# High Prevalence of Vitamin D Inadequacy and Implications for Health

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During the past decade, major advances have been made in vitamin D research that transcend the simple concept that vitamin D is important for the prevention of rickets in children and has little physiologic relevance for adults. Inadequate vitamin D, in addition to causing rickets, prevents children from attaining their genetically programmed peak bone mass, contributes to and exacerbates osteoporosis in adults, and causes the often painful bone disease osteomalacia. Adequate vitamin D is also important for proper muscle functioning, and controversial evidence suggests it may help prevent type 1 diabetes mellitus, hypertension, and many common cancers. Vitamin D inadequacy has been reported in approximately 36% of otherwise healthy young adults and up to 57% of general medicine inpatients in the United States and in even higher percentages in Europe. Recent epidemiological data document the high prevalence of vitamin D inadequacy among elderly patients and especially among patients with osteoporosis. Factors such as low sunlight exposure, age-related decreases in cutaneous synthesis, and diets low in vitamin D contribute to the high prevalence of vitamin D inadequacy. Vitamin D production from cutaneous synthesis or intake from the few vitamin D–rich or enriched foods typically occurs only intermittently. Supplemental doses of vitamin D and sensible sun exposure could prevent deficiency in most of the general population. The purposes of this article are to examine the prevalence of vitamin D inadequacy and to review the potential implications for skeletal and extraskeletal health.

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$1\alpha(OH)D_3$ = $1\alpha$-hydroxyvitamin $D_3$; $1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; $25(OH)D$ = 25-hydroxyvitamin D; BMD = bone mineral density; PTH = parathyroid hormone; RCT = randomized controlled trial; RECORD = Record Evaluation of Calcium or Vitamin D; VDR = vitamin D receptor

During the past decade, important advances in the study of vitamin D have been made. In addition to its important role in skeletal development and maintenance, evidence is mounting that vitamin D produces beneficial effects on extraskeletal tissues and that the amounts needed for optimal health are probably higher than previously thought.[1] At the same time, numerous reports have shown that relatively high proportions of people have inadequate levels of vitamin D. The extraskeletal health benefits of vitamin D and high prevalence of inadequate levels of vitamin D have been largely unrecognized by both physicians and patients.[2] The purposes of this review article are to examine the prevalence of vitamin D inadequacy as defined by low serum 25-hydroxyvitamin D (25[OH]D), the major circulating form of vitamin D and standard indicator of vitamin D status, and to review the potential implications on both skeletal and extraskeletal health.

## SOURCES OF VITAMIN D

Solar UV-B (wavelengths of 290-315 nm) irradiation is the primary source of vitamin D (other than diet supplements) for most people.[1,3,4] Dietary sources of vitamin D are limited. They include oily fish such as salmon (approximately 400 IU per 3.5 oz), mackerel, and sardines; some fish oils such as cod liver oil (400 IU/tsp); and egg yolks (approximately 20 IU). Some foods are fortified in the United States, including milk (100 IU per 8 oz) and some cereals (100 IU per serving),

orange juice (100 IU per 8 oz), some yogurts (100 IU per serving), and margarine.[4-6] Milk is not vitamin D enriched in most European countries; however, margarine and some cereals are. There are 2 forms of vitamin D. Vitamin $D_2$ (ergocalciferol) comes from irradiation of the yeast and plant sterol ergosterol, and vitamin $D_3$ (cholecalciferol) is found in oily fish and cod liver oil and is made in the skin. Vitamin D represents vitamin $D_2$ and vitamin $D_3$.

Vitamin D from cutaneous synthesis or dietary sources typically occurs only intermittently. Irregular intake of vitamin D, irrespective of the source, can lead to chronic vitamin D inadequacy. This condition has been reported across all age groups, geographic regions, and seasons.[7-16] Enhancing vitamin D levels by taking supplements is usually necessary to achieve the minimum recommended daily intakes; however, compliance is often problematic. In particular, some groups who may be at high risk of vitamin D inadequacy often do not follow regular daily dosing guidelines. Adherence to vitamin D supplementation recommendations is low among elderly patients with osteoporosis. One study showed that, despite receiving counseling on the importance of vitamin D and calcium supplementation, 76% of elderly patients with hip fractures did not comply with recommendations.[17] This is not surprising given that
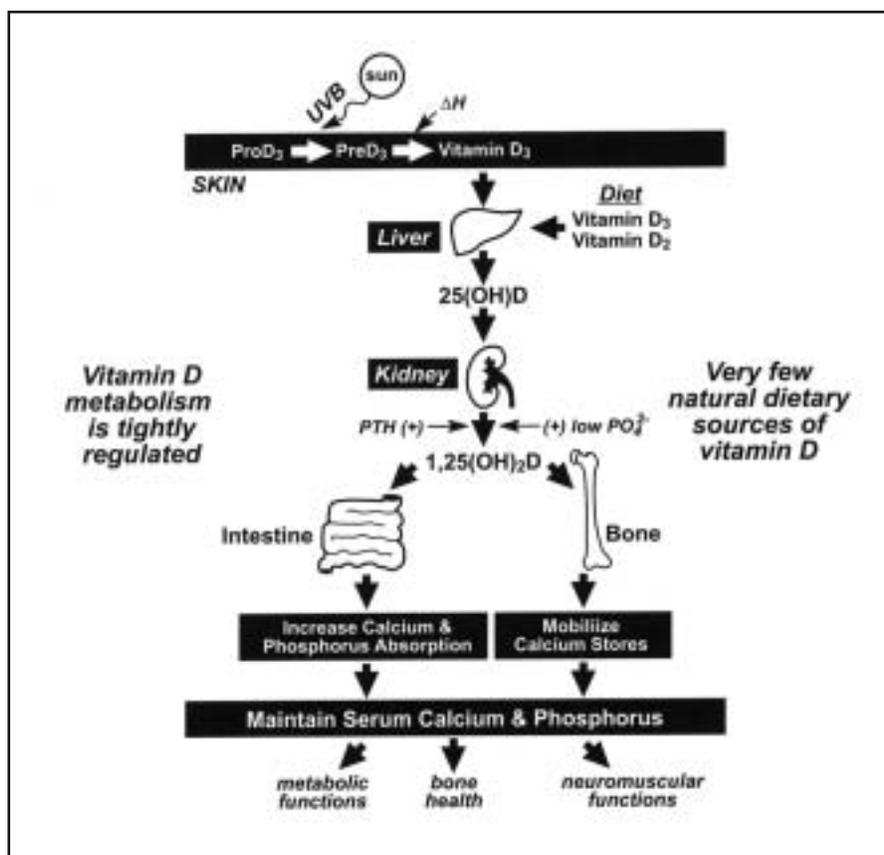
FIGURE 1. Cutaneous production of vitamin D and its metabolism and regulation for calcium homeostasis and cellular growth. 7-Dehydrocholesterol or provitamin $D_3$ (proD$_3$) in the skin absorbs solar UV-B radiation and is converted to previtamin $D_3$ (preD$_3$). $D_3$ undergoes thermally induced ($\Delta H$) transformation to vitamin $D_3$. Vitamin D from the diet or from the skin is metabolized in the liver by the vitamin D-25-hydroxylase to 25-hydroxyvitamin $D_3$ (25[OH]D$_3$). 25(OH)D$_3$ is converted in the kidney by the 25(OH)D$_3$-1$\alpha$-hydroxylase to 1,25-dihydroxyvitamin $D_3$ [1,25(OH)$_2$D$_3$]. A variety of factors, including serum phosphorus (PO$_4^{2-}$) and parathyroid hormone (PTH), regulate the renal production of 1,25(OH)$_2$D$_3$. 1,25(OH)$_2$D regulates calcium metabolism through its interaction with its major target tissues, the bone and the intestine. From *Osteoporos Int,*[21] with permission from Springer Science and Business Media.

compliance declines as the number of medications increases, and elderly patients often take many medications. Similarly, achieving adequate vitamin D intake through milk consumption is unreliable among elderly patients because of the high prevalence of lactose intolerance among this population and the often low levels of vitamin D in the milk supply.[6]

## VITAMIN D PHOTOBIOCHEMISTRY, METABOLISM, AND FUNCTIONS

UV-B irradiation of skin triggers photolysis of 7-dehydrocholesterol (provitamin $D_3$) to previtamin $D_3$ in the plasma membrane of human skin keratinocytes.[18-20] Once formed in the skin, cell plasma membrane previtamin $D_3$ is rapidly converted to vitamin $D_3$ by the skin's temperature. Vitamin $D_3$ from the skin and vitamin D from the diet undergo 2 sequential hydroxylations, first in the liver to 25(OH)D and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) (Figure 1). Excessive solar UV-B irradiation will not cause vitamin D intoxication because excess vitamin $D_3$ and previtamin $D_3$ are photolyzed to biologically inactive photoproducts.[19,20,22] Melanin skin pigmentation is an effective natural sunscreen, and increased skin pigment can greatly reduce UV-B–mediated cutaneous synthesis of vitamin $D_3$ by as much as 99%, similar to applying a sunscreen with a sun protection factor of 15.[23,24] Keratinocytes are also capable of hydroxylating 25(OH)D to produce 1,25(OH)$_2$D.[25] The 1,25(OH)$_2$D (from keratinocyte or renal sources) may regulate keratinocyte differentiation, melanocyte apoptosis, and melanin production,[25-27] and this may be another mechanism for

regulating the cutaneous synthesis of vitamin $D_3$ by negative feedback.

