Benefits and Requirements of Vitamin D for Optimal Health: A Review

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Abstract

Vitamin D sufficiency is required for optimal health. The conditions with strong evidence for a protective effect of vitamin D include several bone diseases, muscle weakness, more than a dozen types of internal cancers, multiple sclerosis, and type 1 diabetes mellitus. There is also weaker evidence for several other diseases and conditions. There are good reasons that vitamin D sufficiency be maintained during all stages of life, from fetal development to old age. Adequate calcium intake is also recommended. The current vitamin D requirements in the United States are based on protection against bone diseases. These guidelines are being revised upward in light of new findings, especially for soft-tissue health. The consensus of scientific understanding appears to be that vitamin D deficiency is reached for serum 25-hydroxyvitamin D (25(OH)D) levels less than 20 ng/mL (50 nmol/L), insufficiency in the range from 20-32 ng/mL, and sufficiency in the range from 33-80 ng/mL, with normal in sunny countries 54-90 ng/mL, and excess greater than 100 ng/mL. Solar ultraviolet-B (UVB) irradiation is the primary source of vitamin D for most people. In general, the health benefits accruing from moderate UV irradiation, without erythema or excess tanning, greatly outweigh the health risks, with skin pigmentation (melanin) providing much of the protection. In the absence of adequate solar UVB irradiation due to season, latitude, or lifestyle, vitamin D can be obtained from fortified food, oily fish, vitamin D supplements, and artificial sources of UVB radiation. ***(Altern Med Rev*** **2005;10(2):94-111)**

Introduction

There is a growing awareness that vitamin D sufficiency is required for optimal health. The role of vitamin D in calcium absorption and metabolism for bone health is well known.[1] Research during the past two decades has illustrated the importance of vitamin D in reducing the risk of cancer,[2-4] multiple sclerosis,[5,6] and type 1 diabetes mellitus.[7] A number of reviews on the role of vitamin D and prevention of disease and maintenance of optimal health have appeared in the past 2-3 years,[8-21] and several recent conferences have been devoted solely to exploring the role of vitamin D in health and disease prevention.[22-24] Finally, organizations in Australia and New Zealand have recognized a sufficiently high prevalence of vitamin D deficiency, even in these sunny lands, to have issued guidelines for solar UVB irradiation.[25,26]

This article discusses the importance of vitamin D sufficiency at various stages of life as a guide to health practitioners, policy makers, and interested individuals.

Pre- and Postnatal Vitamin D Benefits

One of the primary roles of vitamin D is the regulation of calcium and phosphorus absorption and metabolism for bone health. This role is especially important during pregnancy and lactation because bones develop rapidly during this period. Women

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have less skin pigmentation than men, a finding attributed to women's greater need for vitamin D during pregnancy and lactation.[27] Insufficient vitamin D intake during infancy can result in biochemical disturbances, reduced bone mineralization, slower growth, bone deformities, and increased risk of fracture – the hallmarks of rickets.[28] Indeed, rickets has been reported among breast-fed African-American infants in several southern states.[29,30]

The relationship between maternal vitamin D/calcium and fetal bone development was reviewed by Specker.[31] Most of the papers reviewed reported an effect of maternal vitamin D status on both maternal and infant calcium homeostasis, but did not report whether infant bone mineral density (BMD) was affected.

Low birth weight (LBW) appears to be a consequence of vitamin D insufficiency during pregnancy. The topic was reviewed by Fuller, who hypothesized that insufficient serum 25(OH)D levels disrupted calcium homeostasis, leading to intrauterine growth retardation, premature labor, and hypertension, all of which are risk factors for LBW infants.[32] Subsequent papers seem to support the hypothesis that African-American and Asian-Indian mothers have much higher rates of LBW infants in the United States than do European Americans or Hispanic Americans.[33-35] This may be in part because Hispanic Americans have a slightly higher consumption of vitamin D than African Americans,[36] as well as lighter skin. Also, Koreans born in winter tend to have lower BMD than those born in summer.[37]

Children born prematurely are likely to have enamel defects in both primary and permanent teeth.[38] Maternal vitamin D sufficiency is required for proper fetal tooth development,[31,39] as well as adequate calcium. An additional benefit of sufficient vitamin D and calcium during pregnancy is good maternal bone health. Studies report 2-4 percent bone density losses during pregnancy that are exacerbated by calcium and vitamin D deficiency.[31]

