

The vitamin D questions: How much do you need and how should you get it?

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UV radiation is a well-documented human carcinogen, indisputably linked to the current continued increased rate of skin cancer. UV radiation is also responsible for cutaneous synthesis of vitamin (vit) D₃, a substance that is then sequentially hydroxylated in the liver and kidney to yield 1,25(OH)₂ vit D, a hormone critical for calcium homeostasis and skeletal maintenance. Because the UV action spectra for DNA damage leading to skin cancer and for vit D photosynthesis are virtually identical, the harmful and beneficial effects of UV irradiation are inseparable. This has given rise to the argument that sun avoidance, with a goal of skin cancer prevention, may compromise vit D sufficiency. Public interest in this matter has been heightened in recent years by multiple studies correlating the level of 25-OH vit D, the readily measurable “storage” precursor form of the vit, with a variety of benefits separate from skeletal health. Although the studies are of variable quality and all alleged treatment benefits are based on dietary supplementation with vit D, not on increased sun exposure, they have been interpreted by some as support for advocating increased sun exposure of the public at large. The goal of this review is to provide a detailed, balanced, and referenced discussion of the complex literature underlying the current popular interest in vit D and sun exposure for the purpose of increasing vit D photosynthesis. We review the nomenclature, metabolism, and established functions of vit D; the evidence supporting the less well-established but purported vit D effects; the concept of vit D insufficiency; populations at risk for vit D deficiency; and finally the risk/benefit of obtaining vit D from cutaneous photosynthesis versus diet or supplementation. (J Am Acad Dermatol 2006;54:301-17.)

THE CONTROVERSY

The vitamin (vit) D controversy is nearly 100 years old. It pits established risks of sun exposure against established benefits of cutaneous production of vit D and, more recently, against a variety of potential unproven benefits.

Two discoveries in the 1920s reinforced Coco Chanel’s trendy new “tanned is beautiful” message¹ and led to the public opinion that unprotected sunshine exposure was beneficial to health: (1) vit D is the active compound in cod liver oil that prevents childhood rickets²; and (2) UV radiation causes vit D synthesis.³ This favorable public perception of UV radiation was further reinforced both by exaggerated claims of health benefits by some

Abbreviations used:

DHC: dehydrocholesterol
 DM: diabetes mellitus
 FDA: Food and Drug Administration
 GI: gastrointestinal
 PTH: parathyroid hormone
 RDA: recommended daily allowance
 SPF: sun protection factor
 VDR: vitamin D receptor
 vit: vitamin

members of the medical community, including, but not limited to increased resistance to upper respiratory infections, improved metabolism, treatment of anemia, improved “tissue tone” and “skin tone,” increased mental activity, improved circulation, and decreased risk of hepatic cirrhosis, chronic constipation, nephritis, heart disease, and eclampsia. These salutary effects were also advocated by the makers of home UV lamps who financially benefited from this favorable attitude.³ Ironically, such emotionally charged arguments regarding the risks and benefits of UV exposure persist to the present day, fueled by both sound and questionable research, by differing psychological perspectives within society, and by strong financial interests.

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Funding sources: None.

Conflicts of interest: None identified.

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Published online January 4, 2006.

0190-9622/\$32.00

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doi:10.1016/j.jaad.2005.11.1057

The suspicion that UV radiation is a human carcinogen existed in the medical literature since at least the 1890s³ and evidence continued to accrue through the 1950s. In the 1960s, UV radiation–induced DNA mutations were characterized, and in the 1990s, specific genes and signaling pathways targeted by these mutations were identified.³ There is now overwhelming evidence that UV radiation is carcinogenic, and UV is among the officially recognized environmental carcinogens.* In this regard, the legacy from the first half of the 20th century has been a near epidemic of melanoma and nonmelanoma skin cancers, and the incidence of all types of skin cancer continues to increase. As of 2005, more than 1.5 million skin cancers will be diagnosed yearly in the United States.⁴ Approximately 1 in 70 people in the United States is expected to develop malignant melanoma during his/her lifetime,⁵ resulting in nearly 60,000 new cases and 8000 deaths annually. In addition, the adverse psychosocial and physiologic effects of photoaging fuel the demand for effective interventions among the progressively increasing absolute number and proportion of the population who are elderly.⁶ Nevertheless, society still maintains that tanned skin is cosmetically attractive, a message that is most enthusiastically embraced by teenagers and young adults, and a multibillion dollar a year tanning industry exists to capitalize on this perception.^{7,8} The societal disconnect between the perceived cosmetic benefit of suntanning and incontrovertible consequences of photoaging and increased skin cancer risk is greatly facilitated by the decades-long delay in development of the unwanted sequelae, compounded by the psychologic near-impossibility of young adults visualizing themselves as middle-aged or elderly.

On the current sophisticated battlefield of public opinion, it is often very difficult for the layman or even the physician to obtain accurate information and to dissect the scientific and medical issues from philosophic posturing and financial conflicts of interest. The goal of this review is to provide a detailed, balanced, and referenced discussion of the complex literature underlying the current popular interest in vit D and the political crusade of some to promote UV exposure with the stated intent of increasing vit D photosynthesis in the skin. Accordingly, this article reviews the nomenclature, metabolism, and established and putative functions of vit D; the known and

putative clinical consequences of vit D deficiency versus insufficiency; populations at risk for vit D deficiency; and the risks versus benefits of obtaining vit D from cutaneous photosynthesis versus diet or oral supplementation.

NOMENCLATURE AND SOURCES

Vit D obtained its name in the early part of the 20th century after the discovery of the antirachitic effect of cod liver oil. The suspected vit in cod liver oil was designated “D,” as vits A, B, and C had already been identified.² The nomenclature for vit D precursors and metabolites is provided in Table I. The sources and production of vit D are summarized briefly in Fig 1 and extensively reviewed elsewhere.⁹ The term “vitamin D” specifically refers to two biologically inert precursors: vit D₃ (cholecalciferol) and vit D₂ (ergocalciferol).^{10,11} Vit D₃ is produced in the skin from 7-dehydrocholesterol (DHC) in cell membranes after exposure to UV radiation in the UVB spectrum (290–320 nm).^{12,13} However, cutaneous vit D₃ production after a single prolonged UVB exposure is capped at approximately 10% to 20% of the original epidermal 7-DHC concentration,^{12,14} a limit achieved with suberythemogenic UV exposures.¹⁵ Additional UVB transforms previt D₃ into biologically inactive metabolites, tachysterol, and lumisterol (Fig 1).¹⁴ In contrast, UV-induced DNA damage increases linearly with increasing dose at least through exposures that cause massive epidermal cell death.

Vit D₂ is plant derived, produced exogenously by irradiation of ergosterol, and enters the circulation through diet.¹⁶ Vit D₃, like vit D₂, is available from foods (eg, vit D₃ is found in cod liver oil) and vit supplements, and can enter the circulation through gastrointestinal (GI) absorption. Studies have shown that dietary supplementation with vit D₂ is effective in preventing vit D deficiency,^{16,17} although others have found that vit D₃ is more efficacious than vit D₂ in increasing serum 25-OH vit D levels, possibly because of a greater affinity for the serum vit D binding protein.^{18,19} Whether this difference is biologically significant is unknown, as Rapuri et al,¹⁶ in 2004, found no significant difference in serum 25-OH vit D levels between elderly women who self-reported taking a daily vit D₂-versus D₃-containing supplement. In addition, the vit D₂-supplemented but not the vit D₃-supplemented group had wintertime total serum 25-OH vit D levels significantly greater than the unsupplemented group.¹⁶ Importantly, these studies used dietary vit D₃, obviating the need for sun exposure to obtain this vit D precursor metabolite.

*Report on Carcinogens, 11th ed; US Department of Health and Human Services, Public Health Service, National Toxicology Program; <http://ntp-server.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932>.