The 1,25$(OH)_2$D ligand binds with high affinity to the vitamin D receptor (VDR) and triggers an increase in intestinal absorption of both calcium and phosphorus. In addition, vitamin D is involved in bone formation, resorption, and mineralization and in maintaining neuromuscular function[1,3] (Figure 1). Circulating 1,25$(OH)_2$D reduces serum parathyroid hormone (PTH) levels directly by decreasing parathyroid gland activity and indirectly by increasing serum calcium. The 1,25$(OH)_2$D regulates bone metabolism in part by interacting with the VDR in osteoblasts to release biochemical signals, leading to formation of mature osteoclasts. The osteoclasts release collagenases and hydrochloric acid to dissolve the matrix and mineral, releasing calcium into the blood.[1,3,4]

When vitamin D levels are inadequate, calcium and phosphorus homeostasis becomes impaired. Vitamin D is primarily responsible for regulating the efficiency of intestinal calcium absorption. In a low vitamin D state, the small intestine can absorb approximately 10% to 15% of dietary calcium. When vitamin D levels are adequate, intestinal absorption of dietary calcium more than doubles, rising to approximately 30% to 40%.[1,3,4,28] Thus, when vitamin D levels (25[OH]D) are low, calcium absorption is insufficient to satisfy the calcium requirements not only for bone health but also for most metabolic functions and neuromuscular activity. The body responds by increasing the production and release of PTH into the circulation (Figure 1). The increase in PTH restores calcium homeostasis by increasing tubular reabsorption of calcium in the kidney, increasing bone calcium mobilization from the bone, and enhancing the production of 1,25$(OH)_2$D.[1,3]

## ASSESSMENT OF VITAMIN D STATUS

Serum 25(OH)D is the major circulating metabolite of vitamin D and reflects vitamin D inputs from cutaneous synthesis and dietary intake. The serum 25(OH)D level is the standard clinical measure of vitamin D status.[1,14] Although 1,25$(OH)_2$D is the active form of vitamin D, it should not be measured to determine vitamin D status. It usually is normal or even elevated in patients with vitamin D deficiency.[1,3,4] Testing of serum 25(OH)D is most useful in patients who are at risk of vitamin D deficiency, including elderly patients, infirm patients, children and adults with increased skin pigmentation, patients with fat malabsorption syndromes, and patients with osteoporosis. This measurement is also useful for purposes of planning or monitoring vitamin D therapy. Clinical assays of 25(OH)D include the Nichols Advantage Assay (chemiluminescence protein-binding assay, the DiaSorin radioimmunoassay,

and the benchmark high-performance liquid chromatography assays[29] and liquid chromatography mass spectroscopy assays.[30] The chemiluminescence protein-binding assay and the radioimmunoassay are most commonly used to determine patient vitamin D status. Recent reports have raised concerns about the degree of variability between assays and between laboratories, even when using the same assay.[29-33] Although reliable and consistent evaluation of serum 25(OH)D levels remains an issue, reliable laboratories currently exist, and efforts are in progress to improve and standardize assays to enhance accuracy and reproducibility at other laboratories.[30,32,33]

As noted previously, vitamin D plays a central role in calcium and phosphorus homeostasis and skeletal health. Since impaired calcium metabolism due to low serum 25(OH)D levels triggers secondary hyperparathyroidism, increased bone turnover, and progressive bone loss,[1,34-38] the optimal range of circulating 25(OH)D for skeletal health has been proposed as the range that reduces PTH levels to a minimum[9,11,35] and calcium absorption is maximal.[28] Several studies have shown that PTH levels plateau to a minimum steady-state level as serum 25(OH)D levels approach and rise above approximately 30 ng/mL (75 nmol/L)[9,30,35-38] (Figure 2, left).

## EPIDEMIOLOGY OF VITAMIN D INADEQUACY

Vitamin D inadequacy constitutes a largely unrecognized epidemic in many populations worldwide.[39-47] It has been reported in healthy children,[7,8,13,15,48] young adults,[38,39,49] especially African Americans,[7,41,42,49,50] and middle-aged and elderly adults.[9-12,14,36,37,40,43-49,51-56] Typically, the prevalence of low 25(OH)D levels (<20 ng/mL [50 nmol/L]) is approximately 36% in otherwise healthy young adults aged 18 to 29 years,[49] 42% in black women aged 15 to 49 years,[50] 41% in outpatients aged 49 to 83 years,[11] up to 57% in general medicine inpatients in the United States,[57] and even higher in Europe (28%-100% of healthy and 70%-100% of hospitalized adults).[40,55,58]

Vitamin D inadequacy is particularly common among patients with osteoporosis (Table 1). A recent systematic review by Gaugris et al[39] concluded that the prevalence of inadequate 25(OH)D levels appears to be high in postmenopausal women and especially those with osteoporosis and a history of fracture. This review, which included 30 studies published between January 1994 and April 2004, examined the prevalence of vitamin D inadequacy reported as serum 25(OH)D levels below various values. The results of a recent cross-sectional, observational study conducted at 61 sites across North America showed that 52% of postmenopausal women receiving therapy for osteoporosis had 25(OH)D levels of less than 30 ng/mL (75 nmol/L).[30]
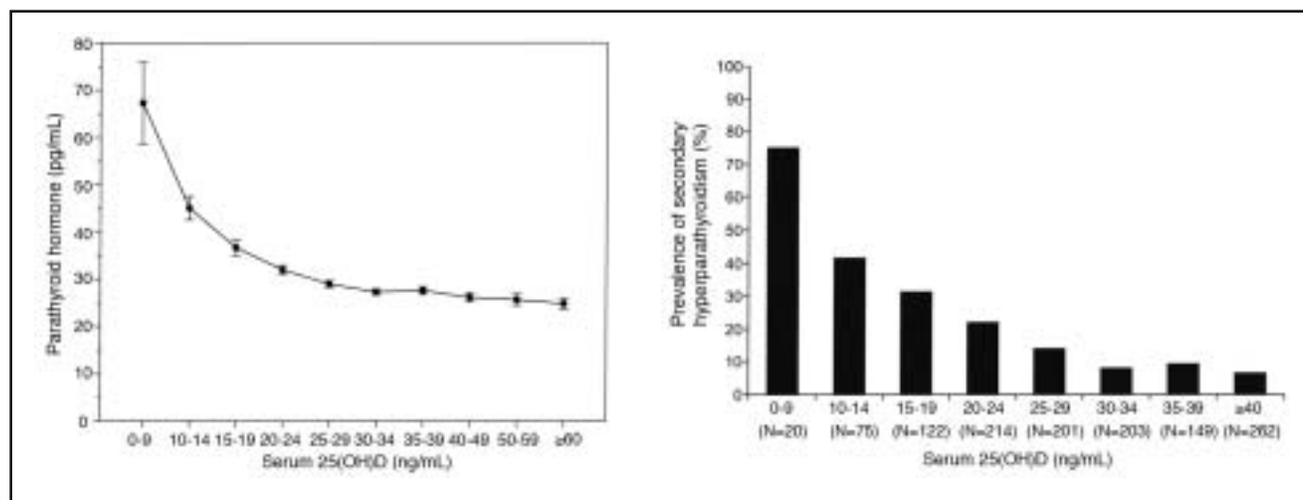
FIGURE 2. Left, Relationship between serum 25-hydroxyvitamin D (25[OH]D) concentrations and mean ± SE (error bars) serum concentrations of parathyroid hormone in patients with osteoporosis receiving treatment. Right, Percentage of subjects with secondary hyperparathyroidism by 25(OH)D level. The percentage of subjects with secondary hyperparathyroidism (parathyroid hormone level >40 pg/mL) sorted by subgroups with serum 25(OH)D concentrations delineated by predefined cutoffs for analyses of 25(OH)D inadequacy. Left and right, From *J Endocrinol Metab*,[30] with permission from The Endocrine Society, Copyright 2005.

