breast-fed and do not receive vitamin D supplementation are at high risk of vitamin D deficiency, particularly if they have dark skin and/or receive little sun exposure (20). Human milk generally provides 25 IU of vitamin D per liter, which is not enough for an infant if it is the sole source of vitamin D. Older infants and toddlers exclusively fed milk substitutes and weaning foods that are not vitamin D fortified are also at risk of vitamin D deficiency (19). The American Academy of Pediatrics recommends that all infants that are not consuming at least 500 ml (16 ounces) of vitamin D fortified formula or milk be given a vitamin D supplement of 200 IU/day (20).

- **Dark skin:** People with dark-colored skin synthesize less vitamin D on exposure to sunlight than those with light-colored skin (1). The risk of vitamin D deficiency is particularly high in dark-skinned people who live far from the equator. One U.S. study reported that 42% of African American women between 15 and 49 years of age were vitamin D deficient compared to 4% of White women (25).
- **Aging:** The elderly have reduced capacity to synthesize vitamin D in skin when exposed to UVB radiation, and the elderly are more likely to stay indoors or use sunscreen, which blocks vitamin D synthesis. Institutionalized adults who are not supplemented with vitamin D are at extremely high risk of vitamin D deficiency (26, 27).
- **Covering all exposed skin or using sunscreen whenever outside:** Osteomalacia has been documented in women who cover all of their skin whenever they are outside for religious or cultural reasons (28, 29). The application of sunscreen with an SPF factor of 8 reduces production of vitamin D by 95% (1).
- **Fat malabsorption syndromes:** Cystic fibrosis and cholestatic liver disease impair the absorption of dietary vitamin D (30).
- **Inflammatory bowel disease:** People with inflammatory bowel disease like Crohn's disease appear to be at increased risk of vitamin D deficiency, especially those who have had small bowel resections (31).
- **Obesity:** Obesity increases the risk of vitamin D deficiency (32). Once vitamin D is synthesized in the skin or ingested, it is deposited in body fat stores, making it less bioavailable to people with large stores of body fat.

Assessing Vitamin D Nutritional Status

Growing awareness that vitamin D insufficiency has serious health consequences beyond rickets and osteomalacia highlights the need for accurate assessment of vitamin D nutritional status. Although there is general agreement that serum 25(OH)D level is the best indicator of vitamin D deficiency and sufficiency, the cutoff values have not been clearly defined (18). While laboratory reference ranges for serum 25(OH)D levels are often based on average values from populations of healthy individuals, recent research suggests that health-based cutoff values aimed at preventing secondary hyperparathyroidism and bone loss should be considerably higher. In general, serum 25(OH)D values less than 20-25 nmol/L (8-10 ng/mL) indicate severe deficiency associated with rickets and osteomalacia (17, 19). Although 50 nmol/L (20 ng/mL) has been suggested as the low end of the normal range (33), more recent research suggests that PTH levels (34, 35) and calcium absorption (36) are not optimized until serum 25(OH)D levels reach approximately 80 nmol/L (32 ng/mL). Thus, at least one vitamin D expert has argued that serum 25(OH)D values less than 80 nmol/L should be considered deficient (17), while another suggests that a healthy serum 25(OH)D value is between 75 nmol/L and 125 nmol/L (30 ng/mL and 50 ng/mL) (37). With this latter cutoff value for insufficiency (i.e., 75 nmol/L or 30 ng/mL), it is estimated that one billion people in the world are currently vitamin D deficient (38). Data from supplementation studies indicate that vitamin D intakes of at least 800-1,000 IU/day are required by adults living in temperate latitudes to achieve serum 25(OH)D levels of at least 80 nmol/L (39, 40).

The Adequate Intake (AI)

In 1997, the Food and Nutrition Board of the Institute of Medicine felt that the issue of sunlight exposure confounded the existing data on vitamin D requirements, making it impossible to calculate a Recommended Dietary Allowance (RDA) (30). Instead, the Food and Nutrition Board set adequate intake (AI) levels that assume no vitamin D is being synthesized in the skin through exposure to sunlight. The AI values established in 1997 (see table below) reflect vitamin D intakes likely to maintain serum 25(OH)D levels of at least 37.5 nmol/L (15 ng/mL), which as discussed above, many experts now feel is too low (3, 17, 18 41-44). Thus, many experts believe that the AI levels should be increased.

