What Is All This Commotion about Vitamin D?

Vitamin D levels and unprotected sun exposure as a means of increasing these levels in the general population have become hot-button issues, polarizing many in the medical community and lay public. Here, we review some of the relevant research findings, discuss prevalent recommendations based on these data, and offer our own recommendations for patient management that reflect our evaluation of the literature.

Vitamin D, long known for its essential role in calcium absorption and bone health, has more recently been implicated in other aspects of health, including prevention of cancer, autoimmune disease, cardiovascular disease, and other chronic diseases (Holick, 2007). A wide range of potential functions is suggested by the discovery that at least 60 human cell types express the vitamin D receptor and more than 200 genes have been identified as directly or indirectly responsive to vitamin D (Holick, 2007). These discoveries have led to understandable speculation that suboptimal vitamin D levels may predispose individuals to many diseases. It is unfortunate for lifelong maintenance of healthy skin that the increased interest in vitamin D has also led some to advocate unprotected sun exposure or sun bed use to attain "sufficient" or optimal levels (Holick, 2007; Schoenmakers *et al.*, 2008). Because of space constraints, we have assumed the reader has a basic knowledge of the rationale for photoprotection, which includes prevention of photocarcinogenesis and photoaging. We discuss instead often poorly articulated issues that fuel the "vitamin D controversy" and appear to lead otherwise well-informed health-care providers to recommend unprotected UV exposure to their patients.

Terms and definitions

Vitamin D level commonly refers to the serum concentration of the inactive storage form, 25-hydroxyvitamin D (25(OH)D), understood to reflect total body stores. The active form of the vitamin, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), is more correctly viewed as a hormone, because it can be made by the body and is transported in the bloodstream to the target tissues possessing its nuclear receptor, a member of the steroid hormone superfamily (Holick, 2007). In contrast to $1,25(OH)_2D$ levels, which are tightly regulated and virtually constant, serum 25(OH)D levels vary widely among apparently healthy individuals and over time in a single individual (Dawson-Hughes *et al.*, 1997; Nesby-O'Dell *et al.*, 2002; Tangpricha *et al.*, 2002).

Irradiation of animal skin with UVB (290–315 nm), the same wavelengths primarily responsible for photocarcinogenesis (Wolpowitz and Gilchrest, 2006), converts 7-dehydrocholesterol in cell membranes to pre–vitamin D_3, which then thermally isomerizes to vitamin D_3 (cholecalciferol) and enters the bloodstream. In an analogous process in plants and fungi, UV irradiation converts ergosterol in cell walls to vitamin D_2 (ergocalciferol or calciferol), which upon oral ingestion also enters the bloodstream. Ingestion of certain fish or other animal products, as well as either vitamin D_2 or D_3 supplements, also results in entry of vitamin D into the bloodstream. Both forms of the vitamin, D_2 and D_3, are measured in standard vitamin D serum assays after hydroxylation in the liver, and both are further hydroxylated to biologically active $1,25(OH)_2D$ (Holick, 2007).

Classically, there are three categories for vitamin D levels. The first level is deficient, a level causing bone disease (rickets in children or osteomalacia in adults), usually defined as <10–20 ng/ml or 25–50 nmol/l (Holick, 2007; Schoenmakers *et al.*, 2008). Signs and symptoms of vitamin D deficiency are rapidly abolished by increasing 25(OH)D levels through supplementation or UV exposure. The next level is normal, any level between deficient and toxic. The third level is toxic, a level leading to hypercalcemia, hypercalciuria, or associated disorders, usually defined as >150 ng/ml or 375 nmol/l. Signs and symptoms of vitamin D toxicity, also termed intoxication, are rapidly abolished by decreasing vitamin D intake. (Because UV exposure in excess of approximately one-third a minimal erythema dose promotes conversion of pre–vitamin D_3 to inactive photoproducts rather than to vitamin D, UV exposure alone cannot lead to toxic levels (Holick *et al.*, 1980).)