The high prevalence of vitamin D inadequacy in that study was consistent across all age groups and North American geographic regions studied.[30] The prevalence of very low serum 25(OH)D levels (<12 ng/mL [30 nmol/L]) was 76% among patients with osteoporosis in another study.[55] A global study of vitamin D status in postmenopausal women with osteoporosis showed that 24% had 25(OH)D levels less than 10 ng/mL (25 nmol/L), with the highest prevalence reported in central and southern Europe.[14] Vitamin D inadequacy is common even among patients with osteoporosis living at lower latitudes in highly sunny climates. For instance, 53% of community-dwelling women with osteoporosis living in Southern California had 25(OH)D levels less than 30 ng/mL (75 nmol/L).[46] In a study of patients 50 years and older hospitalized for nontraumatic fractures, 97% had 25(OH)D levels less than 30 ng/mL (75 nmol/L).[59] Studies in the United Kingdom and South Africa reported that 13% to 33% of patients with hip fractures had histological evidence of osteomalacia that may have been caused by chronic vitamin D deficiency.[60-63]

Vitamin D inadequacy is also common among nonwhite populations and populations with low dietary or supplementary vitamin D intake or minimal exposure to sunlight. A study of Asian adults in the United Kingdom showed that 82% had 25(OH)D levels less than 12 ng/mL (30 nmol/L) during the summer season, with the proportion increasing to 94% during the winter months.[64] A study of 1546 African American women in the United States, ranging in age from 15 to 49 years, showed that more than 40% had serum 25(OH)D levels less than 15 ng/mL (37 nmol/L).[50] A much

higher proportion (84%) of elderly black adults in Boston, Mass, had serum 25(OH)D levels less than 20 ng/mL (50 nmol/L).[3] Even children are at risk. A cross-sectional clinic-based study of 307 children (11-18 years old) in Boston reported that 52% of African American and Hispanic children had 25(OH)D levels of 20 ng/mL (50 nmol/L) or less.[7] Sullivan et al[15] observed that at the end of winter and summer 48% and 17%, respectively, of white girls (9-11 years of age) in Maine also had 25(OH)D levels less than 20 ng/mL (50 nmol/L). Even in sunny countries such as Lebanon, vitamin D inadequacy is common in schoolchildren.[48]

## FACTORS THAT CONTRIBUTE TO VITAMIN D INADEQUACY

Physical factors that attenuate UV-B exposure, including clothing, sunscreens, and glass shielding, markedly reduce or completely eliminate the production of vitamin $D_3$ in the skin.[18] At latitudes above 37°N and below 37°S, sunlight is insufficient to induce cutaneous vitamin $D_3$ synthesis during the winter months.[16,65,66] Nevertheless, latitude is not the only determinant of 25(OH)D levels.[1,3,8,67-69] The high prevalence of osteomalacia in Saudi Arabian women, rickets in Saudi children, and vitamin D deficiencies in both may be attributable to their cultural practice of wearing clothing that covers the entire body and avoiding direct sunlight.[70,71]

Biological factors that inhibit cutaneous vitamin D synthesis and bioavailability include skin pigmentation,[23,72,73]

TABLE 1. **Vitamin D Inadequacy in Osteoporosis: Summary of Reports Published in 2003 and 2004***

| Reference | Population characteristics | Location | Season | Sample size | Mean age (y) | Prevalence of low serum 25(OH)D (%) | Definition of low serum vitamin D (ng/mL) |
|---|---|---|---|---|---|---|---|
| Isaia et al,[40] 2003 | Elderly women referred to an osteoporosis center | Italy | B | 700 | 68 | 27<br>76 | <5<br><12 |
| Plotnikoff et al,[41] 2003 | Various ethnic groups referred for chronic musculoskeletal pain | Minnesota | B | 150 | 10-65 (range) | 33<br>93 | <8<br><20 |
| Carnevale et al,[42] 2004 | Patients with primary hyperparathyroidism | Italy | B | 62 | 50 | 27 | <12 |
| Harwood et al,[43] 2004 | Female patients with hip fractures | United Kingdom | NA | 150 | 81 | 70 | <12 |
| Glowacki et al,[44] 2003 | Postmenopausal osteoarthritic white women | Boston, Mass | B | 68 | 66 | 22 | <15 |
| Segal et al,[17] 2004 | Patients with hip fracture at time of hospitalization | Israel | B | 96 | 72 | 60 | <15 |
| Gomez-Alonso et al,[45] 2003 | Healthy population in osteoporosis study | Spain | B | 268 | 69 | 67 | <18 |
| Holick et al,[30] 2005 | Postmenopausal women receiving antiresorptive or anabolic therapy for osteoporosis | North America | L | 1536 | 71 | 52 | <30 |
| Blau et al,[46] 2004 | Community-dwelling women referred to osteoporosis clinic | Southern California | L | 252 | NA | 53 | <30 |
| Simonelli et al,[47] 2005 | Patients hospitalized for nontraumatic fracture | Minnesota | L | 82 | ≥50 | 97 | <30 |

*25(OH)D = 25-hydroxyvitamin D; B = both low sun/winter-spring and high sun/summer-fall; L = low sun/winter-spring; NA = not available.

medication use,[74] body fat content,[75] fat malabsorption,[76] and age.[77,78] Increased skin pigmentation can reduce cutaneous vitamin $D_3$ production as much as 99.9%.[23,72,73] Certain drugs (eg, anticonvulsants, corticosteroids, rifampin, and cholestyramine) may adversely affect metabolism or bioavailability of vitamin D.[74,79,80] Recent studies have shown that body mass index and body fat content are inversely related to serum 25(OH)D levels and directly related to PTH levels,[75,81-83] which is likely due to vitamin D sequestration in body fat compartments.[75] Dietary sources of vitamin D are limited, and obtaining a sufficient amount from regular diet is often problematic for many people whose diet does not normally include the few foods that are naturally rich in vitamin D. Patients with fat malabsorption syndromes, including sprue, cystic fibrosis, and Crohn disease, are at especially high risk of vitamin D deficiency.[76,84] Among elderly patients, multiple factors contribute to vitamin D inadequacy, including dietary deficiencies and decreased cutaneous synthesis due to reduced ability of the skin to synthesize vitamin $D_3$. A 70-year-old produces approximately 4 times less vitamin D via cutaneous synthesis compared with a 20-year-old.[77,78] Increasing age has been associated with lower 25(OH)D levels regardless of season.[85] Age does not alter dietary vitamin D absorption, but if an individual is taking cholestyramine, vitamin D will not be absorbed efficiently.[84]

## SKELETAL CONSEQUENCES OF VITAMIN D INADEQUACY

Chronic severe vitamin D deficiency in infants and children causes bone deformation due to poor mineralization, commonly known as rickets.[1,4] In adults, proximal muscle weakness, bone pain, and osteomalacia may develop.[55,86-89] Less severe vitamin D inadequacy prevents children and adolescents from attaining their optimal genetically programmed peak bone mass and in adults leads to secondary hyperparathyroidism, increased bone turnover, and progressive loss of bone, increasing the risk of osteoporosis.