Adequate Intake (AI) for Vitamin D			
Life Stage	**Age**	**Males mcg/day (IU/day)**	**Females mcg/day (IU/day)**
Infants	0-6 months	5 mcg (200 IU)	5 mcg (200 IU)
Infants	7-12 months	5 mcg (200 IU)	5 mcg (200 IU)
Children	1-3 years	5 mcg (200 IU)	5 mcg (200 IU)
Children	4-8 years	5 mcg (200 IU)	5 mcg (200 IU)
Children	9-13 years	5 mcg (200 IU)	5 mcg (200 IU)
Adolescents	14-18 years	5 mcg (200 IU)	5 mcg (200 IU)
Adults	19-50 years	5 mcg (200 IU)	5 mcg (200 IU)
Adults	51-70 years	10 mcg (400 IU)	10 mcg (400 IU)
Adults	71 years and older	15 mcg (600 IU)	15 mcg (600 IU)
Pregnancy	all ages	-	5 mcg (200 IU)
Breast-feeding	all ages	-	5 mcg (200 IU)

Disease Prevention

Osteoporosis

Although osteoporosis is a multifactorial disease, vitamin D insufficiency can be an important contributing factor. A multinational (18 different countries with latitudes ranging from 64 degrees north to 38 degrees south) survey of more than 2,600 postmenopausal women with osteoporosis revealed that 64% of subjects had 25(OH)D levels lower than 75 nmol/L (30 ng/mL) (45). Without sufficient vitamin D from sun exposure or dietary intake, intestinal calcium absorption cannot be maximized. This causes PTH secretion by the parathyroid glands; elevated PTH results in increased bone resorption, which may lead to osteoporotic fracture (46). A prospective cohort study that followed more than 72,000 postmenopausal women in the U.S. for 18 years found that those who consumed at least 600 IU/day of vitamin D from diet and supplements had a 37% lower risk of osteoporotic hip fracture than women who consumed less than 140 IU/day of vitamin D (47). The results of most clinical trials suggest that vitamin D supplementation can slow bone density losses or decrease the risk of osteoporotic fracture in men and women who are unlikely to be getting enough vitamin D. However, recent analyses indicate that there is a threshold of vitamin D intake that is necessary to observe reductions in fracture risk. For instance, a recent meta-analysis of randomized controlled trials in older adults found that supplementation with 700 to 800 IU vitamin D daily had a 26% and 23% lower risk of hip fracture and nonvertebral fracture, respectively. In contrast, supplementation with 400 IU of vitamin D daily did not decrease risk of either hip or nonvertebral fracture (48). Additionally, recent results from the Women's Health Initiative trial in 36,282 postmenopausal women showed that daily supplementation with 400 IU of vitamin D_3, in combination with 1,000 mg calcium, did not significantly reduce risk of hip fracture compared to a placebo (49).

Bischoff-Ferrari et al. suggest that daily intakes of greater than 700 IU of vitamin D may be necessary to optimize serum concentrations of 25(OH)D and thus reduce fracture risk (41).

Support for such a threshold effect of vitamin D on bone health also comes from previous studies. One study in 247 postmenopausal U.S. women reported that supplementation with 500 mg/day of calcium and either 100 IU/day or 700 IU/day of vitamin D_3 for two years slowed bone density losses at the hip only in the group taking 700 IU/day (50). Another study found that daily supplementation of elderly men and women with 500 mg/day of calcium and 700 IU/day of vitamin D_3 for three years reduced bone density losses at the hip and spine and also reduced the frequency of nonvertebral fractures (51). A subsequent analysis of this cohort revealed that when the calcium and vitamin D_3 supplements were discontinued, the bone density benefits were lost within two years (52). Another study found that oral supplementation with 800 IU/day of vitamin D_3 and 1,200 mg/day of calcium for three years decreased the incidence of hip fracture in elderly French women (53). Further, oral supplementation of elderly adults in the UK with 100,000 IU of vitamin D_3 once every four months (equivalent to about 800 IU/day) for five years reduced the risk of osteoporotic fracture by 33% compared to placebo (54). However, oral supplementation with 400 IU/day of vitamin D_3 for more than three years did not affect the incidence of fracture in a study of elderly Dutch men and women (55). All of these studies indicate that at least 700 IU of vitamin D_3 daily may be required to observe a beneficial effect on fracture incidence.