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All three categories are strongly influenced by dietary calcium ingestion and absorption because the functions of vitamin D that determine these signs and symptoms require calcium (Wolpowitz and Gilchrest, 2006). The definition of vitamin D deficiency sometimes also includes an elevated level of parathyroid hormone (PTH), a molecule that stimulates intestinal absorption and renal tubular reabsorption of calcium as well as renal production of $1,25(OH)_2D$ (Holick, 2007).

More recently, two new terms have been introduced: "insufficient" is a level above deficient, as defined here, but below a variously defined "sufficient" level. Conceptually, an insufficient level is statistically associated in one or more epidemiologic studies with a higher incidence or prevalence of a disease of interest such as cancer, cardiovascular disease, or diabetes. It is hypothesized on the basis of indirect evidence that a very high serum 25(OH)D level drives the inactive vitamin into cells that express 1-hydroxylase, where it is then converted to active $1,25(OH)_2D$ and exerts healthful effects such as differentiation, thus decreasing cancer risk, for example (Autier and Gandini, 2007; Bischoff-Ferrari *et al.*, 2006; Holick, 2008). Typically, to determine a sufficient level, studied populations have been divided into quartiles or quintiles based on 25(OH)D levels and the disease of interest found to be increased 1.5- to 2-fold among subjects in the lowest group relative to the highest group (Giovannucci, 2005; Melamed *et al.*, 2008). The proportion of affected individuals is low in all subject groups, typically 0.5–2% (Freedman *et al.*, 2008; Wactawski-Wende *et al.*, 2006), and thus the overwhelming majority of "insufficient" subjects do not have the disease of interest. Because each study selects somewhat different 25(OH)D levels as cutoffs within the population, numerous values have been suggested as the lower limit of "sufficient."

A recent consensus conference of five investigators interested in this issue recommended 30–40 ng/ml (75–100 nmol/l) (Bischoff-Ferrari *et al.*, 2006), but some publications and many Internet blogs recommend cutoffs up to twice this level (Hollis *et al.*, 2007; GrassrootsHealth, 2008; Looking Fit, 2008). Some definitions of "sufficient" include the criterion that PTH levels be maximally suppressed—i.e., not lowered further by increasing 25(OH)D levels (Holick, 2007)—but PTH levels are rarely measured in clinical practice and even more rarely before and after vitamin D challenge. In any case, the desirability of keeping PTH levels at their nadir, incapable of reduction by further elevation of 25(OH)D levels, is philosophical: no study has demonstrated a health benefit of minimizing PTH levels in normal individuals.

Of note, by definition, an individual need not have any past, present, or future health problem to be classified as vitamin D insufficient. Equally, there need be no detectable benefit of increasing an individual's 25(OH)D level, even for a period of years; and individuals classified as sufficient are still at risk for all the studied diseases.

The effect of obesity on vitamin D levels

As a fat-soluble molecule, 25(OH)D dissolves in fat, and thus serum measurements of vitamin D tend to decrease with increasing body mass index (Giovannucci, 2005; Holick, 2007). Whether 25(OH)D in fat is as bioavailable as it is when protein bound in the serum is debatable, but serum vitamin D levels in overweight or obese persons underestimate their total body stores (Wortsman *et al.*, 2000) and are considerably lower than in leaner individuals in similar environments (Arunabh *et al.*, 2003; Kumar *et al.*, 2009), placing them disproportionately in the lower quartiles and quintiles of populations stratified by 25(OH)D level. A recent study reporting an association of hypertension, diabetes, and other cardiovascular risk factors with low 25(OH)D levels in children and adolescents claims that the association persists when the data are analyzed after correcting for adiposity (Kumar *et al.*, 2009), but in fact their subanalysis omits only those above the 95% cutoff in weight for infants and those with body mass index >30 kg/m^2 for older children, leaving many severely overweight participants. Thus, obesity remains a likely confounding factor for many, if not all, of the associations between low 25(OH)D levels and poor health outcomes. Of course, it is possible, if seemingly far-fetched, to argue the reverse—that obese and sedentary people are at high risk of many diseases specifically because they have low serum 25(OH)D levels (Garland *et al.*, 2007; Giovannucci, 2005).