Vitamin D deficiency during skeletal maturation disrupts chondrocyte maturation and inhibits the normal mineralization of the growth plates. This causes a widening of the epiphyseal plates at the end of the long bones in rachitic children and bulging of costochondral junctions (rachitic rosary).[1,4] Secondary hyperparathyroidism causes phosphaturia and hypophosphatemia. The resulting inadequate calcium-phosphorus product results in poor mineralization, making the skeleton less rigid. When the rachitic child begins to stand, gravity causes bowing of the long bones in the lower extremities, resulting in bowed legs or knocked knees.[4,18]

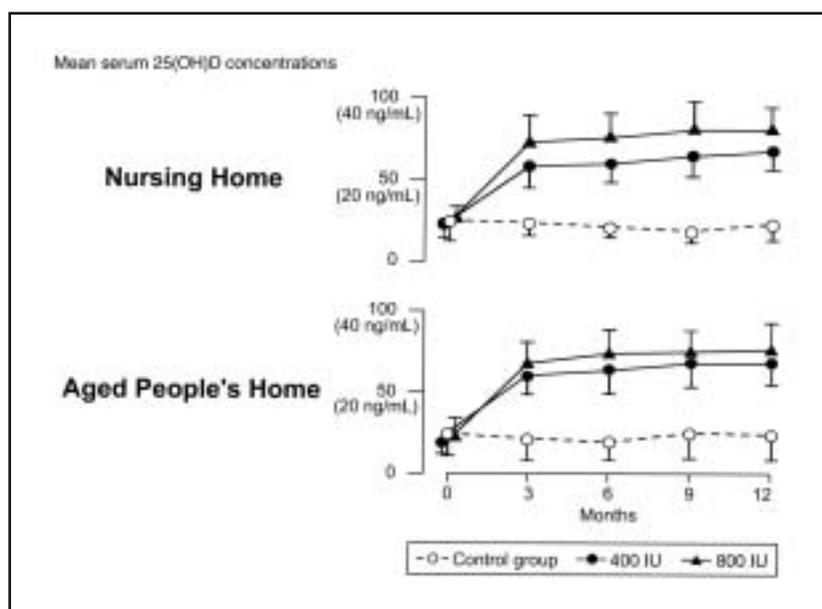In adults, the epiphyseal plates are fused, and secondary hyperparathyroidism and resulting phosphaturia have more

Figure 3. Mean ± SD (error bars) serum 25-hydroxyvitamin D (25[OH]D) concentrations (shown as nmol/L and ng/mL) in women older than 70 years, stratified by supplement use and residential status. Adapted from *J Clin Endocrinol Metab*,[97] with permission from The Endocrine Society, Copyright 1988.

subtle, but equally devastating, skeletal consequences. Chronic vitamin D inadequacy in adults can result in secondary hyperparathyroidism, increased bone turnover, enhanced bone loss, increased risk of fragility fracture, and (rarely) hypocalcemic tetany.[34-37,87-89] The increase in PTH-mediated osteoclastogenesis results in increased numbers and activity of osteoclasts. The osteoclasts resorb bone via enzymatic degradation of the collagen matrix and secretion of hydrochloric acid, releasing calcium and phosphorus into the extracellular space. The result is increased skeletal porosity, defective bone mineralization, decreased bone mineral density (BMD), osteoporosis, and increased fragility-fracture risk.[4,30,50,87,88] When 25(OH)D levels are less than approximately 10 ng/mL (25 nmol/L), osteomalacia is usually present.[7,9,61,88-90] Some studies suggest that serum 25(OH)D levels greater than 30 ng/mL (75 nmol/L) may be required to maximize intestinal calcium absorption[28] and prevent secondary hyperparathyroidism-induced skeletal conditions[14,30,53,81,89,90] (Figure 2).

Unlike patients with osteoporosis, patients with osteomalacia often complain of skeletal pain.[41,86,89] This pain can be elicited on physical examination by applying minimal pressure with the thumb or forefinger on the sternum or anterior tibia. Although the exact cause of the aching sensation that patients often complain of is unknown, it is possible that the collagen-rich osteoid that is laid down on the periosteal surface of the skeleton may become swollen similar to the hydration of gelatin-based food products (eg,

Jell-O). This swelling could put outward pressure on the periosteal covering that is innervated with nocioceptors.[91] Patients with osteomalacia are often misdiagnosed as having fibromyalgia, chronic fatigue syndrome, or myocytis and treated inappropriately with nonsteroidal anti-inflammatory agents.[41,91]

Some, but not all, observational studies have linked vitamin D inadequacy (or lower vitamin D intake) to an increased risk of hip and other nonvertebral fractures.[60,90] Moreover some, but not all, clinical trials and observational studies have reported that dietary vitamin D supplementation (often given together with calcium) lowers fracture risk[34,92-96] (Figure 3). Bischoff-Ferrari et al[98] recently conducted a systematic review and meta-analysis of double-blind randomized controlled trials (RCTs), the highest level of evidence, to assess the efficacy of vitamin D (vitamin $D_3$ [cholecalciferol] or vitamin $D_2$ [ergocalciferol]) supplementation with or without calcium supplementation vs calcium supplementation alone or placebo for preventing hip and nonvertebral fractures in elderly patients (≥60 years of age). Statistical justification was provided for pooling trials with higher vitamin D doses separately from those with lower doses. On the basis of the analysis of 3 RCTs for hip fracture risk involving 5572 subjects and 5 RCTs for nonvertebreal fracture risk involving 6098 subjects, the authors concluded that daily vitamin D supplementation between 700 and 800 IU with or without calcium appears to reduce hip fracture risk by 26% and

nonvertebral fracture risk by 23% vs calcium alone or placebo in ambulatory or institutionalized elderly persons. No effect on fracture risk was observed in 2 trials that used a lower dose of 400 IU/d. A population-based, 3-year cluster randomized intervention study involving 9605 community-dwelling elderly adults (≥66 years of age) found that 400 IU/d of vitamin D with 1000 mg of calcium produced a 16% fracture risk reduction,[95] although this lower-quality trial did not meet the inclusion criteria for the meta-analysis described herein. A separate systematic review and meta-analysis conducted several years earlier that included RCTs involving either vitamin D or its analogues reported a 37% reduction in the relative risk of vertebral fracture.[99,100]

Two trials that failed to detect an effect on fracture risk were published soon after the meta-analysis was conducted. Porthouse et al[101] conducted an open-label RCT to assess whether 1000 mg of calcium daily with 800 IU of vitamin $D_3$ supplementation reduced fracture risk among 3314 women 70 years and older with one or more risk factors for hip fracture. The incidence of hip and other clinical fractures did not differ significantly between groups after a median follow-up of 25 months. Another randomized, double-blinded, controlled trial with a factorial design examined the effect on fracture risk.[102] A total of 5292 patients were randomized to receive vitamin D with or without calcium, calcium alone, or placebo. After a 24-month follow-up, the authors found no significant differences in fracture rates among the 4 groups. However, compliance with the medication had declined to 63% after 24 months and may have been as low as 45% if nonresponders to the evaluation questionnaire were included. Data from a randomized, double-blind, placebo-controlled trial of 9440 community-dwelling adults (75-100 years old) randomized to receive either an annual injection of 300,000 IU of cholecalciferol (comparable to a 822-IU daily dose) or matching placebo disclosed no effect on fracture occurrence between groups.[103] However, since 25(OH)D levels were not evaluated, it is unknown whether the intramuscular vitamin $D_3$ was completely bioavailable. Most intramuscular preparations are not very bioavailable, which is why they are no longer available in the United States.

Decreased BMD is a major risk factor for fractures,[104] and some studies have linked vitamin D inadequacy or low intake of vitamin D to low BMD.[90,105,106] Some randomized trials have also shown a benefit.[99,100,105,107,108] For example, a double-blinded RCT randomized 249 healthy ambulatory postmenopausal women with usual daily intakes of 100 IU of vitamin D to receive 400 IU of vitamin D supplements or placebo daily. All participants also received 377 mg/d of calcium. At the end of 1 year, the vitamin D group had significantly reduced wintertime bone loss and improved net BMD of the spine.[109] By contrast, however, another RCT reported no effect of vitamin D supplementation on bone loss or bone turnover markers in calcium-replete postmenopausal African American women.[110] The earlier meta-analysis that pooled data from RCTs that included vitamin D analogues found a small nonsignificant BMD increase of 0.4% relative to the control groups.[99,100]

Many of the vitamin D supplementation studies reported herein included concurrent calcium supplementation; therefore, the observed benefits of vitamin D supplementation may be confounded or obscured by the effects of concurrent calcium supplements and cannot be ascribed to vitamin D alone. Although the meta-analysis by Bischoff-Ferrari et al[98] reported that vitamin D supplementation with or without calcium supplementation reduced fracture risks, the factorial design of the Record Evaluation of Calcium or Vitamin D (RECORD) trial concluded that vitamin D supplementation with or without calcium supplementation had no significant effect on fracture risk reduction.[102] It is also possible that the benefits of vitamin D on fracture risk reduction (and BMD) may be greater in those with vitamin D deficiency or low calcium intake at baseline. In the RECORD trial, only 60 participants (1.1%) had their serum baseline 25(OH)D levels measured. Thus, we cannot know if the lack of effect on fracture risk in the RECORD trial might be related to pretreatment levels of vitamin D and/or calcium. The hierarchy of evidence for the role of vitamin D in BMD[102-117] changes and fracture reduction is given in Table 2.