However, the Randomised Evaluation of Calcium Or vitamin D (RECORD) trial reported that oral supplemental vitamin D_3 (800 IU/day) alone, or in combination with calcium (1,000 mg/day), did not prevent the occurrence of osteoporotic fractures in elderly adults who had already experienced a low-trauma, osteoporotic fracture (56). A lack of an effect could be possibly due to a low compliance in this study or the fact that vitamin D supplementation did not raise serum 25(OH)D levels to a level that would protect against fractures (41).

To date, clinical trials have generally found that vitamin D_2 (ergocalciferol) is not effective at preventing fractures (57). Indeed, vitamin D_3 (cholecalciferol) is now known to be greater than three times more potent than vitamin D_2 (2, 57). Overall, the current evidence suggests that vitamin D_3 supplements of at least 800 IU/day may be helpful in reducing bone loss and fracture rates in the elderly. In order for vitamin D supplementation to be effective in preserving bone health, adequate dietary calcium (1,000 to 1,200 mg/day) should also be consumed (see the article on Calcium).

Cancer

Two characteristics of cancer cells are lack of differentiation (specialization) and rapid growth or proliferation. Many malignant tumors have been found to contain vitamin D receptors (VDR), including breast, lung, skin (melanoma), colon, and bone. Biologically active forms of vitamin D, such as $1,25(OH)_2D$ and its analogs, have been found to induce cell differentiation and/or inhibit proliferation of a number of cancerous and noncancerous cell types maintained in cell culture (58). Results of some, but not all, human epidemiological studies suggest that vitamin D may protect against various cancers. However, it is important to note that epidemiological studies cannot prove such associations.

Colorectal Cancer

The geographic distribution of colon cancer mortality resembles the historical geographic distribution of rickets (59), providing circumstantial evidence that decreased sunlight exposure and diminished vitamin D nutritional status may be related to an increased risk of colon cancer. However, prospective cohort studies have not generally found total vitamin D intake to be associated with significant reductions in risk of colorectal cancer when other risk factors are taken into account (60-63). However, some more recent studies have reported that higher vitamin D intakes and serum 25(OH)D levels are associated with reductions in colorectal cancer risk. One five-year study of more than 120,000 people found that men with the highest vitamin D intakes had a risk of colorectal cancer that was 29% lower than men with the lowest vitamin D intakes (64). Vitamin D intake in this study was not significantly associated with colorectal cancer risk in women. Moreover, serum 25(OH)D level, which reflects vitamin D intake and vitamin D synthesis, was inversely associated with the risk of potentially precancerous colorectal polyps (65) and indices of colonic epithelial cell proliferation (66), two biomarkers for colon cancer risk. More recently, a case-control analysis from the Nurses' Health Study cohort reported that plasma 25(OH)D levels were inversely associated with colorectal cancer (67). A randomized, double-blind, placebo-controlled trial in 36,282 postmenopausal women participating in the Women's Health Initiative study found that a combination of supplemental vitamin D (400 IU/day) and calcium (1,000 mg/day) did not lower incidence of colorectal cancer (68). However, it has been suggested that the daily vitamin D dose, 400 IU, was too low to detect any effect on cancer incidence (69). In fact, a recent dose-response analysis estimated that 1,000 IU of oral vitamin D daily would lower one's risk of colorectal cancer by 50% (70).