Table I. Nomenclature of vitamin D precursors and metabolites

Common name	Clinical name	Abbreviation	Comments
7-Dehydrocholesterol	Previtamin D ₃	7-DHC	Lipid in cell membranes
Cholecalciferol	Previtamin D ₃	Previt D ₃	Photosynthesized in skin or obtained from diet
Ergocalciferol	Previtamin D ₂	Previt D ₂	Obtained from diet; equivalent to vit D ₃ as precursor for active vit D
Calcidiol	25-Hydroxyvitamin D	25-(OH) vit D	Circulating "storage" form of vit D, biologically inactive
Calcitriol	1,25-Dihydroxyvitamin D	1,25-(OH) ₂ vit D	Active form of vit D, tightly regulated

Biologically inactive vits D₂/D₃ require subsequent hydroxylation reactions in the liver and kidney to form 1,25-dihydroxyvit D (1,25-[OH]₂ vit D; calcitriol), the biologically active metabolite of vit D (Fig 1).¹¹ 1,25(OH)₂ vit D levels are relatively low and tightly regulated (see below), whereas 25(OH) vit D levels reflect recent ingestion and/or cutaneous production of vit D and indicate the size of the vit D reservoir. Thus, dietary consumption and cutaneous vit D production are completely interchangeable precursors of the active hormone, and together determine the level of circulating 25(OH) vit D, the conventionally measured precursor form of the active vit.

ESTABLISHED VIT D HORMONAL FUNCTION AND THE CONSEQUENCES OF DEFICIENCY OR EXCESS

The principal physiologic function of the active vit, 1,25-(OH)₂ vit D, is to maintain calcium homeostasis. In this essential role, vit D functions as a hormone, synthesized far from the sites of its biologic action (GI tract and bone) and reaching these distant sites through the blood stream. Vit D is indeed a member of the superfamily of steroid hormones that also includes corticosteroids, all *trans*-retinoic acid (vit A), and thyroid hormone, and act in the nucleus by binding their cognate nuclear receptors to transactive responsive genes.⁹

By preserving serum levels of calcium and phosphate, vit D maintains the calcium × phosphate product in a range that provides osteoblasts with sufficient ions to mineralize the collagen matrix.^{20,21} The established clinical consequences of hormonal vit D deficiency are primarily a result of the associated elevation in parathyroid hormone (PTH), called secondary hyperparathyroidism (conventionally defined as PTH levels > 65 pg/mL). PTH compensates for inadequate intestinal-derived calcium by mobilizing calcium stores from bone into the blood and wasting phosphorus in urine.^{9,22} Ultimately, insufficient amounts of calcium and/or phosphate deposition in the bone matrix leads to inadequate bone

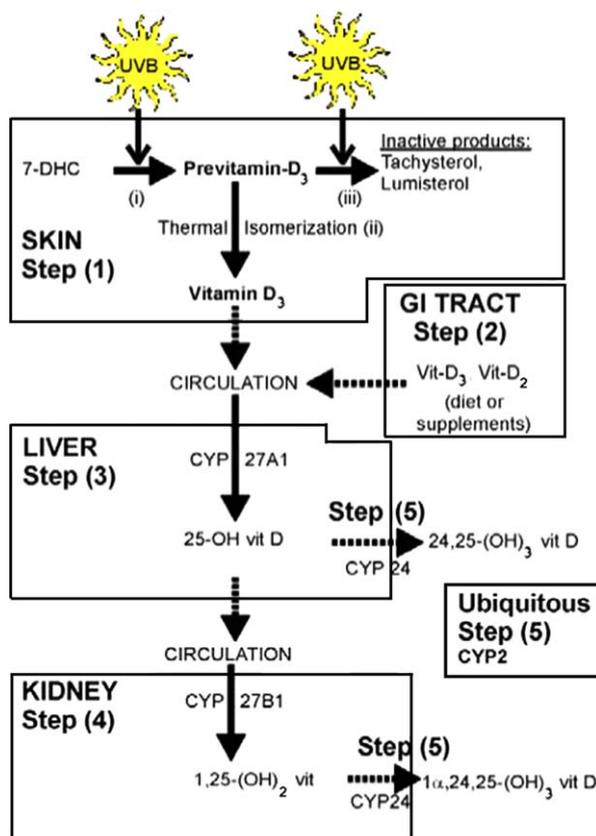


Fig 1. Sources, sites, and processing of vitamin (vit) D metabolites. In skin (step 1), 7-dehydrocholesterol (DHC) is converted by UVB into previt D₃, that further UVB exposure converts into biologically inactive products tachysterol and lumisterol. In this way, tachysterol and lumisterol formation acts as biologic safety valve to prevent UVB-induced vit D toxicity. Thermal isomerization converts previt D₃ into vit D₃, which then enters into circulation. Vit D₃/D₂ also enters circulation by absorption through gastrointestinal (GI) tract (step 2). Vit D₃/D₂, bound to vit D-binding protein, are transported to liver (step 3) where CYP27A1 converts them to the biologically inactive 25-OH vit D. 25-OH vit D is carried to kidney (step 4) where it is converted to 1,25-(OH)₂ vit D, the biologically active metabolite of vit D metabolism. Finally, both 25-OH vit D and 1,25-(OH)₂ vit D are metabolized to biologically inactive products by ubiquitous enzyme, CYP24.

Table II. Terms describing vitamin D status

Status	Serum 25(OH) vit D level ^{31-36,40,42,143}	Characteristics
Deficiency	<20 to <25 nmol/L, depending on author	PTH > 65 pg/mL, rickets or osteomalacia
Sufficiency	Above insufficient level	PTH < 65 pg/mL, no bone disease
Insufficiency	<37.5 to <50 nmol/L to as high as <80 to 100 nmol/L, depending on author	PTH 10-65 pg/mL but reduced by vit D supplementation

PTH, Parathyroid hormone; vit, vitamin.

matrix (osteoid) mineralization: rickets in children and osteomalacia in adults, the classic diseases associated with severe vit D deficiency. Clinically, rickets affects both the growth plate (epiphysis) and the newly formed bone, leading to a well-defined constellation of signs, primarily involving compromised skeletal health.²² Osteomalacia in adults can be asymptomatic but also presents as vague, long-standing diffuse bone and muscle pain and skeletal muscle weakness, pelvic deformities, and a waddling gait.²²⁻²⁴

Conversely, the clinical consequences of excessive vit D are secondary to hypercalcemia and hypercalciuria. Symptoms include weakness, lethargy, headaches, nausea, polyuria, ectopic calcification in tissues, and eventually mental status changes, including confusion, stupor, and coma.²¹ Importantly, however, ingestion of even large amounts of previt D₂/D₃ is unlikely to cause hypervitaminosis D because of stringent regulation of the final renal hydroxylation step required for activation of the hormone.²⁵

VIT D DEFICIENCY VERSUS INSUFFICIENCY

Vit D differs from most other vits and essential nutrients in having a large precursor pool in the body that varies over a wide range in healthy individuals and a small tightly regulated range of the active compound. By consensus, the circulating level of the inactive precursor 25-OH vit D is the universally accepted indicator of vit D status because it is easily measured, has the longest half-life in circulation (approximately 2 or 3 weeks), and the levels of 25-OH vit D correlate with clinical disease states.^{26,27} Currently, although the laboratory range of normal for 25-OH is 20 to 150 nmol/L, there is no universally accepted measure of adequate levels of 25-OH vit D.^{25,28,29}

Terminology is critical to understanding this lack of consensus (Table II). "Sufficiency" classically refers to levels of 25-OH vit D corresponding to the absence of abnormalities in calcium homeostasis. Recently, based on the assumption that human beings evolved in an environment of unprotected sun exposure,³⁰ some have suggested that

sufficiency should be defined as the mean serum 25-OH vit D levels found in lifeguards (161 nmol/L), which is about 2.4 times above the mean of a more sun-restricted population (68.3 nmol/L).²⁹ In this regard, lifeguards with serum 25-OH vit D levels of 148 nmol/L had hypercalciuria (an early sign of hypervitaminosis D), suggesting that the high normal should not exceed 140 nmol/L.²⁵ Deficiency indicates levels of 25-OH vit D corresponding to clinically evident disease states with respect to skeletal health (ie, osteomalacia or rickets). In general, levels of 25-OH vit D less than 20 to 25 nmol/L are associated with deficiency (rickets and histologic evidence of osteomalacia). "Insufficiency" is a more recent term, defined by laboratory values, specifically serum PTH levels within the normal range that can be decreased by vit D supplementation, in the absence of clinically evident osteomalacia or rickets.²³ Philosophically, this has been interpreted to indicate an undesirable vit D status, even in the absence of disease signs or symptoms.