## NEUROMUSCULAR FUNCTION

The VDR has been identified in skeletal muscle tissue,[167-169] and low serum 25(OH)D levels have been associated with reversible myopathy in patients with osteomalacia.[89,170] Patients with nonspecific muscle weakness, muscle aches and pains, and bone pain are sometimes discounted or diagnosed as having fibromyalgia or chronic fatigue syndrome despite strong scientific evidence that they have vitamin D inadequacy.[41,86,89,91] Several studies support the hypothesis that vitamin D inadequacy contributes to age-related muscle weakness[143,171] and falls.[120,126,172-174] A compelling meta-analysis of RCTs of vitamin D supplementation showed a greater than 20% reduced risk of falls among ambulatory or institutionalized older individuals treated with supplements.[173] Additional supporting evidence comes from a study that investigated factors leading to fracture in postmenopausal women with osteoporosis; vitamin D inadequacy was associated with increased body sway, increased risk of falls, and fall-related fractures.[172] A prospective study

TABLE 2. **Hierarchy of Evidence for Studies Relating Vitamin D to Pathologic Conditions***

| Level | Study type | Data source | Treatment or predictor | Outcome | Result | Notes |
|---|---|---|---|---|---|---|
| 1a | Meta-analyses | RCTs | Vitamin D and calcium | BMD[100] | Small ↑ | Effect seen with low base-line vitamin D |
| | | | | Fracture risk[99,100] | Small ↓ or no effect | Effect seen with low base-line 25(OH)D |
| | | | | Falls[173] | Approximately 20% ↓ | Low baseline 25(OH)D |
| 1b | RCTs | | Vitamin D (or analogue) alone | BMD changes[100] | Small ↑ | Effect seen with vitamin D or 1-H-vitamin $D_3$ |
| | | | | Fracture risk[94] | Small ↓ | |
| | | | | Neuromuscular function[118,119] | Small ↓ in sway and reaction time | Single small study in fallers |
| | | | | Falls[119-121] | ↓ number of fallers | Benefit only with good calcium intake[116] |
| | | | | CRP[122] | 25% ↓ with approximately 500 IU; ICU patients | Unblinded study |
| | | | Vitamin D (or analogue) and calcium | BMD changes[111,112] | Small ↑ | Benefits mostly seen with vitamin D deficiency at baseline |
| | | | | Fracture risk[101,102] | No effect | |
| | | | | Falls[43] | Approximately 50% ↓ in falls in post–hip fracture post–hip fracture women | Nonblinded |
| | | | | BP[201] | 9% ↓ | Low baseline 25(OH)D; small trial |
| | | | | Cytokines in patients with MS[200] | ↑ TGF-β1 | No effect on TNF-α, IFN-γ, or IL-13 |
| | | | Exposure to UV-B | BP[125] | BP ↓ to normal | Very small double-blinded single study |
| | | | Exposure to UV-A | BP[201] | No effect on BP | |
| 2 | Cohort studies | Prospective epidemiological studies | Serum 25(OH)D | Fracture risk[113] | ↑ risk of hip fracture when low | Hemiplegic stroke patients |
| | | | Serum 25(OH)D | Fracture risk, gait speed, balance[114] | No effect on fracture; poorer balance and gait speed when low | |
| | | | Serum 1,25(OH)$_2$D | Fracture risk[115] | ↑ risk of hip fracture when low | |
| | | | Vitamin D supplements | Fracture risk[116] | No effect | |
| | | | Serum 25(OH)D | Falls[126] | ↑ risk when low | |
| | | | Serum PTH | Falls[126] | ↑ risk when high | |
| | | | Serum 25(OH)D | Sarcopenia[127] | ↑ risk when low | |
| | | | Dietary vitamin D and calcium | Colon cancer[164] | ↑ risk when low | |
| | | | Serum 25(OH)D | Colon cancer[202] | ↑ risk when low | |
| | | | Dietary vitamin D and calcium | Colorectal cancer[164] | ↑ risk when low | Small effect |
| | | | Dietary vitamin D and sunlight exposure | Breast cancer risk[132,165,166] | ↑ risk when low | NHANES I |
| | | | Latitude | MS[205] | ↑ risk at higher latitudes | NHS I and II—effect seen in earlier cohort |
| | | | Dietary vitamin D | IHD mortality[219] | No effect on MI or IHD | |
| | | | Dietary vitamin D in first year of life | Type 1 DM incidence[207] | ↓ risk with higher intake | Birth cohort, Finland, 11-year follow-up |
| | | | Dietary vitamin D | Rheumatoid arthritis[208] | 33% ↓ risk in highest tertile of intake | |
| 3 | Case-control studies | Fracture cases and nonfracture controls | Fracture vs no fracture | Serum 25(OH)D[60] | ↓ levels in women with hip fracture | |
| | | D-deficient cases, "normal" controls | Case vs control | Muscle function[135] | Reduced vitamin D deficiency | |
| | | Colorectal cancer cases (nested in cohort) | Cancer vs control | Serum 25(OH)D and serum 1,25(OH)$_2$D[123] | ↑ risk with low 25(OH)D level | Blood drawn at baseline, before diagnosis |
| | | Breast cancer cases at diagnosis, clinic controls | Cancer vs control | Serum 25(OH)D and serum 1,25(OH)$_2$D[124] | ↑ race-1,25(OH)$_2$D interaction in black cases, ↓ in white, compared with controls | No difference in 25(OH)D |
| | | Prostate cancer cases (nested in cohort) | Cancer vs control | Serum 25(OH)D[125] | ↑ risk with low levels | 149 cases |
| | | Prostate cancer cases (nested in cohort) | Cancer vs control | Serum 25(OH)D and serum 1,25(OH)$_2$D[128] | No difference | 61 cases |
| | | MS cases, community controls | MS case vs control | Level of sunlight exposure during childhood and adolescence[129,205,225] | ↑ risk with less exposure | |

*(level 3 continued on next page)*

TABLE 2. **Continued***

| Level | Study type | Data source | Treatment or predictor | Outcome | Result | Notes |
|---|---|---|---|---|---|---|
| 3 | | Childhood-onset type 1 DM, community controls, nationwide | Diabetic vs control | Cod liver oil during pregnancy or first year of life[130] | 26% ↓ risk with use in first year of life; no effect with prenatal use | Norway |
| | | Childhood-onset type 1 DM, community controls, 1 county | Diabetic vs control | Cod liver oil during pregnancy or first year of life[131] | 70% ↓ risk with prenatal use; no effect during first year | Norway |
| 4a | Cross-sectional surveys, ecological studies | Older adults | Serum 25(OH)D | Lower-extremity function[143] | Better walking speed and sit-to-stand time with higher levels | |
| | | Breast cancer cases | Sunlight | Cancer mortality [132,165,166,204] | Higher in areas with less sunlight | |
| | | Ovarian cancer cases | Sunlight | Cancer mortality [133,165] | Higher in areas with less sunlight | |
| | | Population-based, geographic area | Serum 1,25(OH)$_2$D | BP[134] | Higher systolic and diastolic BP with higher levels | |
| | | Population-based, Tromsø | Vitamin D intake | BP[136] | No effect | |
| | | Population-based, NHANES III | Serum 25(OH)D | Periodontal disease[137] | ↑ risk with low level, independently of BMD | |
| 4b | Case series (and poor-quality cohort and case-control studies) | Patients with nonvertebral fracture | NA | Serum 25(OH)D inadequacy[117] | 98% <28 ng/mL | |
| | | Patients with minimal trauma fracture | NA | Serum 25(OH)D inadequacy[47] | 97% <30 ng/mL | |
| 5 | Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles" | Laboratory or animal studies | 1,25(OH)$_2$D$_3$ | Leukemia (mouse)[138] | Longer survival with treatment | |
| | | | 1,25(OH)$_2$D$_3$ | Lung cancer cell growth[150] | Regulates cell growth | |
| | | | 1,25(OH)$_2$D$_3$ and analogues | Cancer cells proliferation (breast, osteosarcoma, melanoma)[3] | Antiproliferative effect | |
| | | | Vitamin D analogues | Prostate cancer[139] | Varying effects on serum calcium, depending on analogue used | |
| | | | Vitamin D and nicotine | Aortic calcification[140] | ↑ with treatment | |
| | | | 1α,25(OH)$_2$D | Keratinocytes[27] | ↓ proliferation | |
| | | | 1α,25(OH)$_2$D | Keratinocytes and fibroblasts of patients with psoriasis[141] | ↓ proliferation, ↑ differentiation | |
| | | | 1α,25(OH)$_2$D | DM (NOD mice)[142,144,146] | Protection against developing DM | Up-regulates IL-4 |
| | | | 1α,25(OH)$_2$D | EAE, mice[177] | Prevents EAE | |
| | | | 1α,25(OH)$_2$D | Lyme arthritis, mice[147] | Inhibits progression | IL-10 KO mice |
| | | | 1α,25(OH)$_2$D | IBD, mice[149] | ↓ risk and severity | IL-2 KO mice |
| | | | 1α,25(OH)$_2$D and calcium | IBD, mice[148] | ↑ effect with both | IL-10 KO mice |
| | | | Vitamin D analogues | SLE[153] | Inhibits lupus nephritis | MRL/1 mice |
| | | | Vitamin D analogue | Aortic allograft intimal and advential damage[154] | ↓ damage | |
| | | | 1α,25(OH)$_2$D | Heart allograft survival, mice; heterotopic graft, rats[155] | Prolongs survival without bone loss or ↑ risk of infection | |
| | | | Vitamin D analogue | Xenogenic pancreatic islets, mice[234] | Prolongs graft survival when used with cyclosporine | NOD mice |
| | | | Vitamin D analogue | Liver cancer[156] | Patients with inoperable liver cancer | Human |