Interestingly, in the context of considering how best to correct vitamin D insufficiency in the population, lean and obese subjects are reported to comparably increase serum 25(OH)D levels after a standardized oral supplement, but following a whole-body UVB exposure obese subjects appear to increase 25(OH)D levels less than half as much as lean subjects (Wortsman *et al.*, 2000).

Prevalent recommendations for vitamin D supplementation

The current official daily recommendation for adequate intake of vitamin D is 200–600 international units (IU)/day (American Academy of Dermatology, 2009), depending on age, although this is under review and may be revised upward as early as May 2010 (Grant and Boucher, 2009). These amounts were calculated by committee, from assumptions about typical sun exposure and dietary intake, and are intended to ensure a serum 25(OH)D level in the presumptively adequate range (US National Institutes of Health, 2009). Most multivitamins accordingly contain 400 IU of vitamin D.

Recommendations for higher levels of supplementation have flooded the literature and the Internet. Most appear based on intervention studies that demonstrate a statistically significant health benefit of 700–1100 IU/day of vitamin D (plus 1.0–1.5 g/day of calcium) as an oral supplement (Bischoff-Ferrari *et al.*, 2006; Lappe *et al.*, 2007). To date, such studies have involved primarily elderly women, many of whom were initially vitamin D deficient (not "insufficient"), and pertain largely to reduction in falls and fractures (Wolpowitz and Gilchrest, 2006). No study has documented any benefit of supplementation greater than 700–1200 IU/day. lots of examples

It is estimated that for every 100 IU of vitamin D_2 or D_3 ingested daily, serum 25(OH)D levels increase 1.0 ng/ml, or 2.5 nmol/l (Heaney *et al.*, 2003; Holick, 2008), suggesting that in the complete absence of dietary vitamin D or UV exposure, a daily supplement of at least 1,000 IU is needed to avoid vitamin D deficiency, defined as <10 ng/ml, or <25 nmol/l.

Others base their vitamin D recommendation on the belief that the natural state of humans (implied to be optimal) is living outdoors in the sun scantily clothed, a condition best mimicked in today's world by lifeguards at the beach, who maintain serum 25(OH)D levels of up to 130–190 nmol/l (Haddad and Chyu, 1971; Hollis *et al.*, 2007). In the absence of sun exposure, this requires a vitamin D supplement of at least 5,300 IU/day (Heaney *et al.*, 2003). Still others recommend supplements of up to 10,000 IU/day (Looking Fit, 2008), without a specific rationale, although this level of supplementation for 5 months has been reported not to cause vitamin D toxicity (Holick, 2007).

Most authorities recommend oral supplements containing vitamin D_3 because vitamin D_2 has been reported to be substantially less stable (Holick, 2007; Houghton and Vieth, 2006). However, vitamin D_2 appears to raise 25(OH)D levels as effectively as the D_3 form (Holick, 2008). Only one authority has suggested that vitamin D_3 produced by cutaneous sun exposure is more healthful than vitamin D_3 supplements (Holick, 2009).

Should 25(OH)D levels be monitored?

Serum 25(OH)D levels are increasingly being recommended as part of routine patient monitoring (Weinstock and Moses, 2009). However, the recommended treatment for vitamin D insufficiency is supplementation with 1,000 IU/day (American Academy of Dermatology, 2009; Bischoff-Ferrari *et al.*, 2006; Holick, 2007), at a cost of less than $20/year (as of December 2009, a nationwide pharmacy charged $11.49 for 240 1,000-IU tablets) versus $45–$65 or more per serum determination (Centers for Medicare and Medicaid Services, 2009). Hence, 25(OH)D levels seem indicated only in cases of unexplained signs and symptoms consistent with vitamin D deficiency or toxicity or in patients considering high-dose supplementation while pregnant (to avoid the teratogenic effects of very high 25(OH)D levels) or at known risk of hypercalcemia or hypercalciuria. If an apparently healthy individual or his or her physician is concerned about the possibility of vitamin D insufficiency, oral vitamin D supplementation of 1,000 IU daily appears to be the logical choice, because whatever the 25(OH)D level, by some standard it will likely be insufficient, and risk of toxicity at this dose is negligible. Patients with malabsorption or other disorder that interferes with vitamin D homeostasis should be under the care of an appropriate specialist and monitored as indicated.