Most recently, insufficiency has been redefined by some as 25-OH vit D levels statistically associated with adverse health outcomes in the population (Table III). This expanded definition of insufficiency arises from: (1) attributing a cause-and-effect relationship to the correlation in epidemiologic studies of high serum 25-OH vit D levels and reduced disease prevalence, such as some internal malignancies and autoimmune disorders¹⁵ (Table III); and (2) generalizing the results of controlled trials on muscle strength and fall frequency in the elderly to the entire population, regardless of age or baseline health status. This perspective views 25-OH vit D levels as insufficient if, in population studies, increased disease risk can be ascribed to the value, whether or not there is any evidence of adverse health consequences for the tested individual or indeed for the great majority of the population with similar 25-OH vit D levels.

Defining the range of insufficiency is not straightforward. The serum 25-OH vit D threshold point can be defined as the maximum serum 25-OH vit D level beyond which there no longer exists an association between further increases in serum 25-OH vit D and further decreases in serum PTH. However, in the

Table III. Known or purported associations with serum 25-OH vitamin D levels

Effect on:	Serum 25-OH vitamin D levels, nmol/L		
	Deficient (<20-25)	Insufficient (25-50)	Sufficient (>50)
Serum PTH level	Above normal range	Within normal range*	Maximally suppressed [†]
Skeleton	Rickets/osteomalacia	Osteoporosis [‡]	Normal skeletal homeostasis
Prostate cancer risk ⁸²	Increased (<19)	Baseline (40-60)	Increased (>80)
Colorectal adenoma risk ⁸¹	Baseline (<72)	Baseline (<72)	Decreased (>72)
Mild essential hypertension (>140/80 mm Hg) ¹⁴⁴	Not assessed	Baseline (38-57)	Reduced but still >140/80 mm Hg (>100 [§])
Multiple sclerosis risk ¹⁴⁵	Not assessed	Baseline (40-55)	40% Relative risk reduction (70-75)
Fibromyalgia ^{¶24}	29% of 150 patients (<20)	93% of 150 patients (<50)	7% of 150 patients (>30)

PTH, Parathyroid hormone.

Numbers in parentheses indicate associated serum 25-OH vitamin D levels.

*Serum PTH can be further suppressed with higher serum 25-OH vitamin D levels.

[†]Serum PTH levels are no longer correlated to serum 25-OH vitamin D levels above these values.

[‡]Defined as increased bone turnover/decreased bone mineral density.

[§]Average 25-OH vitamin D level was 151.2 nmol/L, which causes hypercalciuria—in this situation an early sign of hypervitaminosis D.

^{||}40% Risk reduction was only found in patients who took multivitamin supplements containing 25-OH vitamin D (and other vitamins) but not in those who achieved similar levels by dietary intake or environmental exposure.

[¶]Study assessed 25-OH vitamin D levels in 150 patients with fibromyalgia at only one time point and did not assess if vitamin D supplementation improved symptoms.

elderly, large variations in the serum 25-OH vit D threshold point have been found, ranging from as low as 30 nmol/L to greater than 100 nmol/L.³¹⁻³⁶ This broad range is not likely to be an artifact of different laboratory assays,³¹ as variability between laboratories is only 20% to 30%.²⁵ Instead, dietary calcium intake can explain the variation in this serum 25-OH vit D threshold level, as an inverse relationship exists between calcium intake and the serum 25-OH vit D threshold point.³⁵ For example, populations with a daily calcium intake greater than 1100 mg/d versus 700 to 800 mg/d had serum 25-OH vit D threshold points of 30 and 110 nmol/L, respectively.^{31,35} Importantly, calcium enters the circulation through both vit D—dependent active GI absorption and by vit D—dependent passive absorption.³⁵ In populations with ample calcium in the diet, enough calcium enters the blood stream from the gut by passive diffusion, and PTH release to stimulate additional vit D production in the kidney is minimized. Conversely, in populations with lower amounts of calcium in the diet, 25-OH vit D levels as high as 100 nmol/mL are needed to maintain serum calcium through active GI absorption, and PTH levels are higher to generate this compensatory vit D.

In summary, the desire for a definition of vit D insufficiency arose from the assertion that it is advisable to maximally suppress PTH levels and/or maintain 25-OH vit D levels well above levels required for bone health or indeed any detectable individual health benefit. However, the above data indicate that efforts to suppress PTH maximally should also focus

on maintaining adequate dietary calcium intake, in addition to arbitrary serum 25-OH vit D levels. In fact, in children in equatorial Africa who are inarguably vit D sufficient, cases of florid rickets have been documented as a result of deficiency of dietary calcium and completely cured by calcium supplementation alone.³⁷ Because dietary supplementation can simultaneously provide intestinal vit D and calcium, whereas sun exposure alone provides only vit D, dietary supplementation is superior to sunshine alone in suppressing PTH levels—the defining measure of vit D insufficiency.

DOES VIT D INSUFFICIENCY AFFECT SKELETAL HOMEOSTASIS?

Although randomized clinical trials of vit D supplementation have failed to clearly support clinical benefits of treating insufficiency (see below), some authorities have chosen to blur the distinction between insufficiency and deficiency. They suggest that the normal range for 25-OH vit D should be redefined as that required to minimize PTH levels (Table II).^{34,38-41} This change in definition causes individuals with 25-OH vit D levels in the insufficient range to be counted as deficient. The total number of people in the general population with vit D deficiency then increases significantly. For example, setting the bar for deficiency at 50 nmol/L rather than 25 nmol/L increases the number of US African-American women between the ages of 15 and 49 years with vit D deficiency from 12.2% to 42.4%,⁴⁰ and the number of people in Boston, Mass, in winter

Table IV. Efficacy of vitamin D supplementation in preventing osteoporosis-induced fractures and/or increasing serum 25-OH vitamin D levels

Study	Supplement form	Calcium supplement/d, mg	Increase in serum 25-OH vit D, nmol/L	Reduction in hip fractures	Reduction in all nonvertebral fractures
Dawson-Hughes et al ⁴⁷	D ₃ (pill)	500	approximately 29.5*	NS	60% RR (<i>P</i> = .02)
Chapuy et al ⁵¹	D ₃ (pill)	1200	65	27% [†] (<i>P</i> = .004)	26% [†] (<i>P</i> < .001)
Chapuy et al ⁵⁰	D ₃ (pill)	1200	NA	23% [†] (<i>P</i> < .02)	17.2% [†] (<i>P</i> < .02)
Chapuy et al ⁵³	D ₃ (pill)	1200	30-35	NS	NS
Trivedi et al ⁵⁸	D ₃ (pill)	None	NA	NS	33% RR (<i>P</i> = .04)
Heikinheimo et al ⁵⁵	D ² (IM)	None	18.1 and 31.2 [‡]	NS	5.4% [§]
Meyer et al ⁵⁷	D ₃ (cod liver oil)	None	22	NS	NS
Lips et al ⁵⁶	D ₃ (pill)	None	31	NS	NS
Gallagher ⁵⁴	1,25-(OH) ₂ vit D	None	NS	NA	NS
Grant et al ⁵⁹	D ₃ (pill)	None	24.25	NS	NS [§]
Grant et al ⁵⁹	D ₃ (pill)	1000	24	NS	NS [§]
Porthouse et al ⁶⁰	D ₃ (pill)	1000	NA	NS	NS [§]

IM, Intramuscular; NA, not assessed; NS, not significant; RR, relative risk.