Maternal and infant 25(OH)D sufficiency also appears to greatly reduce the risk of type 1 diabetes mellitus (DM). A study of vitamin D supplementation during the first year of life found those receiving the highest amounts in Finland had an odds ratio of 0.2 of developing type 1 DM compared with those receiving no supplements.[7,40] In further support of this hypothesis, mechanisms were investigated in a mouse model,[41] and vitamin D receptor (VDR) alleles have been associated with risk of type 1 DM.[42] The VDR bind 1,25-dihydroxy vitamin D3 ($1,25(OH)_2D$) to its target cells and organs where it performs certain functions. The fact that VDR alleles are associated with a particular disease gives further support to vitamin D having an effect. In addition, there is an excess summer birth rate for those who develop type 1 DM.[43] The most likely explanation is that maternal vitamin D insufficiency occurs during the second trimester of pregnancy, a time when the pancreas is likely to develop. Risk of type 1 DM related to vitamin D status should be considered when revising vitamin D guidelines.[44]

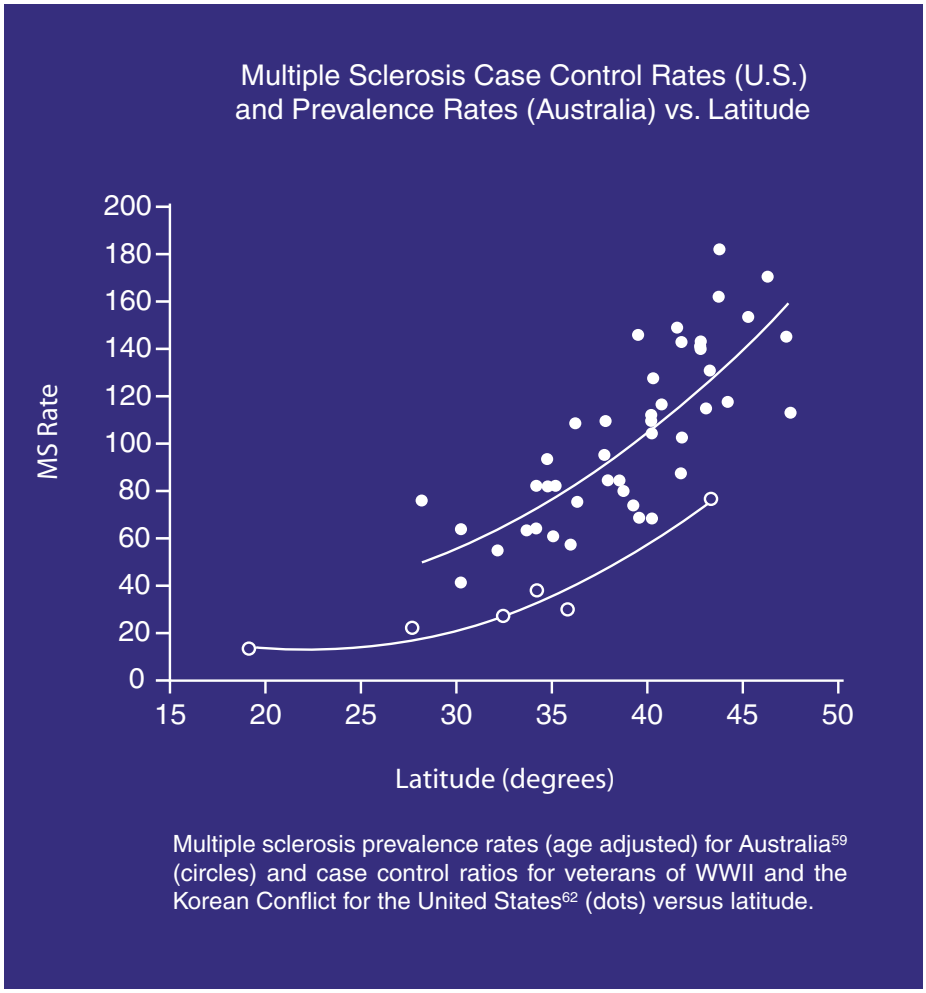
Maternal and infant 25(OH)D sufficiency is also linked to significant reduction of risk for multiple sclerosis (MS). Vitamin D is hypothesized to reduce the risk of MS by strengthening the immune system against viral infections, a theoretical etiological factor in MS.[45-47] Adequate serum 25(OH)D levels during pregnancy appear to reduce the risk of MS, as evidenced by seasonal variations in birth rate for those who later develop MS, with spring being the season of greatest birth rate for MS.[48,49] A recent paper suggests vitamin D supplementation during pregnancy as a way to reduce the risk of fetal inclination toward MS.[50]

A study in England found birth seasonality was related to later diagnosis of bipolar disorder,[51] strongly suggesting that the risk of bipolar disorder can be reduced through sufficient vitamin D intake during pregnancy. The same can be said of anxiety neurosis, for which there is a very pronounced springtime excess birth rate; for example, in New South Wales.[52] It is likely several other mental disorders and birth defects associated with springtime excess birth rates will be linked to maternal vitamin D deficiency earlier in pregnancy.

