REVIEW

Vitamin D in health and disease

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Summary

Background/purpose: Investigations have revealed that vitamin D plays an important role in many areas of health and disease. Questions over whether sun avoidance and sunscreen use will decrease vitamin D levels may concern clinicians when counseling patients at risk for vitamin D insufficiency. A review of the role of vitamin D in health and disease, the impact of photoprotection and skin type on vitamin D levels, and recommendations for adequate vitamin D intake is provided to aid clinicians in counseling patients regarding these issues.

Results: Review of the literature indicates that adequate vitamin D intake is associated with decreased risk of falls and bone fractures in the elderly, breast and gastrointestinal cancer risk, cardiovascular disease, and possibly all cause mortality, diabetes, and multiple sclerosis. While skin type does affect vitamin D levels, regular use of sunscreen is not associated with vitamin D insufficiency.

Conclusions: Adequate intake of vitamin D is important for maintenance of good health, and may be achieved through diet and oral supplementation. Intentional or prolonged exposure to ultraviolet light should not be used as a means of obtaining vitamin D.

The focus on vitamin D in medicine has long been centered on its functionality in mediating calcium absorption in the human body. As investigations around vitamin D continue however, its potential beneficial role in many other areas of health and disease is beginning to surface. Ultraviolet (UV) radiation from sunlight, specifically UVB, is known to induce synthesis of vitamin D_3 in the skin, which has led to the traditional notion that sun exposure was necessary for maintaining good health. However, the ability of UVB to induce photocarcinogenesis has been well-demonstrated. Patients and physicians are thus faced with the challenge of achieving adequate vitamin D status while avoiding the risks associated with excessive UV radiation exposure. This review will discuss sources and metabolism of vitamin D and what is currently known about its role in health and disease. The effects of skin phototypes and photoprotection on vitamin D will be evaluated, and current recommendations on vitamin D intake will also be reviewed.

Sources and metabolism of vitamin D

Vitamin D is a fat-soluble vitamin obtained by the body from three sources (1). Endogenous synthesis of vitamin D occurs in the skin and is induced by UV radiation. UVB at a wavelength of 300 ± 5 nm converts 7-dehydrocholesterol (pro-vitamin D_3) into pre-vitamin D_3 in the basal and suprabasal layers of the epidermis (2–4). Pre-vitamin D_3 then undergoes non-enzymatic isomerization to form cholecalciferol, known as vitamin D_3 (4, 5). Vitamin D_3 enters the circulation and is carried by vitamin D binding protein (DBP) to the liver, where hydroxylation by 25-hydroxylase to 25-hydroxyvitamin D [25(OH)D] occurs (4, 5). Lastly, 25(OH)D is carried again by DBP to the kidney where hydroxylation by 1α-hydroxylase to 1,25-dihydroxyvitamin D [$1\alpha,25(OH)_2D$] occurs, yielding the hormonally active form of vitamin D (Fig. 1) (4–5). Of note, *in vitro* studies showed other sites of conversion of 25(OH)D to $1\alpha,25(OH)_2D$, including keratinocytes, bone, placenta, prostate, macrophages, T-lymphocytes, and dendritic cells (5). Cutaneous metabolism of $1\alpha,25(OH)_2D$ is not thought to be a significant contributor to the total body supply, however, as only the free form of 25(OH)D can be absorbed by keratinocytes, and the supply of free 25(OH)D in the blood stream is sparse (5).

Vitamin D may also be obtained exogenously through dietary intake. Very few foods naturally contain vitamin D_3, which include oily salt water fish (mackerel, salmon, sardines, and tuna), cod liver oil, and egg yolk. Because of this, many nations including the United States fortify foods such as milk, yogurt, orange juice, butter, margarine, cereals, and chocolate mixes with vitamin D (6, 7). Lastly, vitamins D_2 (ergocalciferol) and D_3 are also widely available in the form of over-the-counter dietary supplements. Vitamin D obtained exogenously is converted to 25(OH)D and $1,25(OH)_2D$ through the pathway highlighted above. While once considered equivalent to vitamin D_3, studies

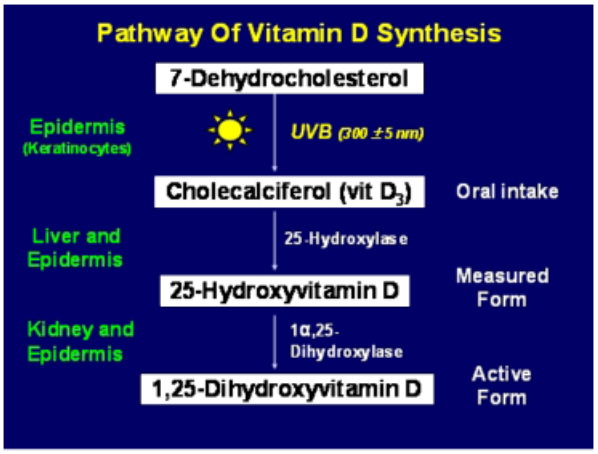

Fig. 1. Pathway of vitamin D synthesis.