What is the evidence that very high vitamin D levels are healthful?

Any discussion of this topic is complicated by the huge numbers of publications, including more than 5,500 studies addressing the relationship of "vitamin D" and "cancer," for example (the result of a search of PubMed on 27 September 2009). Because no single review can critique the entire body of literature, each review tends to selectively discuss studies that support the authors' biases—or at least can easily be accused of doing so. In addition, many reviews and editorials cite not only a favorite study but also multiple other reviews and editorials that cite the same study, creating for the casual reader an impression of overwhelming evidence in support of the conclusion when in fact the data are modest.

There is consensus, however, that the strongest evidence for a beneficial effect of high 25(OH)D supplements has been generated for reducing falls and bone fractures and, less so, a reduction in cancer risk, especially for colorectal cancer. Reductions in breast cancer risk and overall mortality are also frequently cited (Autier and Gandini, 2007; Garland *et al.*, 2007; Giovannucci, 2005).

Supplements of 700–800 IU/day of vitamin D with or without calcium reduced falls and hip and nonvertebral fractures in meta-analysis of randomized, prospective, placebo-controlled trials in frail elderly women (Bischoff-Ferrari *et al.*, 2004, 2005). One randomized controlled trial, using 1,100 IU/day vitamin D with 1.5 gm/day calcium, evaluated a secondary end point, self-reported cancer incidence, and demonstrated a statistically significant reduction in supplemented subjects if the analysis was restricted to women who were cancer-free 1 year after beginning supplementation and were then followed for 3 years (Lappe *et al.*, 2007). However, several methodologic concerns have been raised regarding this study (Bolland and Reid, 2008; Ojha *et al.*, 2007; Schabas, 2008; Sood and Sood, 2007).

Several randomized prospective placebo-controlled trials of 400 IU/day vitamin D, usually with 800–1,000 mg/day calcium, failed to show a benefit of supplementation in a range of diseases selected because at least one epidemiologic study had previously revealed an association with low 25(OH)D levels. The studies include the Women's Health Initiative study of >36,000 women (average age 62 years) followed on average for 7 years, which failed to demonstrate a reduction in incidence, morbidity, or mortality for colorectal cancer (Wactawski-Wende *et al.*, 2006). Subsequent analysis of the same population investigating other possible benefits of vitamin D and calcium supplementation suggested by prior epidemiologic studies further revealed no significant impact on overall mortality, coronary or other cardiovascular death, cerebrovascular death, or total cancer deaths (LaCroix *et al.*, 2009). There were modest and nonsignificant reductions in fractures of the hip and vertebrae (Jackson *et al.*, 2006). Although the Women's Health Initiative studies have been discounted by many in the field for using too small a supplement, they remain the largest and best controlled efforts to date to implicate vitamin D in health outcomes.

Negative results were also noted in a prospective study of nearly 17,000 subjects recruited from the National Health and Nutrition Examination Survey study and followed up to 12 years; there was no effect of 25(OH)D level on mortality risk for five of six cancer types or for overall cancer mortality (Freedman *et al.*, 2007). Subsequently, these investigators performed numerous additional analyses of the data in response to the suggestion that they might have missed important associations detected in previous smaller studies by failing to account for race or season of the 25(OH)D determination or to separately examine only subjects with low 25(OH)D levels. All these analyses, and more, yielded no additional

associations between cancer mortality and 25(OH)D levels (Freedman *et al.*, 2009). Studying a second independent large population of postmenopausal women, these investigators also found no relationship between breast cancer risk and baseline levels of either 25(OH)D or 1,25(OH)D, also suggested by some to affect multiple health outcomes (Freedman *et al.*, 2008).