Vitamin D during Youth and Adolescence

The primary role of sufficient vitamin D during youth and adolescence is optimization of BMD. For example, serum 25(OH)D levels were found to be strongly correlated with BMD for peripubertal Finnish girls[53] and young Finnish men.[54] A study in Boston

Figure 1. Multiple Sclerosis Case Control Rates (U.S.) and Prevalence Rates (Australia) versus Latitude



Multiple sclerosis prevalence rates (age adjusted) for Australia[59] (circles) and case control ratios for veterans of WWII and the Korean Conflict for the United States[62] (dots) versus latitude.

reported that 24 percent of 307 adolescents recruited during an annual physical examination were vitamin D deficient (serum 25(OH)D ≤ 15 ng/mL), with 14 percent severely vitamin D deficient (25(OH)D ≤ 8 ng/mL);[55] the deficiencies were highest among African Americans. A study based on the National Health and Nutrition Examination Survey (NHANES) III found adolescents were more likely to be vitamin D insufficient, rather than deficient, in low-latitude winter and high-latitude summer populations.[56] There are 4-5 months of the year when vitamin D cannot be produced from solar UVB irradiation in Boston at 42.5° N latitude.[57]

Another important role of vitamin D during youth appears to be in reducing the risk of MS. A study in Tasmania found that children ages 6-15 years reporting the highest amount of sun exposure, especially in winter, had an odds ratio of 0.31 (95% confidence interval (CI): 0.16-0.59) of developing MS compared with those experiencing less than one hour of sun exposure daily.[58] It is well known that the risk of MS increases rapidly with increasing latitude. This finding has been demonstrated in Australia,[59] Europe,[60] and the United States.[61,62] Figure 1 shows the latitudinal dependence for U.S. veterans at the time of entry into World War II and the Korean Conflict.[62] Wintertime serum 25(OH)D values are much more likely to follow a simple latitudinal dependence due to the reduced number of days during which vitamin D can be produced from solar UVB at the higher latitudes.[57] In the winter, little if any vitamin D can be made in the skin above 37° N latitude, and serum 25(OH)D levels reach their nadir in February or March in the northern hemisphere.[57,63] In summer, the level of serum 25(OH)D is generally adequate. Summertime UVB irradiation does not follow a simple latitudinal dependence, due to the higher surface elevation and lower stratospheric ozone layer for states west of and including the Rocky Mountains.[64] The best explanation for this latitudinal variation is strengthening of the immune system, especially in winter, which can then help prevent viral infections from giving rise to MS.[11,19,45-47,65-67] For example, vitamin D regulates T-helper 1 (Th1) and dendritic cell function.

In addition to reducing the risk of MS, vitamin D is also beneficial for treating the symptoms of MS. Two papers reported higher numbers of MS lesions in winter than in summer.[68,69] It was suggested that UVB-induced seasonal variations of serum 25(OH)D accounted for the near doubling of MS lesions in the winter versus summer.[70] Seasonal variations for southern California[69] were much lower than in Germany,[68] supporting the UVB/vitamin D hypothesis.

There is also some evidence that solar UVB irradiation/vitamin D during youth reduces the risk of cancer. A study in the United Kingdom found childhood UV exposure was associated with a large reduction in the risk of prostate cancer.[71,72] For example, those with frequent childhood sunburns had an odds ratio of 0.18 (95% CI: 0.08-0.38).[71] A study from Australia reported the risk of developing non-Hodgkin's lymphoma (NHL) was inversely correlated with sun exposure, with the strongest effects found for women and children.[73,74]