*Average of the increases for men and women.

[†]Results of intention-to-treat analysis.

[‡]18.1 nmol/L in outpatients and 31.2 nmol/L in patients who were institutionalized.

[§]Total number of fractures, including vertebral fractures.

^{||}Results of additional 18 months of follow-up of study population from Chapuy et al.⁵¹

aged 18 to 29 years from between 6% and 9% to 30%.⁴² Ironically, however, these studies provided no data on the PTH levels of these subgroups, although in the latter study, the mean PTH for all patients aged 18 to 50 years or older in winter peaked at 44 pg/mL—well below the level that defines secondary hyperparathyroidism.⁴² Redefining the range of abnormal 25-OH vit D levels to include those that cause elevations in PTH but are not associated with osteomalacia or rickets implies that clinical relevance can be ascribed to this laboratory phenomenon alone. In this regard, however, because PTH increases calcium resorption from bone, it has been proposed that vit D insufficiency may promote osteoporosis, especially in the elderly.^{43,44} In support of this concept, prospective randomized trials have demonstrated that vit D supplements, even in patients without secondary hyperparathyroidism, decrease bone turnover and increase bone mineral density.⁴⁵⁻⁴⁷

Ultimately, however, the most relevant clinical benefit of preventing secondary hyperparathyroidism, with respect to skeletal metabolism, is the prevention of osteoporosis-related fractures. Prospective observational studies have produced conflicting results regarding the association between vit D and/or calcium intake and the primary prevention of osteoporotic fractures in women.^{48,49} Ten prospective, randomized controlled studies of vit D metabolites with or without calcium supplementation to prevent osteoporosis-induced fractures have been

reported and are summarized in Table IV.^{47,50-60} These study populations have been limited to elderly and mostly female patients (mean age \geq 70 years), restricting the ability to generalize the findings to other populations. Of the studies, 9 used vit D supplements, and one⁵⁴ used 1,25-(OH)₂ vit D. Of the 9 studies that used vit D supplements, 4 of them^{47,50,51,55,58} found a statistically significant reduction in fractures after vit D supplementation whereas 5 did not. Moreover, 9 of the 10 reported trials found no statistically significant benefit of vit D supplementation in preventing osteoporosis-related hip fractures. The one positive study found an intention-to-treat benefit in the first 18 months that was reduced after 36 months and nonsignificant in a subsequent confirmation trial.⁵⁰⁻⁵³ Consistent with the finding that hip fractures are associated with the highest morbidity and mortality,⁵⁴ there was no significant difference in mortality between treated patients and control subjects in two studies that reported this information.^{55,58}

Of the 4 studies that found a reduction in fractures, the one with the longest follow-up found that the intention-to-treat benefit after 3 years of follow-up was less than after 18 months, and the effect of vit D supplementation was not statistically significant in a subsequent confirmation trial.⁵⁰⁻⁵³ Moreover, one study included a high proportion of patients who were frankly vit D deficient^{51,55} and another was improperly randomized.⁵⁸ Finally, of this group of studies, only one⁵⁸ provided solely vit D

supplementation; the others gave calcium supplementation with vit D.

In contrast, 4 large trials showed no fracture reduction benefit of vit D supplementation alone (3 studies) or with calcium (two studies).^{56,57,59,60} Two of these studies used a lower vit D supplementation (400 vs 700-800 IU in the positive studies described above).^{56,57} This lower vit D intake has been proposed to explain the negative results. For example, selecting some of the trials listed in Table IV, a recent meta-analysis found a statistically significant reduction for hip fractures (26%) and nonvertebral fractures (23%) only when these low-dose trials^{56,57} were excluded from the analysis.⁶¹ However, other recent data suggest that the failure to find a fracture-prevention benefit from vit D supplementation in negative trials cannot be attributed to low doses in the negative trials. Importantly, this meta-analysis did not include two subsequently published large, randomized prospective clinical trials involving more than 8000 patients providing 800 IU vit D₃ that both failed to demonstrate any type of fracture-reduction benefit from vit D supplementation.^{59,60} Moreover, others have reported that increasing intake from 400 to 800 IU marginally affects 25-OH vit D levels,⁶² and one study using 400 IU/d of vit D demonstrated a more robust effect on bone mineral density at the femoral neck than another using 700 IU/d.^{47,63} The results from these negative trials have also been attributed to: (1) the lower final serum 25-OH vit D concentrations (54⁵⁶ and 64⁵⁷ nmol/L) versus two positive trials with final concentrations greater than 100 nmol/L^{47,51}; and (2) too little vit D being supplemented: if the serum 25-OH vit D level of lifeguards is the true normal, adults may require 2000 to 4000 IU/d to obtain beneficial effects of vit D.^{29,30} Alternatively, as described in detail above, dietary calcium intake determines the serum 25-OH vit D threshold point with respect to PTH suppression, so that serum 25-OH vit D concentrations need to be evaluated in the context of the calcium intake of the patient population.³⁵ In this regard, the positive study populations at baseline had lower dietary calcium intakes and received concomitant calcium supplementation. Moreover, the meta-analysis that reported a significant hip and nonvertebral fracture reduction clearly stated these studies could not demonstrate a benefit of vit D independent of calcium.⁶¹ Thus, the negative results of Meyer et al⁵⁷ and Lips et al⁵⁶ are more likely the consequence of having fewer patients with vit D insufficiency, very few with vit D deficiency, and overall higher baseline calcium intakes compared with the study populations of Dawson-Hughes et al⁴⁷ and Chapuy et al.⁵¹ Similar rationale have also been offered for the

negative results of Porthouse et al⁶⁰ and Grant et al,⁵⁹ which studied community-based (not institutionalized), less frail elderly populations. In the study of Grant et al,⁵⁹ the population at baseline was not deficient (mean 25-OH vit D levels 38 nmol/L) and had PTH level within the normal range (50 pg/mL). Porthouse et al⁶⁰ did not report serum levels of 25-OH vit D, calcium, or PTH. Although compliance was suggested to be an issue for both of these latter studies,^{59,60,64} supplementation was effective at least in the study of Grant et al⁵⁹ as after concurrent calcium supplementation, those patients measured were no longer insufficient by almost all criteria (mean 62 nmol/L) and had reduced PTH levels after therapy (32.7 pg/mL).

Thus, evidence from these randomized, prospective clinical trials of frail elderly patients suggests that a beneficial effect of vit D supplementation on skeletal homeostasis: (1) requires concurrent calcium supplementation and/or a diet high in calcium; (2) is limited to preventing nonhip osteoporotic fractures; and (3) occurs primarily or exclusively in patients with severe deficiency (<25 nmol/L 25-OH vit D) and not those with insufficiency. These studies provide no direct information on the effect of daily dietary vit D supplementation on children or on young or middle-aged adults, or when given to adults in excess of 800 IU/d, and do not address sun exposure in any population.