*References are provided for examples of each type of study. The most convincing evidence comes from randomized controlled trials. There is some evidence from clinical trials that vitamin D (often given with calcium) may reduce the risk of falls and fractures. Associations with most other diseases and conditions come from lower levels of evidence. 1α,25(OH)$_2$D = 1α-25-hydroxyvitamin D; 1,25(OH)$_2$D = 1,25 hydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; 1-H-vitamin D$_3$ = 1 hydroxylated vitamin D$_3$; BMD = bone mineral density; BP = blood pressure; CRP = C-reactive protein; DM = diabetes mellitus; EAE = experimental autoimmune encephalitis; IBD = inflammatory bowel disease; ICU = intensive care unit; IFN-γ = interferon-γ; IHD = ischemic heart disease; IL = interleukin; KO = knockout; MI = myocardial infarction; MS = multiple sclerosis; NA = not applicable; NHANES = National Health and Nutrition Examination Survey; NHS = Nurses' Health Study; NOD = nonobese diabetic; PTH = parathyroid hormone; RCT = randomized controlled trial; SLE = systemic lupus erythematosus; TNF-α = tumor necrosis factor α.
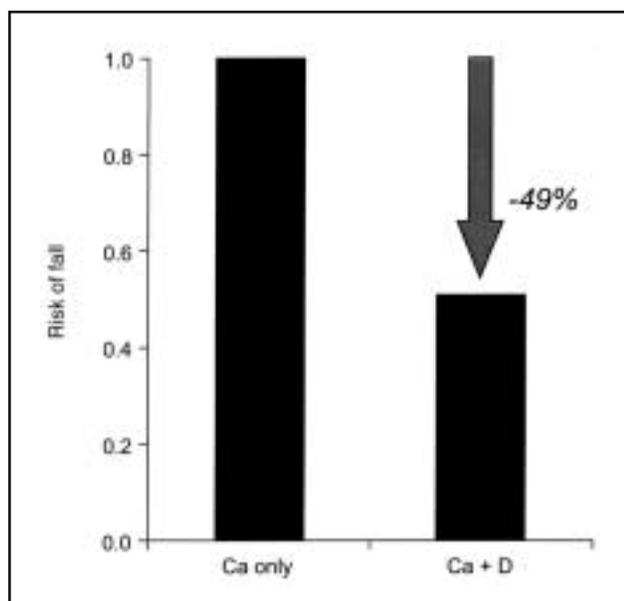
FIGURE 4. Relative to therapy with 1200 mg/d of calcium for 12 weeks, daily therapy with 800 IU of vitamin D and 1200 mg of calcium accounted for a 49% reduction in the relative risk of falls among older women (mean age, 85.3 years) in long-term geriatric care. Ca = calcium; Ca + D = Ca plus vitamin D. Adapted from *J Bone Miner Res*,[174] with permission from The American Society for Bone and Mineral Research.

that examined factors associated with falls in 637 institutionalized ambulatory subjects reported that a low baseline serum 25(OH)D level was significantly associated with increased risk of falling.[126] In a randomized, double-blind trial, treatment with vitamin D plus calcium daily for 3 months reduced the risk of falling by 49% compared with calcium alone among elderly women in long-stay geriatric care[174] (Figure 4). Similarly, a study of community-dwelling elderly adults in Switzerland showed that treatment with $1,25(OH)_2D_3$ and also $1\alpha$-hydroxy-vitamin $D_3$ $(1\alpha[OH]D_3)$ significantly reduced the number of falls for individuals with calcium intake of more than 512 mg/d.[120] These studies suggest that adequate serum 25(OH)D may prevent fractures not only by improving calcium homeostasis but also by improving musculoskeletal function.

Other recent evidence suggests that vitamin D inadequacy may be a factor in loss of muscle mass and muscle strength (sarcopenia).[127,175] One population-based study reported that 25(OH)D levels between 16 and 38 ng/mL (40 and 94 nmol/L) were associated with better musculoskeletal function in the lower extremities of both active and sedentary ambulatory adults 60 years or older compared with levels less than 16 ng/mL (40 nmol/L).[143] The hierarchy of evidence for the role of vitamin D

in muscle function and fall prevention is summarized in Table 2. [118,119,121,135]

## VITAMIN D AND EXTRASKELETAL HEALTH

The small intestine, kidneys, and bones are the primary organs and tissues responsive to vitamin D that are involved in mineral metabolism that affects skeletal health. However, the effects of vitamin D are not limited to mineral homeostasis and the maintenance of skeletal health. The presence of the VDR in other tissues and organs suggests that vitamin D may also be important in nonskeletal biological processes.[176-178] Additionally, the enzyme responsible for conversion of 25(OH)D to the biologically active form of vitamin D $(1,25[OH]_2D)$ has been identified in tissues other than kidney[150,179-181] (Figure 5), and evidence is growing that extrarenal synthesis of $1,25(OH)_2D$ may be important for regulating cell growth and cellular differentiation[1,4,176,177] via paracrine or autocrine regulatory mechanisms.

The VDR is a steroid hormone nuclear receptor that binds $1,25(OH)_2D$ with high affinity and mediates transcriptional gene regulation.[1,4,176,177,182,183] Mounting biochemical and epidemiological evidence suggests that the VDR is also involved in mediating the noncalcemic effects of vitamin D and its analogues and may play a vital role in disease prevention and maintenance of extraskeletal health.[1-3] The VDR has been isolated from many cell types, tissues, and organs, including those not typically associated with calcium homeostasis and bone metabolism. Some of these include the heart, stomach, pancreas, brain, skin, gonads, and various cells of the immune system.[1,4,176,177] Genetic variants of the gene encoding the VDR have also been associated with differential risk of developing various cancers[184,185] and immune disorders, including type 1 diabetes mellitus.[186,187]

In addition, $1,25(OH)_2D$ is involved in non–genomic-mediated intracellular signaling pathways.[188-191] Both $1,25(OH)_2D$ and its synthetic analogues (collectively, VDR ligands) have demonstrated antiproliferative, prodifferentiative, and immunomodulatory activities (which may be mediated by both the genomic and the nongenomic mechanisms) in several clinical and experimental settings,[188] and are being investigated for the potential treatment of many pathologic conditions, including psoriasis, type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, Crohn disease, hypertension, cardiovascular heart disease, and many common cancers.[1,2,151,192,193]