Vitamin D Benefits in Adulthood

Vitamin D levels in adulthood are important for maintaining BMD. The primary risk factors for low BMD, osteoporosis, and osteopenia include vitamin D insufficiency, inadequate calcium intake, lack of exercise, and other dietary factors. Serum 25(OH)D levels have been directly related to bone health in men and women of all ages.[75] It was recently reported that tanners who had robust levels of 25(OH)D (> 40 ng/mL) had higher bone density.[76] Inflammatory bowel diseases (IBD), such as Crohn's disease, can reduce the absorption of dietary vitamin D, especially with resection of the duodenum and jejunum, sites of vitamin D absorption.[77] The decreased vitamin D levels and increased risk of osteoporosis in IBD are associated not only with poor absorption of vitamin D but also with use of corticosteroids,[78,79] which are also frequently prescribed for the treatment of such conditions as collagen vascular diseases, bronchial asthma, and skin conditions.[80] Other medications, including anticonvulsants, heparin, warfarin, and methotrexate, also contribute to low BMD.[81] Therefore, adequate vitamin D and calcium consumption and exercise should be maintained to combat both primary and secondary risk factors for low BMD during adulthood.

Another benefit of vitamin D is maintenance of optimal muscle strength. Vitamin D deficiency can cause osteomalacia, which is associated with muscle and bone pain.[82,83] In one report, of 150 patients at a hospital in Minneapolis presenting with persistent, nonspecific musculoskeletal pain syndromes refractory to standard therapies, 140 had vitamin D deficiencies (mean 25(OH)D level = 12.1 ng/mL; 95% CI: 11.2-13.0).[84] Among different ethnic groups, 16 percent of Asians, 24 percent of Anglo Americans, 40 percent of Hispanics and Native Americans, and 50 percent of African Americans demonstrate severe vitamin D deficiency (25(OH)D < 8 ng/mL).[84] An analysis of walking speed and sit-to-stand times among individuals 60 years or older reported best performance when 25(OH)D levels were at least 30 ng/mL.[85] Serum 25(OH)D levels less than 20 ng/mL have been associated with increased body sway, and levels less than 12 ng/mL with decreased muscle strength.[86]

Sufficient vitamin D levels in adulthood may significantly reduce the risk for many types of cancer. The interest in vitamin D as a risk reduction factor for cancer began in 1980 when Cedric and Frank Garland looked at maps of cancer mortality rates in the United States and noticed colon cancer rates were lowest in the southwest.[2] In trying to determine a mechanism, they reasoned that the primary physiological effect of exposure to sunlight, other than inducing tanning, was the production of vitamin D. A few years later they demonstrated, using sera stored for another purpose, that colon cancer risk was inversely associated with pre-diagnostic serum 25(OH)D levels.[3] It was soon demonstrated that breast, ovarian, and prostate cancer also had inverse correlations with solar UVB radiation.[87-90] By the late 1990s, the mechanisms whereby vitamin D reduces the risk of cancer were fairly well known[91-93] and include facilitation of calcium absorption (colon cancer),[93] increased cell differentiation and apoptosis,[91] and reduction of both metastasis and angiogenesis.[91] Calcium has been shown to decrease proliferation and induce differentiation in epithelial cells.[94] In addition, it was discovered that most organs have VDRs and that various alleles of the gene for VDRs affect the risk of cancer.[95-99] Another important discovery was that most organs convert circulating 25(OH)D to the active hormone, $1,25(OH)_2D$.[100-103]

It is now thought that UVB and vitamin D reduce the risk of 17 types of cancer.[4,104,105] This determination was made using cancer mortality rate data from the Atlas of Cancer Mortality Rates in the United States[106] and UVB data for July from the Total Ozone Mapping Spectrometer (TOMS).[64] The TOMS data provide a convenient index for vitamin D production from UVB irradiation, but are somewhat limited because they cover only one month. Both July UVB irradiation and cancer mortality rates have highly asymmetrical distributions in the United States – UVB levels are highest in the southwest and lowest in the northeast; whereas, the opposite holds for many types of cancer. The reason for the asymmetry in UVB irradiation is that, as the westerly winds prepare to cross the Rocky Mountains, the air masses push up the tropopause west of the Rockies, thereby reducing the thickness of the stratospheric ozone layer. The edge of the ozone absorption band occurs in the UVB region (290-315 nm); therefore, variations in ozone column amounts affect the UVB transmission.