OTHER PUTATIVE INDICATIONS FOR TREATING VIT D INSUFFICIENCY

Skeletal muscle strength

1,25-(OH)₂ vit D, a secosteroid hormone, enters the target cell, then binds and activates a nuclear receptor, the vit D receptor (VDR). This complex, which may form heterodimers with non-VDRs, then binds to specific DNA sequences (vit D-responsive elements), altering transcription of effector genes.^{9,65} Thus, VDR-expressing tissues comprise a population of cells theoretically able to respond to 1,25-(OH)₂ vit D. As would be expected for the classic hormonal function of 1,25-(OH)₂ vit D in maintaining calcium homeostasis, VDR expression has been documented in intestine, bone, and kidney.⁶⁶ In addition, VDR expression has been documented in brain, skeletal muscle, breast, prostate, colon, activated lymphocytes, macrophages, and skin, creating the possibility that these noncalcium-homeostasis tissues might also be regulated by vit D.^{20,23,27,67} In the case of epidermal keratinocytes and dermal fibroblasts, such vit D effects have been well documented at least in cell culture⁶⁸⁻⁷⁰ and are the basis of oral and topical regimens using vit D or its analogs to treat psoriasis.^{71,72}

Evidence of a functional role for vit D in skeletal muscle and the nervous system is more limited and comes from closer analysis of the osteoporosis studies. Strictly limited to the elderly population, some of these studies found a fracture reduction risk even when bone mineral density was only minimally improved. One explanation for this reduction in osteoporotic fractures is that vit D supplementation decreases the number of falls leading to fracture rather than increasing bone strength.³⁰ Studies have supported the assertion that vit D supplementation improves muscle strength and reduces body sway.^{23,73} However, results from clinical trials using vit D supplementation explicitly to prevent falls have been mixed.⁷⁴ The pattern is the same as for the fracture studies: in general, studies that showed positive effects in the elderly used vit D with calcium supplementation and treated populations that were frankly vit D deficient, not insufficient.^{23,73} In this regard, a recent meta-analysis found a fall reduction of 22% (corrected odds ratio 0.78) for 5 trials that met their specific inclusion criteria and 13% (corrected relative risk 0.87) when all relevant studies were pooled. This meta-analysis could not stratify results by baseline 25-OH vit D levels but did suggest that the combination of vit D and calcium was important for fall reduction.⁷⁴ No trial data support the conclusion that vit D supplementation in the absence of concomitant calcium supplementation is effective in preventing falls. By extrapolation, no evidence supports the notion that UVB exposure alone might confer the same benefit as dietary supplements, even in this frail elderly population.

Reduced cancer mortality

Selected epidemiologic data suggest an inverse correlation between solar UVB exposure and mortality from several cancers, including colon, breast, and prostate, and between sun exposure and the incidence of colon cancer.^{39,75-82} These studies are observational in nature and, therefore, cannot establish that solar UVB exposure affects cancer incidence or mortality. Moreover, these data generally rely on correlating region-specific mortality with ambient UV radiation. Such studies may be confounded by geographic variations in population genetics or cultural or lifestyle behaviors and do not correlate disease with actual sun exposure at the individual level.⁸³ In addition, as UV radiation is strongly correlated with latitude, both of these may be confounded by other factors that also vary with geographic location, such as, but not limited to, diet, pollution, or socioeconomic status of the population.⁸⁴

Nevertheless, cutaneous vit D photosynthesis is proposed to account for these epidemiologic

associations.³⁹ Observational cross-sectional or case controlled epidemiologic studies have reported an inverse association between both serum 25-OH vit D levels and vit D intake and several epithelial-derived cancers.^{39,75,77-82,84,85} In addition, for some cultured human cancer cell lines, 1,25-(OH)₂ vit D has been reported to be antiproliferative, induce apoptosis, promote cell differentiation, inhibit telomerase expression, and suppress tumor-induced angiogenesis.^{39,81,82,86} In addition, some 1,25-(OH)₂ vit D analogs have also shown efficacy *in vivo* in animal models of chemical carcinogenesis.⁸⁷ Of note, 1,25-(OH)₂ vit D levels generally need to be in the toxic range to show these *in vitro* and animal model *in vivo* effects.^{11,57}

However, other high-quality epidemiologic and observational studies do not support a role for vit D in preventing these cancers.^{81,82,84,85,88} The situation is reminiscent of vit A and its precursor beta-carotene in that the active form of vit A, all-*trans*-retinoic acid, is strongly antiproliferative *in vitro*, is cancer-therapeutic and cancer-preventative in defined clinical settings, and its ingestion epidemiologically linked to decreased cancer risk; but controlled trials of dietary supplementation have shown no benefit on cancer incidence or mortality.⁸⁹⁻⁹¹ Although these data may be interpreted to show that the benefit of vit A (or vit D) supplementation derives from a lifetime of vit sufficiency and cannot be detected in a study lasting only a few years, the data are also compatible with there being no cause-and-effect relationship between vit levels and occurrence of disease.

Recent studies highlight the necessity of interpreting ecologic and epidemiologic data with caution. In a recent large longitudinal, nested, case controlled study involving 622 patients with prostate cancer and 1451 matched control subjects, a U-shaped curve for prostate cancer risk and serum 25-OH vit D levels was found. Risk of prostate cancer was greatest both in individuals with serum 25-OH vit D serum concentrations below 19 nmol/L and above 80 nmol/L.⁸² Similarly, not all studies observe a consistent relationship between vit D and colorectal cancer risk. One recently randomized, multicenter, placebo-controlled trial found that calcium supplementation (1200 mg elemental calcium daily) reduced colorectal adenomas in patients with serum 25-OH vit D levels greater than 72 nmol/L but had no effect in patients with lower serum 25-OH vit D levels.⁸¹ Conversely, high serum 25-OH vit D levels were associated with reduced risk of colorectal adenomas only in patients randomly assigned to receive calcium supplements. The authors interpreted this large study to demonstrate that calcium and vit D work together, not separately, to prevent colorectal carcinogenesis.⁸¹

The studies of Grau et al⁸¹ in 2003 and Tuohimaa et al⁸² in 2004 clearly demonstrate the potential pitfalls of using data on 25-OH vit D levels alone to make broad recommendations. In combination, the above studies, for example, suggest that supplementing vit D to prevent deficiency as defined for calcium homeostasis (>25 nmol/L) suffices to decrease the prostate cancer risk but supplementing to greater than 80 nmol/L increases the risk of prostate cancer,⁸² whereas serum 25-OH vit D close to 80 nmol/L (>72 nmol/L) is required for a beneficial effect of calcium on colorectal carcinogenesis.⁸¹ Accordingly, Tamimi et al⁸⁸ concluded there was a "lack of clinical trial data demonstrating efficacy and safety of vitamin D supplementation" in cancer chemoprevention. In 2003, Trivedi et al⁵⁸ found no significant effects of vit D on total mortality or incidence of cancer or cardiovascular disease in a prospective, randomized, double-blind study of 100,000 IU of vit D orally every 4 months (approximately equivalent to 800 IU/d) for 5 years. Similarly, in a 2004 review, Vieth states "... there is no evidence from randomized clinical trials showing efficacy of vitamin D (cholecalciferol) for anything beyond osteoporosis ...".³⁰ Finally, in 2005, Gross⁸⁴ called for additional nutritional epidemiologic studies with improved methodology and experimental design because epidemiologic studies to date have yielded mixed results on the antiprostata and anticolon cancer effects of vit D and calcium.

In conclusion, the above data contradict the claim that evidence exists to support a net benefit to public health from the lowering of overall mortality or incidence of epithelial-derived cancers by increasing 25-OH vit D levels above the clear-cut deficiency range as defined for skeletal health. Ultimately, only randomized, clinical trials using relevant study populations will allow rational recommendations regarding 25-OH vit D levels to achieve optimal benefits aside from calcium homeostasis. In fact, such clinical trials using dietary supplementation of vit D and/or calcium are reported to be underway.⁹² Should these studies demonstrate an overall health benefit for higher 25-OH vit D levels, they would simultaneously prove that these benefits can be achieved solely by dietary supplementation, negating the need to promote additional, unprotected sun exposure. Of note, no professional organization has proposed determining whether increased exposure to UV radiation offers a public health benefit.

Reduced risk of autoimmune diseases

The supposition that autoimmune disorders might be prevented or ameliorated by vit D arose from observations in vitro and in animal models.