suggest vitamin D_2 is inferior to vitamin D_3 in raising serum 25(OH)D levels, and may even suppress the endogenous formation of 25(OH)D and $1\alpha,25(OH)_2D$ (8, 9). In contrast, a recent study showed that vitamin D_2 is as efficient as vitamin D_3 in raising serum 25(OH)D levels (10). Because of the above reasons, fortification and supplementation are now mainly carried out with vitamin D_3.

Vitamin D in health and disease

Through epidemiologic studies, there has been a well established association between vitamin D and several aspects of health and disease (Table 1), including bone mineral density and fracture risk, gastrointestinal malignancies, and multiple sclerosis (MS) (11–14). There is a growing pool of evidence suggesting that vitamin D supplementation is effective at preventing falls and reducing fractures. A recent meta-analysis reviewed eight double-blind randomized-controlled clinical trials (RCTs) on fall risk and vitamin D supplementation ($n = 2426$). A daily dose of 700–1000 international units (IU) of vitamin D daily reduced fall risk in elderly patients by 19% compared with a lower dose (< 700 IU) that did not decrease fall risk (13). Meta-analysis of eight RCTs of hip fracture risk ($n = 40\,886$) and 12 RCTs for non-vertebral fracture risk ($n = 42\,279$) performed in 2009 revealed a daily supplementation with 482–770 IU of vitamin D reduced non-vertebral fractures by 20% and hip fractures by 18% (14). No reduction in fracture risk was observed at a dose of 400 IU or less daily.

Colorectal cancer risk also appears to be related to vitamin D levels. Both normal and cancerous cells of the colon express the vitamin D receptor (VDR). Circulating $1\alpha,25(OH)_2D$ has the ability to bind to VDR on these cells and promote normal cellular differentiation while limiting their malignant potential (15, 16). Several observational studies have shown an inverse relationship between colorectal cancer incidence and vitamin D supplementation (17–23). Recent meta-analysis of such studies found that subjects with a serum 25(OH)D level at or near 92.5 nmol/l had a colon cancer risk that was 50% of matched subjects with a serum level of < 15 nmol/l (24). A similar association between vitamin D and pancreatic cancer is suggested by two large prospective studies. Incidence of pancreatic cancer observed in 46 711 men aged 40–75 years (Health Professionals Follow-up Study 1986–2000) and 75 427 women aged 38–65 years (Nurses Health Study 1984–2000) showed that a higher intake of vitamin D (600 IU/day) was associated with a lower risk for pancreatic cancer. This association appears to be stronger in men than in women (25).

In addition, the Health Professionals Follow-up Study found that an incremental increase of serum 25(OH)D by 25 nmol/l was associated with a 45% decrease in digestive system cancer mortality, a 29% decrease in all cancer mortality, and a 17% reduction in total cancer incidence (26). When adjusting for dietary, lifestyle, and medical risk factors in this study, black men were at a higher risk of total cancer incidence and mortality than Whites. Blacks are known to have lower vitamin D levels. When compared with Whites, Blacks with few risk factors for hypovitaminosis D did not have a higher risk of total cancer incidence or mortality (27). These findings suggest that vitamin D may be an important, easily modifiable contributory factor to cancer development.

A large prospective study of > 7 million US military personal examined the relationship of vitamin D levels and the development of MS. New cases of MS were identified through the Army and Navy physical disability database reviewed from 1992 to 2004 and were confirmed with chart review. Each case was then matched with two controls, and serum 25(OH)D levels averaged over two or more draws before the date of MS diagnosis were compared between the groups. In white patients, the risk of MS was significantly decreased with increasing 25(OH)D levels [odds ratio for a 50 nmol/l increase of 25(OH)D = 0.59]. Blacks and Hispanics had lower 25(OH)D levels compared with Whites, and no significant association between vitamin D levels and risk for MS was detected in these cohorts, probably due to relatively smaller sample sizes and lower vitamin D levels in these groups (28).