Statistically significant inverse correlations were found for bladder, breast, colon, esophageal, gastric, ovarian, prostate, rectal, renal, uterine cancer, and NHL.[4] This study was extended by including several additional cancer risk-modifying factors, including degree of urbanization, smoking, alcohol consumption, Hispanic heritage, and fraction of the population living below the poverty level, with all data averaged at the state level.[104] The additional cancers found to be vitamin D sensitive are cervical, gall bladder, laryngeal, oral, pancreatic, and Hodgkin's lymphoma.[104] In most cases the association with UVB irradiation for July is stronger than that for any other factor. The primary exceptions to this relation are cancers strongly linked to smoking. However, in multi-country comparisons, the fraction of energy derived from dietary animal products is the primary risk factor for breast[107] and colon[108] cancer. The link between diet and cancer risk in such cases appears to be mediated through insulin-like growth factor-1 (IGF-1).[109,110] Dietary factors do not vary greatly within the United States. Vitamin D has been shown to counteract the growth-signaling effects of IGF-1.[111,112]

Presently, the role of UVB and vitamin D in reducing the risk of cancer is considered a scientific finding that satisfies most, if not all, the criteria for causality in a biological system given by Hill.[113,114] The most important criteria appear to be: (1) strength of association; (2) consistency in results for different populations; (3) generally linear dose-response gradients; (4) exclusion of possible confounding factors from explaining the observations; and (5) identification of mechanisms to explain the observations. These criteria are generally satisfied for several cancers in particular and many cancers in general.[4]

To be fully accepted by the health policy establishment, there would likely have to be double-blind crossover studies of vitamin D supplementation and cancer outcome. However, given the strength of the evidence regarding cancer and the many benefits of vitamin D, the authors believe the cancer risk-reduction potential should be accepted by public health bodies, and thereafter guidelines be developed and promulgated.

Tuberculosis (TB) is a disease for which vitamin D can strengthen the immune system by enhancing the macrophage phagocytosis of *Mycobacterium tuberculosis*.[115] TB is often associated with lower serum 25(OH)D levels among patients and increased risk among those with low serum 25(OH)D levels.[116] A recent Peruvian study found VDR alleles were associated with response to treatment.[117]

The Effect of Vitamin D in the Elderly Population

The elderly have a particularly strong need to maintain vitamin D sufficiency. Not only are they likely to produce less vitamin D from solar UVB irradiation because they generally spend less time in sunlight than do younger people,[118,119] but their efficiency of photoproduction is less.[119-121] In addition, diseases such as cancer and osteoporotic fractures are most likely among the elderly. A study from Turkey reported it was possible to identify risk of vitamin D insufficiency in elderly subjects simply by asking about clothing habits and exposure to sunlight.[122] In countries where some foods are fortified (such as milk, breakfast cereals, orange juice,[123] and some breads[124] in the United States, and milk and margarine in Canada[36]), and where many take vitamin supplements, dietary patterns and supplement consumption would have to be questioned as well.[125] However,

Table 1. Health Implications of Various Levels of Serum 25(OH)D

25(OH)D Level (ng/mL)	25(OH)D Level (nmol/L)	Health Implications
<20	<50	Deficiency
20-32	50-80	Insufficiency
32-100	80-250	Sufficiency
54-90	135-225	Normal in sunny countries
>100	>250	Excess
>150	>325	Intoxication

in high-latitude countries, serum 25(OH)D levels in winter tend to be low.[126]

Cancer is a disease for which incidence and mortality rates generally increase with age and there is generally a time lag between dietary effects and discovery of cancer. A 23-year lag between the introduction of Western dietary factors, reduced total dietary fiber, and colon cancer was found for Japan after 1947.[127] Exercise is associated with reduced risk for cancer,[128,129] and the elderly generally exercise less than their younger counterparts. The most important reason, however, for increased risk of cancer with increasing age is likely chromosomal changes, such as aneuploidy (having an abnormal number of chromosomes) and telomere erosion.[130] Telomeres, the end caps of chromosomes, are thought to shorten with each instance of cell division, and the rate of division increases with energy consumption and body mass index. Also involved are advanced glycation end products and reactive oxygen species.[131] Active vitamin D induces ovarian cell apoptosis through down-regulation of telomerase.[132] Telomerase activity is inversely correlated with telomere length.[133]

Osteoporotic fractures are of significant concern for the elderly. Several factors contribute to the risk of such fractures, including low BMD, muscle weakness, and neurological control of balance/neuromuscular function.[134,135] Vitamin D sufficiency, adequate dietary calcium and related minerals, and exercise help reduce the risk of falls and fractures.[85,136-138] An added benefit is reduced tooth loss.[139]