Lymphocytes and monocytes express VDRs⁹³ and VDR agonists promote self-tolerance, at least in vitro, by inhibiting the T helper 1 (Th1) cell responsiveness implicated in loss of tolerance to self-antigens⁹⁴ and preventing maturation of antigen-presenting dendritic cells.⁹⁵ In addition, in mouse models, 1,25 (OH)₂ vit D₃, the active form of vit D, can either suppress or prevent several Th1-mediated diseases including type 1 diabetes mellitus (DM), rheumatoid arthritis, experimental autoimmune encephalomyelitis, inflammatory bowel disease, and systemic lupus erythematosus. Of note, however, overwhelmingly these experiments used hypercalcemic VDR analogs and not previt D, the form of the vit obtained from diet or sun exposure.^{93,95} Moreover, in some of these mouse models, suppression of autoimmune disease required concomitant calcium supplementation.^{93,95,96}

Epidemiologic studies suggesting an inverse relationship between incidence of specific autoimmune diseases in the studied population and UV exposure, interpreted as a proxy for cutaneous previt D photosynthesis, are considered far from conclusive by authorities in the field.⁹⁴ As in the case of epidemiologic studies assessing the impact of sun exposure on cancer mortality, such studies do not measure individual UV exposure, and individual exposures within a population vary widely. Moreover, such studies cannot control for possible confounding associations with latitude and season such as infections and diet. The strongest observational evidence for a beneficial effect of vit D on disease incidence is for type 1 DM and derives from European studies.⁹⁷ One case controlled study involving 7 European countries found an odds ratio of 0.65 (0.52-0.83) for onset of type 1 DM by age 15 years in children who during the first year of life were supplemented versus unsupplemented.⁹⁸ A second case controlled study in Norway found a significant reduction in type 1 DM in children supplemented with cod liver oil versus no supplementation (odds ratio 0.74) but no benefit from other types of vit D supplementation (\leq 400 IU/d).⁹⁹ These case controlled studies relied on recall after many years to determine vit D intake, potentially biasing the quality of the vit D intake data.¹⁰⁰ One prospective, cohort study from Finland found that supplementing infants (2000 IU/d) on a regular basis reduced relative risk of type 1 DM to 0.12.¹⁰¹ There is no clear explanation for why vit D supplements were so much more effective in the Finnish study than in the Norwegian study, but the difference can be attributed to very high versus customary supplementation doses.¹⁰⁰ Finally, because none of the studies measured 25-OH vit D levels, it is unclear if these conclusions can be extrapolated to other populations of children with different levels.¹⁰⁰

A thorough critique of these studies or of the observational studies linking supplemental vit D intake to reduced incidence of other autoimmune diseases is beyond the scope of this article, but lack of control subjects,¹⁰² confounding lifestyle variables,¹⁰³ and other methodologic concerns have been noted in other reviews.⁹⁶

In summary, no clinical trials confirm a link between vit D supplementation and reduced incidence or slowed progression of autoimmune diseases.^{96,104} Moreover, all existing data pertain to oral vit D supplementation, in some instances with explicit concomitant calcium supplementation, and no studies support sun exposure.

THE CASE FOR DIET/SUPPLEMENTATION VERSUS UV EXPOSURE

Overwhelming evidence asserts that vit D through dietary supplementation can correct both deficiency and insufficiency, except for those patients with GI malabsorption as the cause of vit D deficiency. The endocrine community, through its consensus groups, and journal editorials, reviews, and letters, recognizes the carcinogenic potential of UV radiation and calls for more dietary vit D supplementation, not more sun exposure or tanning bed usage.^{25,30,105-108} Dietary supplementation or intramuscular injection is so efficacious that even the major advocates for increasing sun exposure also recommend these routes.^{39,109}

Two primary arguments against dietary supplementation exist. The first major criticism of dietary vit D is that given the currently limited number of foods that are fortified, adequate amounts of vit from the standard US diet are difficult to obtain (eg, Moore et al¹¹⁰). The current recommended daily intakes of vit D interpret adequate as preventing vit D deficiency (ie, maintaining serum 25-OH vit D levels > 25 nmol/L).²⁵ The 1997 recommended daily allowance (RDA) Standing Committee of the US Department of Agriculture, therefore, recommends 200 IU/d for children and younger adults (<50 years old), 400 IU/d for older adults (>50 years old), and 600 to 800 IU/d for the elderly (>70 years old).¹¹¹ Eight ounces of fortified milk or orange juice contains 100 IU (2.5 μ g), the amount of vit D found in approximately half a teaspoon of cod liver oil.^{25,112} Beyond these two foods, at least in the United States (margarine is supplemented in some parts of Europe), the population would have to rely on salmon, mackerel, and sardines.^{56,113} Moreover, foods that claim to be fortified, such as milk, were shown in the early 1990s to have variable and sometimes inadequate or excessive amounts of

vit D,^{114,115} although this has not recently been reassessed.

However, this scarcity argument fails to acknowledge the ease of oral supplements (one or even two vit pills/d) or the contribution of incidental sun exposure to total 25-OH vit D stores. In one study, a suberythemogenic exposure of 5% of the skin surface produced mean serum 25-OH vit D levels of 35 nmol/L, already above the deficient range.¹¹⁶ These data were produced in elderly patients and so would underestimate the serum 25-OH levels from the same UVB exposure of younger individuals. The face and backs of hands have a total body surface area greater than 5%, and it is likely that despite the best efforts of sun protection campaigns, most non-institutionalized or nonhome-bound people at baseline already receive at least 15 minutes of incidental unprotected sun exposure daily to these areas without encouraging additional unprotected sun exposure.¹¹⁷ The precise impact of each exposure on vit D production will of course depend on UVB intensity, which varies with latitude, season of the year, and time of day, among other factors. However, at noon in June in Boston, Mass, a fair-skinned individual will maximize his or her vit D photosynthesis in well less than 5 minutes,¹⁵ and additional sun exposure will produce only photodamage. After applying a sun protection factor (SPF)-15 sunscreen in the customary manner,¹¹⁸ an exposure of perhaps 20 minutes would then be required to maximally produce vit D.

Thus, incorporating incidental sun exposure mandates a dietary intake of only 200 IU (5 μ g/d) to prevent vit D deficiency.²⁵ In the past, the demand for 800 to 1000 IU/d from diet applied to distinct subsets of the population, such as those who lived in submarines and the frail elderly with health issues limiting their access to incidental sunshine.²⁵ However, the above-described current RDA guidelines are being challenged on two fronts: (1) because 800 IU supplemental vit D did not reduce osteoporotic fractures in community-based, vit D-replete individuals,⁶⁴ investigators have called for higher supplemental daily doses, in some cases in excess of 2000 IU/d²⁸⁻³⁰; and (2) if insufficiency, defined as serum 25-OH vit D less than 50 nmol/L³⁴ to less than 70 nmol/L,²⁹ is to be corrected, daily dietary intake of 850 IU (21.25 μ g/d) to 2000 IU (approximately 51 μ g/d) is required—certainly pushing the limits of serum 25-OH level attainable by customary diet alone given current levels of food fortification. If future clinical trials provide evidence for overall health benefits of these higher daily intakes, effective and almost effortless alternatives exist to achieving these intakes versus increasing cutaneous exposure above incidental levels. This would include

increasing levels of food fortification and/or supplementation.¹¹⁰ Thus, in the adult population, the 25-OH vit D levels can be easily and sufficiently increased out of the deficient and very stringent insufficiency (<70 nmol/L) ranges with as little as two 50,000-IU vit pills every 4 months.⁵⁸ Finally, although vit D₂ has been shown to be effective,^{16,17} in instances when supplementing patients infrequently and in large amounts, it is prudent to recommend supplements with vit D₃ instead.^{18,19}