Since the primary function of vitamin D is to modulate calcium homeostasis, the use of analogues for the treatment of conditions other than osteoporosis or osteomalacia could trigger hypercalcemia or other unwanted adverse effects.
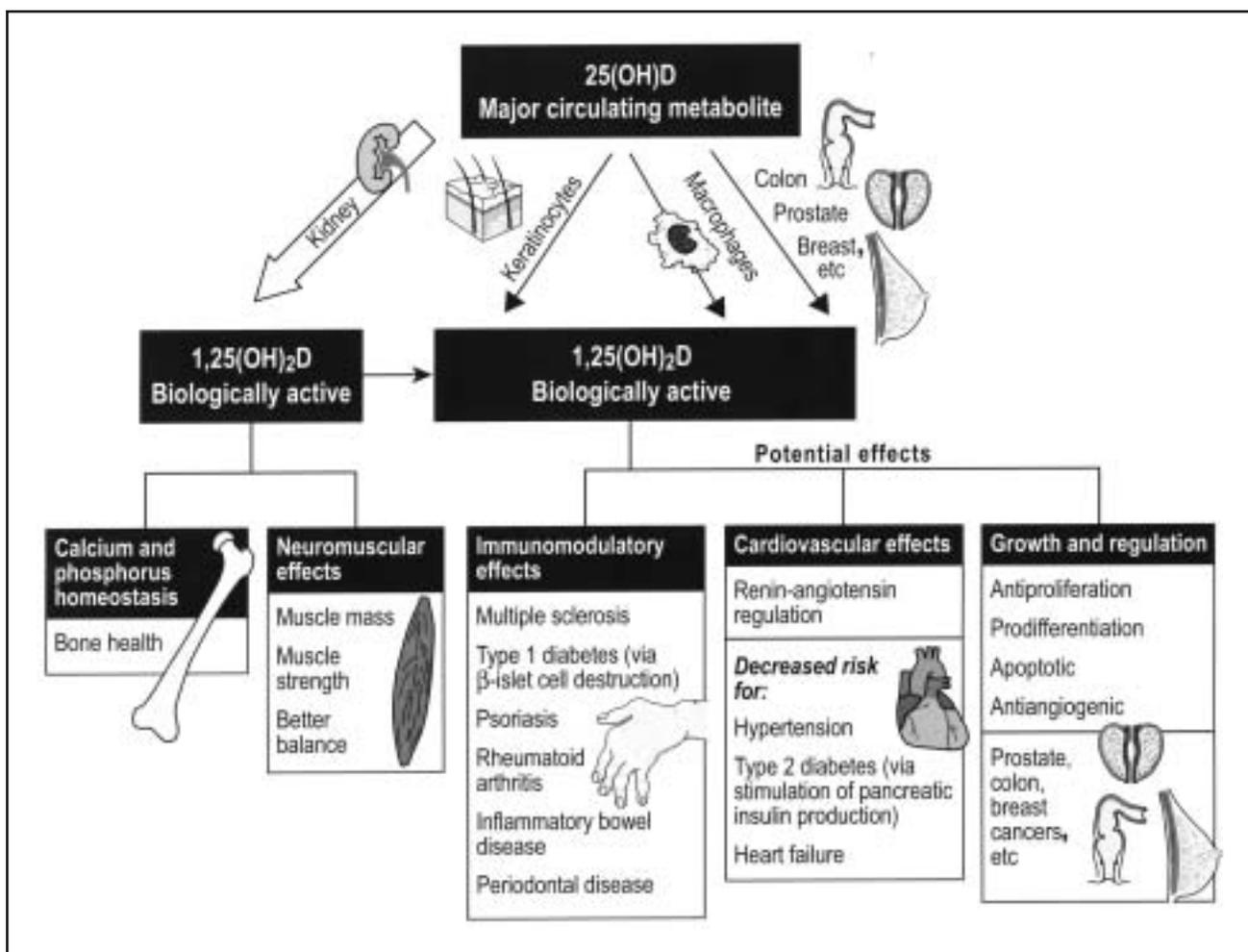
FIGURE 5. Endocrine and autocrine or paracrine functions of 1,25-dihydroxyvitamin D (1,25[OH]$_2$D). The kidneys serve as the endocrine organ to convert 25-hydroxyvitamin D (25[OH]D) to 1,25(OH)$_2$D. 1,25(OH)$_2$D carries out its calcium-regulating functions for bone health by stimulating intestinal calcium and phosphorus absorption. The circulating levels of 1,25(OH)$_2$D can also potentially influence the activity of other tissues and cells that have a vitamin D receptor (VDR) and have no function in regulating calcium homeostasis and bone health. These include, among others, the heart skeletal muscle, active T and B lymphocytes, breast, colon, and prostate. In addition, a multitude of in vitro studies with human and animal cells have shown that most tissues and cells not only express the VDR but also express the same 1α-hydroxylase as the kidney. Thus, it has been suggested that most cells, including lung, colon, prostate, and breast, locally produce 1,25(OH)$_2$D$_3$ to help regulate a variety of cellular functions including growth and differentiation. This may help explain the epidemiological evidence that sun exposure at lower altitudes and higher serum levels of 25(OH)D are related to a decreased risk of a wide variety of chronic illnesses. It has been speculated that when 25(OH)D levels are above 30 ng/mL this serves as the substrate for the external 25(OH)D$_3$-1α-hydroxylase to produce 1,25(OH)$_2$D in the colon, prostate, breast, and lung to modulate cell growth and reduce risk of the cells becoming malignant.

Researching the development of VDR ligands with attenuated calcemic potential is a difficult challenge. More than 1000 VDR ligands with various bioactivities have been synthesized.[191,194] Analogues that are able to effect antiproliferative, prodifferentiative, blood pressure, and immunomodulation changes while maintaining calcium homeostasis are of particular interest as potential treatments for nonskeletal diseases. The hierarchy of evidence for the role of vitamin D and its analogues on these nonskeletal effects is summarized in Table 2.

## VITAMIN D AND CANCER

Vitamin D is one of the most potent hormones for regulating cell growth; 1,25(OH)$_2$D inhibits proliferation and induces differentiation into normally functioning cells.[1,4,176,177,197] Some evidence suggests that 1,25(OH)$_2$D helps to regulate cell growth and prevent cancer progression[1,176,177,198] by reducing angiogenesis,[153] increasing cell differentiation and apoptosis of cancer cells, and reducing cell proliferation[156-158] and metastases.[1,4,126,151,156,176,177,179,181] The antiproliferative

and prodifferentiative activity of VDR ligands was noted almost 3 decades ago.[158,176,177] Tanaka et al[159] showed that mouse and human leukemic cells that expressed the VDR had growth inhibition and were stimulated to differentiate into mature macrophages when treated with $1\alpha,25(OH)_2D_3$. Suda et al[138] were then able to show that leukemic mice survived longer if they were treated with $1\alpha(OH)D_3$, a $1,25(OH)_2D_3$ analogue. However, results of human trials for the treatment of preleukemia with VDR ligands were disappointing. Although some patients experienced remission, the treatment caused severe hypercalcemia, and all patients eventually died.[160]

Several in vitro studies have shown that breast, colon, and prostate cancer cells, osteosarcomas, and melanomas are responsive to the antiproliferative effects of $1,25(OH)_2D,$[1,4,161,162,176,177,182] and several epidemiological studies have reported that higher 25(OH)D levels are associated with reduced cancer incidence and decreased cancer-related mortality.[1,2,161,182,204] As early as 1941, people who live at higher latitudes in the United States were noted to have increased risks of breast, colon, and prostate cancers.[163] This insightful observation went unnoticed until the 1980s, when Garland et al[132,164,202] reported increased breast and colon cancer risks for those living at higher latitudes in the United States. Evidence now exists to support the link between increased sunlight exposure and a lower incidence of many cancers.[165,166,209-211] Such ecologic studies can be a weak form of evidence, particularly since latitude is not always a strong predictor of vitamin D status. Adding to these data are several retrospective and prospective observational studies that have reported decreases of 50% or greater in risk of large bowel cancer and prostate cancer when serum 25(OH)D levels are greater than 20 ng/mL (50 nmol/L) or vitamin D intake is increased.[2,123,125,162,164,182,202-204]

Similar results have been observed for breast cancer.[212] In one study, women in the highest quartile of serum $1,25(OH)_2D$ had one fifth the risk of breast cancer vs those in the lowest quartile.[124] Women in the National Health and Nutrition Examination Survey with self-reported high intake of vitamin D from supplements or high lifetime sun exposure had a significantly reduced risk of breast cancer.[204] Grant[166,209] postulated that roughly 25% of deaths due to breast cancer among women in northern Europe could be attributed to inadequate vitamin D levels, possibly due to living at higher latitudes, and that both men and women with greater sun exposure were less likely to die prematurely of cancer.