Association of vitamin D in other aspects of wellness, such as breast cancer, prostate cancer, diabetes mellitus, cardiovascular health, and immune function, has also been assessed. The Nurses Health Study, Health Professionals Follow-up Study, and Physician's Health Study showed a 30% reduction in breast cancer when comparing the highest with the lowest quintiles of 25(OH)D levels, while no clear association was observed with prostate cancer (29).

Epidemiologic data also suggest a correlation with vitamin D and diabetes. In a Dutch study of 142 men between the ages of 70 and 88 years, serum levels of 25(OH)D were inversely correlated with serum insulin levels ($r = -0.18$ to -0.23) and glucose concentrations ($r = -0.26$) during an oral glucose tolerance test (30). In a large survey of adults aged 20 years and older in the United States, the odds ratio for diabetes in individuals with serum levels of 25(OH)D ≥ 81 nmol/l compared with those with levels ≤ 43.9 nmol/l was 0.25 in whites and 0.17 in Mexican-Americans. No difference in risk was observed in African-Americans (31). An RCT of 445 subjects aged 65 years or older treated with either 700 IU of vitamin D_3 plus 500 mg of calcium daily or placebo found a lower overall rise in fasting

Table 1. Summary of health effects of vitamin D

Musculoskeletal health	700–1000 IU of vitamin D daily reduced fall risk in elderly patients by 19% (13) 482–770 IU of vitamin D daily reduced non-vertebral fractures by 20% and hip fractures by 18% (14)
Multiple sclerosis	In white patients, the risk of MS was significantly decreased with increasing serum 25(OH)D levels (28)
Diabetes	Serum levels of 25(OH)D were inversely correlated with serum insulin levels and glucose concentrations during an oral glucose tolerance test (30) Odds ratio for diabetes in individuals with serum levels of 25(OH)D $\geq$ 81 nmol/l compared with those with levels $\leq$ 43.9 nmol/l was 0.25 in Whites and 0.17 in Mexican-Americans. No difference in African-Americans (31). 700 IU of vitamin D3 plus 500 mg of calcium daily vs. placebo found a lower overall rise in fasting blood glucose levels and a lower increase in insulin resistance over a three year period in the treatment group (32)
Cardiovascular health	Men with 25(OH)D levels $\leq$ 15 ng/ml had an increased risk for myocardial infarction (MI) compared with those with $\geq$ 30 ng/ml (33) Patients in the lower two quartiles of serum 25(OH)D levels (7.6 and 13.3 ng/ml) had higher all-cause and cardiovascular mortality compared with the highest quartile (28.4 ng/ml) (34) Relationship between low vitamin D levels at baseline and a higher risk of cardiovascular and cerebrovascular death may exhist (35)
Immunity	$1,25(OH)_2D$ induces cathelicidins and other anti-microbial peptides (38) Addition of vitamin D supplementation to tuberculosis treatment regimens was superior to standard treatment alone (40)
Colorectal cancer	Serum 25(OH)D levels near 92.5 nmol/l was associated with 50% colon cancer risk compared with levels of $<$ 15 nmol/l (24)
Pancreatic cancer	Intake of vitamin D $\geq$ 600 IU/day was associated with a lower risk for pancreatic cancer (25)
Gastrointestinal cancer	Incremental increase of serum 25(OH)D by 25 nmol/l was associated with a 45% decrease in digestive system cancer mortality (26)
Breast cancer	30% decrease in breast cancer incidence was observed between the highest to lowest quintiles of serum 25(OH)D levels (29)
All cancer incidence	Incremental increase of serum 25(OH)D by 25 nmol/l was associated with a 17% reduction in total cancer incidence (26)
All cancer mortality	Incremental increase of serum 25(OH)D by 25 nmol/l was associated with a 29% decrease in all cancer mortality (26)
All cause mortality	Average of 528 IU of vitamin D daily had a 7% decrease in all cause mortality compared with the untreated group (36, 37)

blood glucose levels ($P = 0.04$) and a lower increase in insulin resistance ($P = 0.03$) over a 3-year period in the treatment group (32). However, the addition of calcium to the treatment regimen confounds the ability to attribute this effect solely to vitamin D.