The second criticism of dietary vit D supplementation is that excessive dietary intake of vit D can lead to vit D toxicity,¹¹⁹ whereas cutaneous production of vit D alone does not.¹² This suggests that dietary supplementation or increased levels of food fortification to meet the above described increased demand for 25-OH intake by 1000 to 4000 IU/d is less safe than enhanced unprotected sun exposure. However, recent reviews have summarized an impressive amount of data showing that hypervitaminosis D from diet is more a theoretic concern than a reality.^{25,29,107} In this regard, limiting total cumulative daily vit D to less than 10,000 IU/d will maintain serum 25-OH vit D levels less than 140 nmol/L, preventing hypercalciuria—an early sign of hypervitaminosis D.²⁵ Specifically, dietary intake of 4000 IU/d (5 times the maximal upper RDA limit for daily adult intake) did not adversely affect serum or urine calcium levels.¹²⁰ With dietary contribution of 4000 IU/d, cutaneous production would need to produce more than 6000 IU to exceed the cumulative daily sum of 10,000 IU. However, such high levels of cutaneous production would require the most unlikely scenario of daily exposure, equivalent to 1 minimum erythema dose, to greater than 27% of total body surface area. Therefore, keeping dietary supplementation to levels of 1000 to 4000 IU or lower would avoid hypervitaminosis D (ie, hypercalciuria and loss of bone mineral density) and still afford the clinical benefits seen in some randomized controlled studies, especially if given with concurrent calcium supplementation.

THE CASE AGAINST PROMOTING RELIANCE ON PHOTOSYNTHESIS

The action spectra for previt D₃ formation, erythema, and formation of cyclobutane pyrimidine dimers in DNA all peak in the UVB range (Fig 2). Hence, vit D photosynthesis cannot be dissociated from acute and chronic photodamage, including photocarcinogenesis.¹²¹⁻¹²⁵ As few as 6 sunburns in a lifetime have been shown to increase an individual's risk for nonmelanoma and melanoma skin cancer.¹²⁵⁻¹²⁸ Moreover, in fair-skinned individuals maximum possible vit D synthesis occurs rapidly,

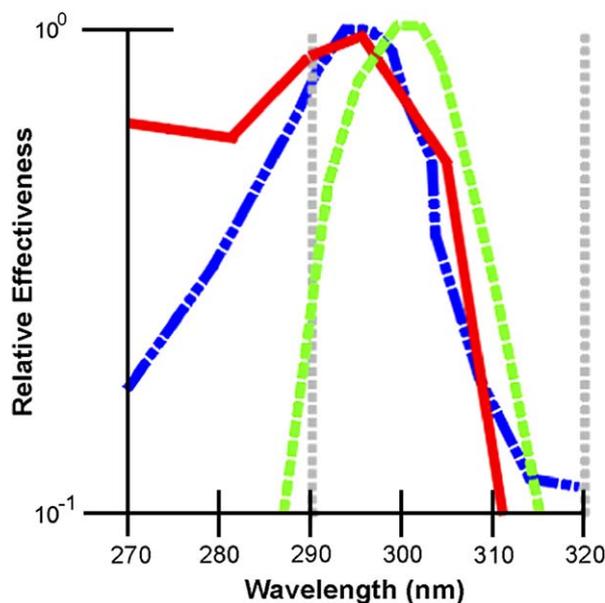


Fig 2. Cutaneous vitamin (vit) D synthesis cannot be dissociated from harmful effects of UV radiation. Dashed and dotted line (blue) shows spectrum of previt D₃ formation obtained from plotting reciprocal of photoenergy ($1/w \text{ cm}^{-2}$) (adapted¹²² by converting from a linear to power-of-10 scale). Dashed line (green) represents both action spectrum of induction of squamous cell carcinoma in human beings mathematically derived from experimental data obtained from murine skin, and wavelength dependence of induction of DNA damage, in this case cyclobutane pyrimidine dimers, in human skin (adapted¹²¹). Solid line (red) shows erythema action spectrum from human skin (m^2/J) (adapted²⁶). Note that peaks of these 3 curves all occur within UVB spectrum (290-320 nm) (dashed gray lines).

within a few minutes of summer sun exposure.³⁹ Maximum vit D photosynthesis in all individuals occurs at suberythemogenic UV doses,¹² and longer exposures add nothing to vit D stores despite increasing DNA damage in a linear fashion. The trade-off of vit D production today for photoaging and skin cancer several decades hence may have made excellent sense from an evolutionary perspective millennia ago, when life expectancy was 40 years or less, but it is a poor exchange in a society in which life expectancy has doubled, skin rejuvenation is a \$35 billion/year industry, and one in 3 Caucasians develops skin cancer.

Moreover, cutaneous vit D production is compromised in all groups identified as being at high risk for vit D deficiency.

The elderly

The elderly are particularly at risk of vit D deficiency or insufficiency because they often have

a combination of decreased skin 7-DHC (the precursor for cutaneous synthesis of vit D), decreased mobility or institutionalization that discourages sun exposure, decreased renal production of 1,25-(OH)₂ vit D, and decreased intake of fortified foods.^{129,130} For those at highest risk, increasing serum 25-OH vit D levels by planned unprotected exposure to sunlight or artificial UV radiation^{113,131,132} is likely to pose practical difficulties, in contrast to the convenient and well-tolerated oral or intramuscular supplementation, as in the osteoporosis fracture-prevention studies.

Darkly pigmented racial groups

Dark skin pigmentation, especially in African Americans, is correlated with increased risk of vit D deficiency because melanin in the skin competes with 7-DHC for absorption of UVB photons. Pigmented and nonpigmented skin have the same overall capacity to make vit D₃, but pigmented skin requires longer exposure times.¹³³ As a group, dark-skinned individuals are also likely to be lactose intolerant and, hence, to avoid milk, a major dietary source of vit D. One study found that African American women aged 15 to 49 years have a more than 20-fold risk of being vit D deficient as defined by serum 25-OH vit D less than 25 nmol/L versus Caucasian counterparts (12.2% vs 0.5% of the population), although adverse effects on health were not apparent.⁴⁰ In addition, the re-emergence of rickets in US infants is virtually restricted to dark-skinned infants exclusively fed human milk, a poor source of vit D.^{2,134} Hence, drawing on the well-documented success of vit D dietary supplementation in eradicating rickets in the last century, the American Academy of Pediatrics recommends for infants and children at risk dietary supplementation of vit D not sun exposure and its undisputed long-term risks.^{2,135}

Those living in poorly insolated environments

At latitudes above 35°, for example New York City (40°), Paris (48°), and Moscow (55°), winter sunlight lacks UVB and is incapable of producing previt D₃.³⁹ Air pollution, usually associated with urban settings, also reduces the amount of UVB reaching the earth's surface.¹³⁶ Regardless, latitude alone will not predict vit D deficiency as it fails to account for the contribution of dietary vit D to overall stores. For example, Van der Wielen et al⁴⁴ found that elderly Northern Europeans had 25-OH vit D levels (mean 54 nmol/L) well above deficient and insufficient levels (by most definitions) as a consequence primarily of a diet high in vit D—containing fish oils and/or vit D supplementation. Finally, in one study in Boston, Mass (latitude 42°), where very little to no previt D₃ can be made from sunlight during winter, 400 IU multivit

supplement easily corrected a stringent definition of insufficiency/deficiency (>50 nmol/L) in those age 18 to 29 year.⁴² Importantly, winter dietary supplementation avoids the need for carcinogenic UVB exposure from artificial sources, such as tanning beds, to maintain sufficient 25-OH vit D in this 18- to 29-year-old population that has decades to develop the harmful consequences of chronic, unprotected UV exposure.^{8,127,137}

Certain cultural groups

Cultural and lifestyle practices that minimize sun exposure and/or dietary vit D intake may adversely affect vit D status. One study found that in Southern Europe, where latitude favors cutaneous previt D synthesis, people nevertheless often have insufficient wintertime levels of 25-OH vit D, attributed to sun avoidance, long clothing, and increased disability in the absence of adequate dietary intake or supplementation.⁴⁴ Moreover, increasing cutaneous vit D production by increasing the area of exposed skin surface may not be an option in some cultures. Thus, whereas lifestyle/cultural practices may reduce cutaneous production of vit D even more than latitude, dietary supplementation can prevent ensuing vit D deficiency. Thus, Glerup et al⁷³ showed that in veiled Arab female individuals, although they continued to have minimal cutaneous production of vit D, vit D injections or oral supplementation efficiently corrected their deficiency.