Breast Cancer

Although breast cancer mortality follows a similar geographic distribution to that of colon cancer (59, 71), direct evidence of an association between vitamin D nutritional status and breast cancer risk is limited. A prospective study of women who participated in the first National Health and Nutrition Examination Survey (NHANES I) found that several measures of sunlight exposure and dietary vitamin D intake were associated with a reduced risk of breast cancer 20 years later (72). More recently, a 16-year study of more than 88,000 women found that higher intakes of vitamin D were associated with significantly lower breast cancer risk in premenopausal women but not postmenopausal women (73). Garland et al. conducted a pooled, dose-response analysis of two case-control studies in which women with breast cancer had significantly lower plasma 25(OH)D levels compared to controls (74, 75). These authors reported that women with a 25(OH)D level of 52 ng/ml (130 nmol/L) experienced a 50% lower risk of developing breast cancer compared to women with 25(OH)D levels lower than 13 ng/mL (32.5 nmol/L) (76). The authors state that to obtain a 25(OH)D level of 52 ng/mL, around 4,000 IU of vitamin D_3 would need to be consumed daily, or 2,000 IU of vitamin D_3 daily plus very moderate sun exposure (76). The current tolerable upper limit of intake (UL) for adults, set by the Food and Nutrition Board of the Institute of Medicine, is 2,000 IU/day (see Safety).

Prostate Cancer

Epidemiological studies show correlations between risk factors for prostate cancer and conditions that can result in decreased vitamin D levels (58). Increased age is associated with an increased risk of prostate cancer, as well as with decreased sun exposure and decreased capacity to synthesize vitamin D. The incidence of prostate cancer is higher in African American men than in white American men, and the high melanin content of dark skin is known to reduce the efficiency of vitamin D synthesis. Geographically, mortality from prostate cancer is inversely associated with the availability of sunlight. Findings that prostate cells in culture can synthesize the 25(OH)D_3-1-hydroxylase enzyme and that, unlike the renal enzyme, its synthesis is not influenced by PTH or calcium levels also provide support for the idea that increasing 25(OH)D levels may be useful in preventing prostate cancer (77). In contrast, prospective studies have not generally found significant relationships between serum 25(OH)D levels and subsequent risk of developing prostate cancer (78-81). Although a prospective study of Finnish men found that low serum 25(OH)D levels were associated with earlier and more aggressive prostate cancer development (82), another prospective study of men from Finland, Norway and Sweden found a U-shaped relationship between serum 25(OH)D levels and prostate cancer risk. In that study serum 25(OH)D concentrations of 19 nmol/L or lower and 80 nmol/L or higher were associated with higher prostate cancer risk (83). Further research is needed to determine the nature of the relationship between vitamin D nutritional status and prostate cancer risk.

Autoimmune Diseases

Insulin-dependent diabetes mellitus (IDDM; type 1 diabetes mellitus), multiple sclerosis (MS), and rheumatoid arthritis (RA) are examples of autoimmune diseases. Autoimmune diseases occur when the body mounts an immune response against its own tissue, rather than a foreign pathogen. In IDDM, insulin-producing beta-cells of the pancreas are the target of the inappropriate immune response. In MS, the targets are the myelin-producing cells of the central nervous system, and in RA, the targets are the collagen-producing cells of the joints (84). Autoimmune responses are mediated by immune cells called T cells. The biologically active form of vitamin D, $1,25(OH)_2D$, has been found to modulate T cell responses, such that the autoimmune responses are diminished. Treatment with $1,25(OH)_2D$ has beneficial effects in animal models of IDDM, MS, and RA. Epidemiological studies have found that the prevalence of IDDM, MS, and RA increases as latitude increases, suggesting that lower exposure to UVB radiation and associated decreases in endogenous vitamin D synthesis may play a role in the pathology of these diseases. The results of several prospective cohort studies also suggest that adequate vitamin D intake may decrease the risk of autoimmune diseases. A prospective cohort study of children born in Finland during the year 1966 and followed for thirty years found that those who received supplemental vitamin D during the first year of life had a significantly lower risk of developing IDDM, while children suspected of developing rickets (severe vitamin D deficiency) during the first year of life had a significantly higher risk of developing IDDM (85). Vitamin D deficiency has also been implicated in MS. A recent case-control study in U.S. military personnel, including 257 cases of diagnosed MS, found that white subjects in the highest quintile of serum 25(OH)D (>99.1 nmol/L) had a 62% lower risk of developing MS (86). A relationship between this indicator of vitamin D status and MS was not observed in blacks or Hispanics, but the power to detect such an association was limited by small sample sizes and overall low serum 25(OH)D concentrations (86). In two large cohorts of U.S. women followed for at least ten years, vitamin D supplement use was associated with a significant reduction in the risk of developing MS (87). Similarly, postmenopausal women with the highest total vitamin D intakes were at significantly lower risk of developing RA after 11 years of follow-up than those with the lowest intakes (88). Thus, evidence from both animal model studies and human epidemiological studies suggests that maintaining sufficient vitamin D levels may help decrease the risk of several autoimmune diseases.