Several studies also suggest a correlation of vitamin D levels with cardiovascular health. After 10 years of observation, 454 of the 18 225 men in the Health Professionals Follow-up Study had a myocardial infarction (MI). Men in the study with 25(OH)D levels $\leq$ 15 ng/ml had an increased risk for MI compared with those with $\geq$ 30 ng/ml after controlling for factors known to be associated with coronary artery disease (33). In a prospective study of 3258 male and female patients scheduled for angioplasty, serum 25(OH)D and $1\alpha,25(OH)_2D$ levels were measured. Over 7.7 years of follow-up, 737 patients died (463 of them from cardiovascular causes). Patients in the lower two 25(OH)D quartiles (median 7.6 and 13.3 ng/ml) had a higher all-cause and cardiovascular mortality compared with the highest quartile (median 28.4 ng/ml) (34). Similar results were observed for $1\alpha,25(OH)_2D$ levels. An additional cohort study of 6219 patients measured baseline 25(OH)D levels. Follow-up of cardiovascular and cerebrovascular deaths from 1978 to 1980 through 2006 showed a possible relationship between low vitamin D levels at baseline and a higher risk of cardiovascular and more strongly cerebrovascular death (35).

In addition, vitamin D also appears to be correlated with overall mortality. A meta-analysis of data collected on the risk of death from any cause in subjects participating in RCTs testing the impact of vitamin D supplementation on any health condition was completed. Eighteen studies published before November 2006 that incorporated a total of 57 311 subjects were included. The trial-size adjusted mean daily dosage of vitamin D was 528 IU (range of 300–2000 IU). The vitamin D treatment group enjoyed a statistically significant 7% decrease in all cause mortality compared with the untreated group (36, 37). It should be noted, however, that when considering these studies alone, it is unclear whether this represents a causal relationship of Vitamin D and mortality, or whether vitamin D levels are merely an indicator of overall health status.

Vitamin D is also involved in aspects of innate immunity and immune-related disease. In the face of infection, $1\alpha,25(OH)_2D$ is able to induce the production of cathelicidins and other anti-microbial peptides (AMPs) through binding with VDR on numerous immune cells, such as T-cells, B-cells, NK cells, and monocytes (38). This interaction has particular importance in *Mycobacterium tuberculosis* infection. Cathelicidins are important in eliminating Mycobacterium, and the addition of $1\alpha,25(OH)_2D$ to macrophages infected with this organism leads to decreased levels of viable bacilli (38, 39). This is further supported by the finding that a majority of patients with *M. tuberculosis* have low levels of serum vitamin D, and the addition of vitamin D supplementation to tuberculosis treatment regimens has proved superior to standard treatment alone (38, 40).

Table 2. Selected food sources of vitamin D (7)

Food	IUs/serving	% daily value*
Cod liver oil, 1 tablespoon	1360	340
Mushrooms, enriched with vitamin D, 3 oz	400	100
Salmon, cooked, 3.5 oz	360	90
Mackerel, cooked, 3.5 oz	345	86
Sardines, canned in oil, drained, 1.75 oz	250	63
Tuna fish, canned in oil, 3 oz	200	50
Orange juice fortified with vitamin D, one cup (check product labels, as amount of added vitamin D varies)	142	36
Milk, non-fat, reduced fat, and whole, vitamin D-fortified, 1 cup	98	25
Yogurt, fortified with 20% of the DV for vitamin D, 6 oz (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75–1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Egg, one whole (vitamin D is found in yolk)	20	5
Liver, beef, cooked, 3.5 oz	15	4
Cheese, Swiss, 1 oz	21	3

*Daily values were developed by the US Food and Drug Administration to help consumers to compare the nutrient contents of products within the context of a total diet. The daily value for vitamin D is 400 IU for adults and children age 4 and older. Food labels, however, are not required to list vitamin D content unless a food has been fortified with this nutrient. Foods providing 20% more of the daily value are considered to be high sources of a nutrient.
IUs, International Units.

Vitamin D may be of special importance in stimulating innate immunity in the setting of atopic dermatitis, where the ability to generate AMPs is inhibited by increased levels of Th2 cytokines IL-4 and IL-13 (38). Large doses of oral vitamin D have been shown to increase cathelicidin levels in atopic dermatitis patients (38, 41). In contrast, vitamin D may play an anti-inflammatory role in psoriasis, where topical vitamin D analogs have shown therapeutic efficacy toward the disease in humans and demonstrated an increased regulatory T cell activity in psoriatic mouse models (38).

Photoprotection, skin types, and vitamin D

Recently, the effects of regular sunscreen use on vitamin D levels have been questioned. Concern was raised that a significant decrease in the amount of pre-vitamin D_3 generated by UVB exposure could occur with sunscreen use and potentially lead to insufficient levels of vitamin D in individuals. However, data from studies examining this issue have not provided support to this notion (42, 43). A review of reports published up to 2008 regarding this topic concluded that while sunscreens may significantly reduce the production of vitamin D under very strictly controlled conditions, their normal usage does not generally result in vitamin D insufficiency; a potential explanation being the well-documented fact that individuals do not apply sunscreens at the concentration that they are tested in the laboratory (2 mg/cm^2) (44).