Sunscreen users

There is no evidence that customary sunscreen use causes vit D deficiency or insufficiency in otherwise healthy individuals. However, two studies are extensively cited in support of the opposite conclusion. First, Matsuoka et al¹²² documented that in a laboratory situation, applying ethanol with 5% (wt/vol) para-aminobenzoic acid to pieces of normal human skin prevented UVB-induced conversion of 7-DHC to previt D₃. Matsuoka et al¹²² also showed that applying a 5% para-aminobenzoic acid solution with an SPF-8 rating 1 hour before exposure to a previously determined minimum erythema dose of UVB from a light box effectively prevented an increase in serum vit D₃ levels in 4 individuals.³⁹ These findings are not surprising given the great overlap of the action spectrum for previt D₃ formation (Fig 2) and the absorption spectrum of para-aminobenzoic acid sunscreens (260-340 nm, peak approximately 310 nm).¹³⁸

Most people's real-life experience with sunscreen is that despite its application, they still sunburn or tan after casual sun exposure. SPF is a strictly defined and Food and Drug Administration (FDA)-regulated

measurement based on applying 2 mg/cm² of product.¹³⁸ Studies have shown that most users apply insufficient amounts of sunscreen to meet this FDA standard, and the true SPF obtained is usually less than 50% of that written on the package.¹³⁹ In addition, sunscreen efficacy depends on its uniform application to all relevant body parts, its durability and substantivity and its periodic reapplication.¹³⁸ Finally, even if properly applied, by definition sunscreens do not completely block UVB, with SPF-15 allowing by definition approximately 1/15 or 6% of UVB photons to penetrate the skin.¹³⁸ Thus, it is highly unlikely that even regular sunscreen use will cause vit D deficiency or insufficiency. Indeed, Matsuoka et al¹⁴⁰ also published a case controlled study of 20 long-term sunscreen users versus 20 control subjects. Long-term users were patients with documented skin cancer who stated they had regularly used sunscreen on all exposed skin for longer than 1 year, at their doctor's recommendation. In these users, the mean 25-OH vit D level was 40.2 ± 3.2 versus 91 ± 6.2 nmol/L in control subjects. Thus, although they had lower 25-OH vit D levels than control subjects, long-term users were not vit D deficient, contradicting the claims that sunscreen use causes vit D deficiency (mean 25-vit OH levels < 20 nmol/L) or insufficiency (mean 25-vit OH levels 20-37.5 nmol/L) by widely used definitions.^{14,32,33,36} Thus, this study shows that UVB transmission through sunscreen as regularly used by long-term consistent (and older adult) users, in addition to diet-derived 25-OH vit D (not quantified by this study), was sufficient to maintain nondeficient serum 25-OH vit D levels.

Marks et al¹¹⁷ demonstrated in a prospective randomized controlled clinical trial that SPF-17 sunscreen use at levels sufficient to prevent actinic keratoses did not induce vit D insufficiency or deficiency. This trial of 113 individuals took place in Australia at a latitude of 37°S (a location where the angle of the sun is not sufficient to produce previt D₃ all year round), and both sunscreen use and sun exposure were quantified for each individual. Moreover, all participants were instructed to avoid sun exposure at midday and to wear hats and other appropriate clothing for sun protection. No individual was vit D deficient or insufficient (<50 nmol/L) at baseline, and after the intervention, 25-OH vit D levels increased by greater than 7 nmol/L in all groups, even those 70 years or older, with no statistically significant differences between the mean changes for sunscreen users and control subjects in any category.¹¹⁷ Other studies support the conclusion of Marks et al¹¹⁷ that, under standard conditions, sunscreen use does not cause vit D deficiency.

One prospective, longitudinal clinical trial comprising 24 individuals for 2 years in Barcelona, Spain (latitude 41°N) found no vit D efficiency or secondary hyperparathyroidism in sunscreen (SPF-15) users, and no statistically significant change in markers of bone remodeling in sunscreen users versus control subjects.¹⁴¹ Finally, another cross-sectional study of 8 patients with xeroderma pigmentosum who practiced rigorous photoprotection found that the serum 25-OH vit D levels were in the low normal range (mean 44.5 [3.75] nmol/L) with normal levels of PTH and calcitriol after 6 years of follow-up.¹⁴²

Thus, even when used effectively to reduce actinic damage, under actual use conditions sunscreens do not cause vit D deficiency or adversely affect markers of bone remodeling and skeletal homeostasis.

CONCLUSION

Given the scarcity of naturally occurring vit D in many otherwise adequate diets, human beings may once have depended on unprotected exposure to natural sunlight as the primary environmental source of vit D, at least during those periods of the year when sunlight can produce previt D₃ in the skin.³⁰ However, chronic unprotected exposure to carcinogenic UV radiation in sunlight not only results in photoaging, but also greatly increases the risk of skin cancer. This risk is further exacerbated by the extended lifespan of human beings in the 21st century. Fortunately, there is a noncarcinogenic alternative—intestinal absorption of vit D-fortified foods and/or dietary supplements.

This issue of dietary absorption versus cutaneous production to maximize vit D intake becomes particularly relevant in light of the proposed upward revision of recommendations for serum 25-OH vit D levels. Currently, these higher recommended serum 25-OH vit D levels have been shown in the elderly to benefit skeletal health, muscle strength, and balance without preventing osteoporosis-induced fractures, and to offer other as yet unproven benefits, such as lowering blood pressure, reduction in mortality from some cancers, and prevention of autoimmune diseases, such as type 1 DM and multiple sclerosis. Accepting the above as possible, although unproven in most instances, argues in favor of increasing the daily intake of vit D to achieve these higher serum 25-OH vit D levels.

Augmenting cutaneous production of previt D₃ through intentional unprotected exposure to UV radiation is proposed currently by some as the preferred method to maintain serum 25-OH vit D levels at or above a desired level.³⁹ Aside from recommending a carcinogen in moderation despite

an equally effective noncarcinogenic alternative, this approach is problematic in that cutaneous production does not offer concomitant calcium supplementation and is known to be inefficient in those statistically most at risk to have low serum 25-OH levels, such as the elderly and dark-skinned persons. Moreover, the tanning message inherent in this proposal targets primarily young, lighter-skinned individuals who have the longest available time span to develop the harmful consequences of chronic, unprotected UV exposure,^{8,127,137} and who are most likely to be achieving maximal potential previt D photosynthesis through incidental sun exposure, even when wearing sunscreen, negating any possible benefit from increased UV exposure.

All available evidence indicates that younger, lighter-skinned individuals easily maintain desirable serum 25-OH vit D levels year-round by incidental protected sun exposure and customary diet. Daily intake of two 8-oz glasses of fortified milk or orange juice or one standard vit or incidental protected exposure of the face and backs of hands to 0.25% minimum erythema dose of UVB radiation 3 times weekly each generates adequate serum 25-OH levels by classic criteria. Dietary supplementation of vit D is efficient, efficacious, and safe. Thus, it is prudent for those at high statistical risk for vit D deficiency, such as patients who are highly protected against the sun, to take daily supplemental vit D (200-1000 IU) with concurrent dietary calcium to meet current and future RDA levels.

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