What's concerning about the definition of vitamin D insufficiency?

More than one-half to three-fourths of many studied populations of apparently healthy people are now classified as vitamin D insufficient (Ginde *et al.*, 2009; Holick, 2007), and it is suggested that they are at increased risk of disease or early death and require interventions whose long-term risks are unknown. From a dermatologic perspective, the major concern is the position of the Indoor Tanning Association and a small number of authors who advocate increased UV exposure as the best way to correct this situation, despite the anticipated increases in skin cancer, including melanoma, and photoaging. From a broader public health perspective, however, other problems exist.

First and most critically, having the media and certain physician groups propagate alarmist health messages that later prove to be incorrect may cause needless fears and ultimately undermine public confidence in all public health messages. Although of interest and deserving of further study, the epidemiologic associations observed between low 25(OH)D levels and various diseases—in some studies (Crew *et al.*, 2009; Garland *et al.*, 2007; Holick, 2007) but certainly not all (Arslan *et al.*, 2009; Freedman *et al.*, 2008, 2009; Giovannucci, 2005; Grant and Boucher, 2009; Wolpowitz and Gilchrest, 2006)—do not establish cause and effect. In our opinion, this must be done in prospective, randomized, double-blind trials in which vitamin D supplementation is compared with placebo. To determine musculoskeletal and at least some other benefits, calcium intake and supplementation should also be controlled (Wolpowitz and Gilchrest, 2006). Prospective randomized controlled trials are required to eliminate the possibility that already reported statistical associations are not confounded by obesity, sedentary lifestyle, or other factors known to incidentally lower 25(OH)D levels and to predispose individuals to many of the diseases being attributed by some to vitamin D insufficiency. Others disagree with the need for such trials, noting that a preponderance of nonrandomized, noncontrolled studies supports a healthful effect of high 25(OH)D levels and that the scientific community is simply resistant to new ideas (Grant and Boucher, 2009).

Second, authorities in the endocrine and renal communities warn that potential risks of long-term high-dose vitamin D supplementation (>1,000 IU/day) are unknown. For example, studies of modest supplements (400 IU/day), far below the levels now being widely advocated, increased the incidence of kidney stones in well-controlled studies (Jackson *et al.*, 2006; Wactawski-Wende *et al.*, 2006). Although these risks are probably small, any risk must be weighed against an established benefit.

Why worry about a recommendation for modest unprotected sun exposure to generate vitamin D?

Recommendations by the American Academy of Dermatology (2009) and leading dermatologists for daily use of high-SPF (sun protection factor) sunscreens by almost everyone have been ridiculed by some as excessive or criticized as evidence of bias toward the sunscreen industry. However, typical sunscreen use has not been shown to induce vitamin D insufficiency (Norval and Wulf, 2009). Typical recommendations for "modest" UV exposure suggest 5–30 minutes, depending on skin type, latitude, and season, to arms and legs only, three times a week (Holick and Jenkins, 2004). Even the Australian College of Dermatologists (2005) recommends unprotected sun exposure, ranging from less than 5 minutes to 2–3 hours, depending on season and region of residence, to face, arms, and hands and only when the UV index is low to moderate, although persons at high risk for skin cancer are advised to consult a physician.

Concerns with recommending time- and site-limited unprotected sun exposure include the following: (i) few persons successfully limit their sun exposure to restricted sites for a brief and quite highly variable period determined by difficult-to-judge UV intensity, (ii) most daily sunscreen users already achieve adequate (Australian College of Dermatologists, 2005) or even maximal (Gilchrest, 2008) vitamin D in exposed skin during incidental exposures, and (iii) the message is easily distorted by the Indoor Tanning Association and others who tell the public that doctors support regular unprotected UV exposure year round, for example, through sun bed subscriptions (Gilchrest, 2008; Holick, 2009; LA Tan, 2009; TanningTruth.com, 2009). It is apparent that most sunbathers (largely fair-skinned young people) seek UV exposure not to improve their health but to tan over most or all of their body surface. Any recommendation for unprotected UV exposure, however modest, is interpreted as an endorsement of their tanning behavior.