In contrast to sunscreen use, individual skin type does appear to affect serum vitamin D levels. An examination of different racial groups in the United States found mean 25(OH)D levels of 72.1 nmol/l in Whites aged $\geq$50 years and 82.8 nmol/l in Whites aged 20–49 years at baseline. Lower levels were observed in Mexican -Americans (59.3 nmol/l and 61.5 nmol/l), and Blacks (52.4 nmol/l and 46.8 nmol/l) of the same age groups (45). Gozdzik examined skin pigmentation (via melanin index), serum 25(OH)D levels, and daily vitamin D intake in a total of 107 patients of different racial groups in Toronto, Canada. As expected, melanin index was the highest in South Asians (38.3), followed by East Asians (32.0), and Europeans (28.6). Serum 25(OH)D levels were inversely related to skin pigmentation, with Europeans averaging 55.9 nmol/l, East Asians averaging 34.5 nmol/l, and South Asians averaging 30.5 nmol/l. Oral Vitamin D intake was the highest among Europeans (231.0 IU/day), followed by South Asians (164.3 IU/day), and East Asians (133.4 IU/day) (46). In contrast, Bogh *et al.*(47) found that an increase in 25(OH)D levels following BB-UVB exposure was not correlated with skin pigmentation. This study was performed in the winter when melanin is present mostly in the basal layer, which is a limitation of this study. Additionally, a negative correlation with baseline 25(OH)D levels and a positive correlation with baseline total cholesterol levels were observed.

Recommendations

Clinically, serum 25(OH)D levels are accepted as a barometer for overall vitamin D status, with a level of $\geq$30 ng/ml (75 nmol/l) being considered adequate. Individuals with levels between 21 and 29 ng/ml (51–74 nmol/l) are considered to be insufficient of the vitamin and those with levels $\leq$ 20 ng/ml (50 nmol/l) have vitamin D deficiency (48).

A consensus as to the exact amount of daily vitamin D intake needed has not been reached, however, and recommendations

currently vary by organization. In the United States, the Institute of Medicine (IOM) of the National Academies recommends a daily intake of 200 IU for children and adults up to the age of 50 years, 400 IU for adults aged 51–70, and 600 IU for adults over 70 years of age (6, 49). It is of note that these recommendations were released in 1997 and at the time of this writing are undergoing a 24-month review process with a new set of guidelines expected by the end of 2010. However, many other organizations recommend a more generous daily allowance. The American Academy of Pediatrics revised their guidelines in 2008, calling for 400 IU daily for all children ages 0–18 years (6, 50). This is an increase from the previously released recommendation in 2003 of 200 IU. The Dietary Guidelines established by the United States Department of Agriculture (USDA) and Department of Health and Human Services (HHS) in 2005 call for a recommended dietary intake of 1000 IU of total vitamin D daily for all individuals at risk for vitamin D insufficiency (51). Both the American Academy of Dermatology and the United States National Council on Skin Cancer Prevention have issued similar recommendations (52, 53).

Groups at risk for developing vitamin D insufficiency include the following: breast-fed infants, as human milk contains only 25 IU/l of vitamin D; older adults, as aged skin synthesizes less vitamin D than that of young skin; individuals with limited sun exposure secondary to climate, rigorous photoprotection, or practice of complete coverage of the skin due to religious or cultural traditions; people with dark skin; and patients who suffer from fat malabsorption or obesity, as vitamin D is fat soluble (11).

The recommended intake of 1000 IU of vitamin D daily can be met through a combination of foods and dietary supplements. The amount of vitamin D contained per serving of natural and fortified food sources is available through the National Institutes of Health Office of Dietary Supplements (Table 2) (6, 7). For example, intake of roughly 3 oz or 100 gm of salmon (300 IUs), two 8 oz or 250 ml glasses of milk (total 200 IU), one 8 oz glass of fortified orange juice (100 IU), and 400 IU in the form of a dietary supplement would together amount to the recommended 1000 IUs.

Although UVB radiation drives the formation of vitamin D in the skin, it is also the main contributor to sunburns and is associated strongly with the development of skin cancer. Exposure to tanning beds has been documented to be associated with the development of melanoma and squamous cell carcinoma (54). Therefore, unprotected or intentional exposure to natural or artificial UV *should not* be recommended as a means of obtaining vitamin D. In addition, scientific evidence currently does not support the concern that sunscreen use may lead to vitamin D deficiency. All patients, including those at risk for vitamin D deficiency, should be counseled on photoprotection, and when appropriate, intake of adequate amounts of vitamin D.

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