Hypertension (High Blood Pressure)

The results of epidemiological and clinical studies suggest an inverse relationship between serum $1,25(OH)_2D$ levels and blood pressure, which may be explained by recent findings that $1,25(OH)_2D$ decreases the expression of the gene encoding renin (see Function). Data from epidemiological studies suggest that conditions that decrease vitamin D synthesis in the skin, such as having dark-colored skin or living in temperate latitudes, are associated with increased prevalence of hypertension (89). A controlled clinical trial in 18 hypertensive men and women living in the Netherlands found that exposure to UVB radiation three times weekly for six weeks during the winter increased serum 25(OH)D levels and significantly decreased 24-hour ambulatory systolic and diastolic blood pressure measurements by an average of 6 mm Hg (90). In randomized controlled trials of vitamin D supplementation, a combination of 1,600 IU/day of vitamin D and 800 mg/day of calcium for eight weeks significantly decreased systolic blood pressure in elderly women by 9% compared to calcium alone (91), but supplementation with 400 IU of vitamin D daily or a single dose of 100,000 IU of vitamin D did not significantly lower blood pressure in elderly men and women over a two-month period (92, 93). At present, data from controlled clinical trials are too limited to determine whether vitamin D supplementation will be effective in lowering blood pressure or preventing hypertension.

Sources

Sunlight

Solar ultraviolet-B radiation (UVB; wavelengths of 290 to 315 nanometers) stimulates the production of vitamin D_3 in the epidermis of the skin (94). Sunlight exposure can provide most people with their entire vitamin D requirement. Children and young adults who spend a short time outside two or three times a week will generally synthesize all the vitamin D they need to prevent deficiency. One study reported that serum vitamin D concentrations following exposure to 1 minimal erythemal dose of simulated sunlight (the amount required to cause a slight pinkness of the skin) was equivalent to ingesting approximately 20,000 IU of vitamin D_2 (95). People with dark-colored skin synthesize markedly less vitamin D on exposure to sunlight than those with light-colored skin (1). Additionally, the elderly have diminished capacity to synthesize vitamin D from sunlight exposure and frequently use sunscreen or protective clothing in order to prevent skin cancer and sun damage. The application of sunscreen with an SPF factor of 8 reduces production of vitamin D by 95%. In latitudes around 40 degrees north or 40 degrees south (Boston is 42 degrees north), there is insufficient UVB radiation available for vitamin D synthesis from November to early March. Ten degrees farther north or south (Edmonton, Canada) the “vitamin D winter” extends from mid-October to mid-March. According to Dr. Michael Holick, as little as 5-10 minutes of sun exposure on arms and legs or face and arms three times weekly between 11:00 am and 2:00 pm during the spring, summer, and fall at 42 degrees latitude should provide a light-skinned individual with adequate vitamin D and allow for storage of any excess for use during the winter with minimal risk of skin damage (37).

Food sources

Vitamin D is found naturally in very few foods. Foods containing vitamin D include some fatty fish (mackerel, salmon, sardines), fish liver oils, and eggs from hens that have been fed vitamin D. In the U.S., milk and infant formula are fortified with vitamin D so that they contain 400 IU (10 mcg) per quart. However, other dairy products, such as cheese and yogurt, are not always fortified with vitamin D. Some cereals and breads are also fortified with vitamin D. Recently, orange juice fortified with vitamin D has been made available in the U.S. Accurate estimates of average dietary intakes of vitamin D are difficult because of the high variability of the vitamin D content of fortified foods (30). Vitamin D contents of some vitamin D-rich foods are listed in the table below in both international units (IU) and micrograms (mcg). For more information on the nutrient content of specific foods, search the USDA food composition database.