Vitamin D Recommendations

Having demonstrated the importance of optimal vitamin D at all stages of life, from fetal development to old age, dosage recommendations for vitamin D can be addressed. The most important consideration is serum 25(OH)D levels. The consensus of scientific understanding[13,14,140-143] is presented in Table 1. Several studies have found calcium absorption and parathyroid hormone (PTH) levels plateau for 25(OH)D levels near 30 ng/mL.[140,144-147] Although the optimal range of 25(OH)D is still the subject of debate, it is assumed to be approximately 30-50 ng/mL (75-125 nmol/L) or higher.[142] Exposure to solar UVB irradiation as it contributes to serum 25(OH)D levels depends on latitude, time of day, season, fraction of body exposed, whether one visits indoor tanning facilities,[76] skin pigmentation, body mass index, and amount of body fat.[148] Non-UVB factors include diet, vitamin D supplementation, and use of certain pharmaceutical drugs, such as glucocorticoids.[149,150]

The guidelines currently in place in the United States recommend 5 μg/day (200 IU/day) of vitamin D for children and younger adults, 400 IU/day for those ages 51-70, and 600 IU/day for those over age 70.[151] These guidelines are based on maintaining bone health. Since 1997, much has been learned

Table 2. Variation of Serum 25(OH)D Levels with Season and Latitude

Location	Latitude	Population, age range (y)	Summer/ Fall high, SD* (ng/mL)	Winter/ Spring low, SD* (ng/mL)	Reference
Miami, Florida	26˚ N	Men and women >18	26.8 ± 10.3 (males) 25.0 ± 9.4 (females)	23.3 ± 8.4	152
United States (overall)		African-American women	19.8	15.5	153
		Caucasian women	36.4	26.4	153
Omaha, Nebraska	41.3˚ N	Elderly women	34.2 ± 2.0	27.4 ± 2.7	154
Framingham, Massachussetts	42.5˚ N	Men 67-95	39.1	31.6	155
		Women 67-95	31.6	24.4	155
Boston, Massachussetts	43.3˚ N	African-American women 20-40	16.4 ± 6.6	12.1 ± 7.9	156
		Caucasian women 20-40	34.2 ± 13.2	24.0 ± 8.6	156
Toronto, Ontario	43.7˚ N	Young women	30.4 ± 11.2	23.2 ± 9.6	157
Portland, Oregon	45.5˚ N	Men and women	24.7 ± 8.0	20.4 ± 7.6	158
Paris, France	49˚ N	Adolescent males	23.4 ± 8.0	8.2 ± 2.8	159
Calgary, Alberta	51˚ N	Men and women 27-89	28.6 ± 9.4	22.9 ± 8.5	160

*SD = standard deviation

about the non-calcemic benefits of vitamin D, essentially making these guidelines obsolete. From evaluation of vitamin D consumption among nurses and male health professionals in cohort and other studies, the mean intake of vitamin D at age 50 and older is approximately 320 IU/day in the United States, with about 200 IU/day coming from dietary sources.[125,136]

By one assessment, no child or adult received the recommended vitamin D dose from dietary sources alone.[125] The average summertime serum 25(OH)D levels for white adults in Canada and the northern portions of the United States are in the range of 30-35 ng/mL, dropping to 25 ng/mL in winter (Table 2), putting most people in the insufficient range.

In France, where food fortification with vitamin D is perhaps lowest,[161] the wintertime serum 25(OH)D level for adolescents drops to as low as 8-10 ng/mL, clearly in the deficient range. From the average adult vitamin D intake of 320 IU/day and the wintertime 25(OH)D level of 25 ng/mL, minus the value of 8-10 ng/mL from France, the ratio of vitamin D intake to serum 25(OH)D levels is 0.05 ng/mL/IU/day. Clinical studies found 500-1,000 IU of vitamin D/day maintains serum levels of 30 ng/mL (0.06 ng/mL/IU/day).[123,162,163] Thus, using the clinical value, to reach the upper end of the optimal range (50 ng/mL) in the absence of solar or artificial UVB irradiation, vitamin D intake should be 1,000 IU/day. Levels as high as 4,000 IU/day have been demonstrated to be safe for up to six months.[141,164,165] However, there are concerns that at higher doses (>1,000 IU/day) over extended periods of time, some adverse effects may occur, such as increased risk of prostate cancer.[166,167] At higher values of 25(OH)D, vitamin D resistance may occur.[168] However, modest levels of 25(OH)D (15-25 ng/mL) seem to provide the optimal reduction of risk for prostate cancer.[166,167,169]

Guidelines for Solar UV Irradiation

Given the importance of vitamin D sufficiency for optimal health, and the fact that solar UVB irradiation is the primary source of vitamin D for most people, it is imperative that guidelines for solar UV exposure be revised in consideration of overall health, rather than only for reducing the risk of skin cancer and melanoma.