Why is modest unprotected sun exposure inferior to oral vitamin D supplementation as a public health message?

Whether or not one believes that one-half to three-fourths of the entire population of Europe and the United States is suffering from impaired health due to vitamin D insufficiency, there is strong evidence that lack of vitamin D is a health problem for some persons with darkly pigmented skin and for many elderly persons (Holick, 2007; US National Institutes of Health, 2009; Webb, 2006). These groups often limit their sun exposure for reasons unrelated to skin cancer concerns and are unlikely to use sunscreen daily. They also photosynthesize vitamin D inefficiently because of, respectively, a high epidermal content of melanin that absorbs UV photons and epidermal atrophy, which reduces the amount of available 7-dehydrocholesterol, the vitamin D precursor (Holick, 2007; Webb, 2006). In contrast, their absorption of oral vitamin D is not impaired relative to fair-skinned or younger groups (Harris and Dawson-Hughes, 2002; Talwar *et al.*, 2007).

If very high vitamin D levels are truly desirable, sun exposure is an unreliable means of achieving them. Effective UV wavelengths (290–315 nm) are present in sunlight for only part of the year over much of the earth's surface because of the sun's zenith angle (Webb, 2006). Above 40°N latitude (encompassing

Philadelphia, New York, Boston, Portland (both Oregon and Maine), and all of Europe above central France), for example, detectable photosynthesis of vitamin D does not occur during sun exposure for at least 4 months of the year (Webb *et al.*, 1988). Inadequate exposure occurs even in generally sunny parts of the world; for example, in a cohort of 93 healthy, lean young men in Hawaii (latitude 21°N), most recruited from a surf shop and averaging 29 hours/week of direct, largely unprotected sun exposure over the preceding 3 months, more than half were classified as vitamin D insufficient with 25(OH)D levels <30 ng/ml (75 nmol/l) (Binkley *et al.*, 2007). This suggests that the reasonable-sounding recommendations for very modest sun exposure would not in practice raise 25(OH)D levels sufficiently in the opinion of many. Sun bed use, proposed as an alternative to sun exposure during the winter (Holick, 2007), is virtually nonexistent in the demographic groups at highest risk for vitamin D deficiency and customarily entails exposures that far exceed those from casual sun exposure (US Department of Health and Human Services, 2005) or that maximize vitamin D production (Holick *et al.*, 1980), resulting in needless excess photodamage and increased risk of skin cancers. Moreover, sun bed use (often $3–15/single session or $20/month for unlimited sessions) is far more expensive and less convenient than a daily oral supplement of 1,000 IU ($0.05 per capsule at several large pharmacies), eliminating the common "cost argument" in favor of UV exposure versus supplements as a means of increasing vitamin D levels. Finally, the cost of UV-induced skin cancer to patients and society is billions of dollars annually (Bickers *et al.*, 2006).

Our conclusions

Individuals at high risk of skin cancer, including persons with skin phototype I or II (generally fair-skinned persons), those with a personal history of skin cancer, and those with numerous or atypical nevi or moles, should wear protective clothing, use a high-SPF sunscreen daily, and avoid midday sun when possible. Those wishing to minimize photoaging of their skin should do the same. Persons at intermediate risk of skin cancer should be urged to protect themselves similarly at times of anticipated intense sun exposure, such as during sunny vacations or outdoor recreation. Everyone should be strongly discouraged from using sun beds. Elderly or dark-skinned individuals who practice safe sun exposure or who are infrequently exposed to the sun for any reason should be encouraged to take a daily vitamin D_3 supplement of 1,000 IU, preferably with 1 g/day of calcium. Oral supplementation of 1,000 IU per day or more can also be safely recommended to virtually any adult concerned about his or her vitamin D status, especially during the winter months.

Neither the biologic validity of "vitamin D insufficiency" nor the health benefit of maintaining high serum 25(OH)D levels has been established for the general population.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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