Food	Serving	Vitamin D (IU)	Vitamin D (mcg)
Pink salmon, canned	3 ounces	530	13.3
Sardines, canned	3 ounces	231	5.8
Mackerel, canned	3 ounces	213	5.3
Quaker Nutrition for Women Instant Oatmeal	1 packet	154	3.9
Cow's milk, fortified with vitamin D	8 ounces	98	2.5
Soy milk, fortified with	8 ounces	100	2.5

vitamin D			
Orange juice, fortified with vitamin D	8 ounces	100	2.5
Cereal, fortified	1 serving (usually 1 cup)	40-50	1.0-1.3
Egg yolk	1 large	21	0.53

Supplements

Most vitamin D supplements available without a prescription contain cholecalciferol (vitamin D_3), which is more potent than ergocalciferol (vitamin D_2) (2, 57, 96). Multivitamin supplements for children generally provide 200 IU (5 mcg) and multivitamin supplements for adults generally provide 400 IU (10 mcg) of vitamin D. Single ingredient vitamin D supplements may provide 400-1,000 IU of vitamin D, but 400 IU is the most commonly available dose. A number of calcium supplements may also provide vitamin D.

Safety

Toxicity

Vitamin D toxicity (hypervitaminosis D) induces abnormally high serum calcium levels (hypercalcemia), which could result in bone loss, kidney stones, and calcification of organs like the heart and kidneys if untreated over a long period of time. Hypercalcemia has been observed following daily doses of greater than 50,000 IU of vitamin D (38). When the Food and Nutrition Board of the Institute of Medicine established the tolerable upper intake level (UL) for vitamin D, published studies that adequately documented the lowest intake levels of vitamin D that induced hypercalcemia were very limited. Because the consequences of hypercalcemia are severe, the Food and Nutrition Board established a very conservative UL of 2,000 IU/day (50 mcg/day) for children and adults (see table below) (30). Research published since 1997 suggests that the UL for adults is likely overly conservative and that vitamin D toxicity is very unlikely in healthy people at intake levels lower than 10,000 IU/day (39, 97, 98). Vitamin D toxicity has not been observed to result from sun exposure (38). Certain medical conditions can increase the risk of hypercalcemia in response to vitamin D, including primary hyperparathyroidism, sarcoidosis, tuberculosis, and lymphoma (39). People with these conditions may develop hypercalcemia in response to any increase in vitamin D nutrition and should thus consult a qualified health care provider regarding any increase in vitamin D intake.

Tolerable Upper Intake Level (UL) for Vitamin D	
Age Group	**mcg/day (IU/day)**
Infants 0-12 months	25 mcg (1,000 IU)
Children 1-18 years	50 mcg (2,000 IU)
Adults 19 years and older	50 mcg (2,000 IU)

Drug interactions

The following medications increase the metabolism of vitamin D and may decrease serum 25(OH)D levels: phenytoin (Dilantin), fosphenytoin (Cerebyx), phenobarbital (Luminal), carbamazepine (Tegretol), and rifampin (Rimactane). The following medications should not be taken at the same time as vitamin D because they can decrease the intestinal absorption of vitamin D: cholestyramine (Questran), colestipol (Colestid), orlistat (Xenical), mineral oil, and the fat substitute Olestra. The oral anti-fungal medication, ketoconazole, inhibits the 25(OH)D_3-1-hydroxylase enzyme and has been found to reduce serum levels of 1,25(OH)D in healthy men. The induction of hypercalcemia by toxic levels of vitamin D may precipitate cardiac arrhythmia in patients on digitalis (Digoxin) (99, 100).

Linus Pauling Institute Recommendation

The Linus Pauling Institute recommends that generally healthy adults take a multivitamin supplement that supplies 400 IU (10 mcg) of vitamin D_3 daily. Additionally, at least 10-15 minutes of sun exposure on the arms and legs or face and arms at least three times weekly between 11:00 am and 2:00 pm during the spring, summer, and fall may help residents of temperate latitudes (much of the U.S.) avoid vitamin D deficiency at the end of winter.

Older adults (> 50 years) and people with minimal sun exposure

In addition to the 400 IU (10 mcg) of vitamin D_3 provided by a multivitamin supplement, people over the age of 50 and people who get minimal sun exposure throughout the year should take an additional vitamin D_3 supplement of 400 IU/day (10 mcg/day) to provide a total of at least 800 IU/day (20 mcg/day).

http://lpi.oregonstate.edu/infocenter/