The amount of UVB irradiation required for vitamin D sufficiency can be calculated from the amount of vitamin D produced from one minimal erythemal dose (MED) – 10,000-25,000 IU of oral vitamin D.[17] If 10,000 IU of vitamin D is produced from exposure of the full body to one MED, exposing the full body to 25 percent of the MED would produce 2,500 IU. In order to achieve 1,000 IU, 40 percent of the body should be exposed to 25 percent of the MED; if production is more efficient, less of the body need be exposed.

For pale skin, the exposure time for one MED in the summer noonday sun in the southern United States is about 4-10 minutes; for dark skin, such as for African Americans, the corresponding time is 60-80 minutes.[17,63] Exposure times should be 25-50 percent of the MED. The length of time varies with geographical location, skin pigmentation, percent body fat, and age.

The best time of day for vitamin D production is near solar noon, when the ratio of UVB to UVA is highest. Typically, vitamin D3 can be produced from 10 a.m. to 3 p.m. during the spring, summer, and fall.[17] Because UVB radiation occurs at shorter wavelengths than UVA, it experiences greater attenuation from atmospheric scatter than UVA. Also, UVB is absorbed by ozone. Thus, the exposure time required for a given level of vitamin D photoproduction is lowest near solar noon. In addition, basal cell carcinoma (BCC) and cutaneous malignant melanoma (CMM) are probably more susceptible to UVA irradiation than UVB irradiation,[170-172] so that minimizing UVA rather than UVB exposure may be appropriate. For these two reasons, midday solar UV irradiation, short of erythema, will reduce the risk of both BCC and CMM. BCC and CMM are also linked more to intermittent UV exposure, such as during a vacation in a sunny location, than to occupational exposure, which seems to be protective.[173-175] This protective effect of regular exposure may be via vitamin D production[176] or perhaps through conditioning of the skin for higher UV radiation. BCC is the most common form of skin cancer for those with lightly pigmented skin, whereas CMM is the most deadly. On the other hand, actinic keratosis (AK) and squamous cell carcinoma (SCC) are more likely related to total lifetime UVB irradiation. SCC, although a rarer form of skin cancer, is more deadly than BCC and accounts for most non-melanoma skin cancer deaths in the United States. Thus, sunscreens, which have much greater protection against UVB than UVA radiation, appear to protect against AK and SCC but not BCC[177] and CMM.[178,179]

In addition, indoor tanning using artificial lamps with a UV spectral output that mimics that of solar UV radiation reaching the Earth's surface near summertime noon at midlatitude (3-5% UVB, 95-97% UVA) can also be used to produce vitamin D.[76] Lower fractions of UVB, such as 1.5 percent in France and Sweden, are associated with increased risk of melanoma.[180] However, those who do not tan easily should not use such lamps since they are less well protected

Table 3. Sources of Vitamin D and a Comparison of Advantages and Disadvantages

Source	Amount Obtained	Advantages	Disadvantages
Fish, fatty, cold ocean	100-500 IU/serving		Fish stocks are being depleted;[182] fish contain mercury
Milk	400 IU/quart		Milk associated with increased risk of hip fracture[136] and other diseases such as prostate cancer[183] and acne vulgaris[184]
Orange juice	400 IU/quart[123]	Source of vitamin C; can decrease LDL-HDL ratio[185]	
Bread	In process of being developed	Whole-grain cereals reduce the risk of chronic disease[124, 186-188]	
Solar UVB	0 (winter in north) to 10,000 IU per day[17,63]	The natural way;[27] maintains 25(OH)D longer compared to ingested vitamin D	Not always available, risk of melanoma, skin cancer, especially with intermittent exposure and sunburn[175]
Artificial UVB	10-minute tanning session yields 2,000-4,000 IU[123, 162,163]	Generally available	Lamps may be high in UVA,[180] a likely risk factor for melanoma[171,180]
Supplements	200-1,000 IU per pill	Convenient, inexpensive	May contain vitamin A (retinol), which in high doses might increase risk of hip fracture[189,190] and birth defects[191]

against free radical formation. Higher fractions of UVB may be more beneficial, but research on this topic has not been conducted. The vitamin D-production potential of both the sun and artificial UVB sources can be determined by various means.[181]

A summary of the advantages and disadvantages of various sources of vitamin D is given in Table 3. While solar UVB is the natural way to obtain vitamin D for most people, other sources may be more convenient or have other health advantages.

However, the disadvantages have to be weighed as well.

Discussion

Despite the mounting scientific evidence that vitamin D sufficiency is required for optimal health, and that solar UVB irradiation is the main source of vitamin D for most Americans, the recommendations regarding vitamin D requirements and solar UVB exposure have not changed recently. There are signs, however, that the interest in vitamin D is increasing[22,192] with subsequent increases in vitamin D requirements in the near future.[193-195] The obstacles to doing so have been little profit in selling solar UVB or vitamin D and concern that UV exposure carries with it the risk of skin cancer. However, it is noted that the amount of UVB irradiation required for optimal vitamin D levels is not very high and can be achieved with minimal risk of developing skin cancer or CMM. Frequent sunburns are an important risk factor for melanoma[175] and BCC,[170] and excess UV irradiation is an important risk factor for SCC;[170] sunburn rates are high in the United States.[196]

Another impediment to increasing vitamin D dosage recommendations is that traditional epidemiological approaches have been slow to find inverse correlations between vitamin D and cancer rates. However, a recent review revealed many of the studies considered only dietary vitamin D intake, which is generally inadequate and represents a small portion of total vitamin D intake and production. Studies that considered measures of total vitamin D intake and production generally found a significant cancer risk reduction.[105]

Although the emphasis in this review is the effects of vitamin D in the United States, there is also a substantial vitamin D insufficiency in the United Kingdom (U.K.)[197] and many other European countries. A recent review estimated that the economic burden due to vitamin D insufficiency in the United States is $40-53 billion per year; whereas, the economic burden due to excess UV irradiation is $5-7 billion. It is estimated that 50,000-70,000 U.S. citizens and 30,000-35,000 U.K. residents die prematurely from cancer annually due to insufficient vitamin D. Given the smaller U.K. population, the effect of vitamin D insufficiency is proportionally greater.

The problems regarding vitamin D status in Europe arise from several factors: (1) the countries are generally at higher latitudes; (2) the populations have become increasingly urbanized and spend more time indoors; (3) vitamin D fortification is minimal in most European countries[198] and recommended supplementation levels are too low (200 IU/day),[199] resulting in widespread hypovitaminosis D;[126,200] and (4) public health policy guidelines have not yet recognized the importance of vitamin D sufficiency for optimal health.[197]

Conclusion

There is ample and compelling evidence that a blood level of 30-50 ng/mL is necessary for optimal health. In the absence of adequate sun exposure, 1,000 IU vitamin D daily for children and adults is required to achieve these levels.

With the recent announcement that health care expenditures in the United States reached $1.7 trillion in 2003, accounting for 15.3 percent of the U.S. gross domestic product,[201] more effort must be made to maintain optimal health and prevent disease.

It is becoming increasingly apparent that vitamin D sufficiency is required for optimal health; however, most people living outside the tropical regions do not have serum 25(OH)D levels high enough for optimal health. Vitamin D is beneficial at all stages of life. It is hoped that researchers will increase their focus on the importance of vitamin D for optimal health and reduced risk of many diseases, that public health guidelines will be revised to acknowledge solar UVB irradiation is more beneficial than harmful, and that people should try to maintain optimal serum levels of 25(OH)D through a combination of diet, supplements, and solar and artificial UVB irradiation.

Several recent reports have found vitamin D is beneficial, not only for cancer prevention, but also for those recently diagnosed with cancer. The first two such reports were from Norway, where it was observed those whose breast, colon, or prostate cancer is discovered in summer or fall have a higher survival rate than those for whom the discovery is made in winter or spring.[202,203] It was hypothesized that these

observations were related to vitamin D status at the time of discovery, with a higher 25(OH)D level providing an improved prognosis. In a vitamin D supplementation study, for those with elevated prostate-specific antigen (PSA) levels, a dose of 2,000 IU/day led to an increase of 75 percent in the average PSA doubling time; in other words, PSA levels increased more slowly.[204] This appears to be in contrast to data above that indicated vitamin D in high doses might contribute to prostate cancer. There may be a difference in effect of vitamin D at different stages of prostate cancer development – a subject of ongoing research.

In a poster presented at a recent conference, it was reported that male health professionals with early stage non-small cell lung cancer with higher vitamin D indices (based on geographic location, race, leisure time outdoor activities, oral vitamin D, and body mass index) had a higher survival rate than those with lower vitamin D indices.[205] These results strongly suggest that those diagnosed with cancer should be immediately placed on a vitamin D enhancement program, especially African Americans, who have a heretofore unexplained lower cancer survival rate than white Americans[206] and have a much lower vitamin D status than white Americans.[156]

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