Although it was recognized that most cells, including the prostate, breast, and colon, had VDR, it was perplexing how increased exposure to sunlight, higher vitamin D intake, and higher serum 25(OH)D levels could reduce risk of cancer in these tissues. It was known that the kidney tightly controls the amount of $1,25(OH)_2D$ it produces. Although PTH and hypophosphatemia increase the renal production of $1,25(OH)_2D$, an increase in sun exposure or dietary vitamin D intake does not. In 1998, Schwartz et al[179] reported that normal prostate tissue and prostate cancer tissue from prostate biopsy specimens had the enzymatic machinery (25[OH]D-1$\alpha$-hydroxylase; CYP27B) to convert 25(OH)D to $1,25(OH)_2D$. Similar observations have been made in breast, colon, lung, skin, and a multitude of other organs and tissues.[150,180,181] Thus, a new autocrine or paracrine function for vitamin D was revealed (Figure 5). This concept was supported by the observation that when a prostate cancer cell line LNCaP that did not express CYP27B was incubated with $25(OH)D_3$, there was no effect on the cancer cell's proliferation activity. When similar cells were transfected with a plasmid that contained the *CYP27B* gene, the cells were able to convert $25(OH)D_3$ to $1,25(OH)_2D_3$. When the CYP27B transfected cells were treated with $25(OH)D_3$, the cellular proliferative activity decreased similarly to cells treated with $1,25(OH)_2D_3$.[213] This observation supports the hypothesis that increasing circulating concentrations of 25(OH)D provide most cells with the substrate to make $1,25(OH)_2D$ locally to regulate cell growth and differentiation. Once $1,25(OH)_2D$ completes this task, it then induces the 25(OH)D-24-hydroxylase gene (*CYP24B*) to catabolize it to the biologically inactive calcitroic acid (Figure 1).[1,4,176,177,189]

## VITAMIN D AND CARDIOVASCULAR DISEASE

Adding to the evidence of the effect of vitamin D on extraskeletal tissues are data that suggest that inadequate vitamin D and calcium and living at higher latitudes may be independent contributing factors in the pathogenesis and progression of hypertension and cardiovascular disease.[1,2,201,214] $1,25(OH)_2D$ is involved in controlling the production of renin, one of the most important hormones for regulating blood pressure.[215] Ecological evidence also exists that African Americans, who have been shown to be at greater risk of vitamin D deficiency, also have a greater risk of hypertension and cardiovascular disease.[199,214,216] These studies do not directly provide a cause-and-effect relationship between vitamin D and cardiovascular health but suggest a provocative hypothesis for further research.

In a small blinded study of 18 hypertensive patients randomized to receive repeated exposure to artificial UV-A radiation (which cannot produce vitamin $D_3$) or UV-B radiation (which leads to cutaneous vitamin $D_3$ synthesis) treatment, the UV-B treatment group showed an average 6-mm Hg decrease in both systolic and diastolic blood pressure and a 180% increase in serum 25(OH)D levels vs the group exposed to UV-A, who showed no change in serum

25(OH)D levels or blood pressure.[201] A randomized, placebo-controlled, double-blind clinical trial of 148 elderly women (mean age, 74 years) found that vitamin D and calcium were more effective in reducing systolic blood pressure than calcium alone.[216] Sowers et al[134] also reported a positive association between $1,25(OH)_2D$ and vitamin D inadequacy and hypertension. Although this evidence suggests that increased vitamin D is associated with reduced risk of hypertension, some studies have reported contradictory findings. Jorde and Bonaa[136] reported no link between vitamin D intake and blood pressure. The authors noted that most participants older than 50 years were receiving less than 400 IU of vitamin D from their diet, which meant that they were not receiving enough vitamin D. Furthermore, blood levels of 25(OH)D were not obtained, making it difficult to know the vitamin D status of the subjects who were studied.

Elevated C-reactive protein levels have been associated with increased cardiovascular events.[217] In one unblinded study, 22 patients with prolonged critical illnesses were compared with matched controls and then randomized to daily vitamin D supplement of either ±200 IU or ±500 IU. The results demonstrated that a 500-IU/d dose of vitamin D reduced C-reactive protein levels by more than 25% in the critically ill patients vs the matched controls who did not receive supplementation.[217] McCarty[218] hypothesized that the excess of coronary mortality observed in winter may be related to inadequate levels of vitamin D and suggested a possible role for vitamin D in maintaining vascular health.

However, as with hypertension, contradictory findings suggest that increased vitamin D may be a causative factor or play no role in cardiovascular disease. In an observational study of vitamin D and myocardial infarction, Lindén[219] reported that vitamin D intake was elevated in patients with myocardial infarctions vs randomly selected age- and sex-matched controls who had no prior myocardial infarction or angina pectoris. However, this study was confounded because the patients in general were at high risk of cardiovascular heart disease and there was no measure of vitamin D status to substantiate the "high intake." Two other studies, one observational with age-matched controls[220] and a prospective cohort study of 34,486 postmenopausal women (55-69 years of age),[206,221] found that 25(OH)D levels were not elevated in patients with myocardial infarctions and ischemic heart disease.

## VITAMIN D AND PSORIASIS

One of the great successes of vitamin D therapy for treating an extraskeletal disorder is in the treatment of psoriasis.[193,196] Smith et al[27] showed that $1,25(OH)_2D_3$ inhibited the prolif-

eration of human keratinocytes that express the VDR in vitro and accelerated their differentiation. This suggested that hyperproliferative skin disorders such as psoriasis might be responsive to treatment with $1,25(OH)_2D_3$.[222] Initial treatments with topical $1,25(OH)_2D_3$ showed great improvements in reducing the severity and area of psoriatic lesions, with little or no adverse effects.[25,141,193,223] Today, 3 vitamin D analogues including calcipotriene, $1,24(OH)_2D_3$, and 22-oxo-$1,25(OH)_2D_3$, are among the first-line treatments used for psoriasis.[141,193,196,223]

## VITAMIN D AND MULTIPLE SCLEROSIS

As with previous epidemiological data reporting a latitudinal risk gradient for cancer and cardiovascular disease,[2,161,163,166,204,209,215] a similar risk gradient exists for developing multiple sclerosis.[205,224-226] Subjects who were born and/or lived below 35°N latitude for the first decade of life had decreased overall lifetime risks of developing multiple sclerosis.[205,225] However, as with other ecological studies, the observed differences could be related to any number of other factors that were not measured.

One double-blinded RCT involving patients with multiple sclerosis who were randomized to receive either vitamin D supplementation or placebo showed that patients who received supplementation had increased serum transforming growth factor β1 levels vs those who did not receive supplementation.[200] Elevated transforming growth factor β1 levels have been associated with the stable phase of multiple sclerosis, whereas reduced levels have been associated with relapsing-remitting multiple sclerosis.[227,228] Two related observational studies[229] (the Nurses' Health Study [N=92,253, from 1980 to 2000] and the Nurses' Health Study II [N=95,310, from 1991 to 2001]) reported that higher intake of vitamin D was associated with a lower risk of developing multiple sclerosis.

## VITAMIN D AND TYPE I DIABETES MELLITUS

$1,25(OH)_2D$ acts as an immunomodulator, reducing cytokine production and lymphocyte proliferation, which have been implicated in the destruction of insulin-secreting β cells in the pancreas and the development of type 1 diabetes mellitus.[142] In addition, β-islet cells express the VDR and respond to $1,25(OH)_2D$ by increasing insulin production.[1,142,230,231]

In animals, the administration of $1,25(OH)_2D$ prevents the development of experimentally induced type 1 diabetes mellitus.[142,144] Zella and DeLuca[145] have also shown that very large doses of vitamin D were able to suppress the development of insulitis and diabetes in the nonobese diabetic mouse, a model of human type 1 diabetes mellitus. A birth

cohort study involving 10,366 children conducted in Finland showed that higher dietary vitamin D supplementation was associated with reduced risk of type 1 diabetes mellitus. Children who regularly took the recommended supplemental dose of 2000 IU/d of vitamin D during their first year of life had a rate ratio of 0.22 (range, 0.05-0.89) for type 1 diabetes mellitus compared with those who regularly received less than 2000 IU/d.[207] Likewise, Stene et al[130] reported a lower risk of type 1 diabetes mellitus in the children of mothers who took cod liver oil during their pregnancy. These data do not support a direct cause-and-effect relationship but suggest that further studies are warranted.

## VITAMIN D IN OTHER DISEASES

A possible role of vitamin D has also been implicated in several other diseases, including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, osteoarthritis, and periodontal disease. Many of these studies are epidemiological studies and animal models, and the effect in humans is unknown. Recent findings suggest that vitamin D intake is inversely associated with rheumatoid arthritis[208] and that $1,25(OH)_2D_3$ supplementation can inhibit disease progression in mouse models of human Lyme arthritis.[147] Merlino et al[208] tracked approximately 30,000 women throughout 11 years and found that those whose daily vitamin D intake was less than 200 IU were 33% more likely to develop rheumatoid arthritis compared with women with higher intake levels. Cantorna et al[148,152] have shown that $1,25(OH)_2D_3$ can prevent and ameliorate symptoms of inflammatory bowel disease in a mouse model. Abe et al[153] were also able to alleviate symptoms in a mouse model of systemic lupus erythematosus without inducing hypercalcemia by using $22$-oxa-$1,25(OH)_2D_3$, a synthetic analogue of $1,25(OH)_2D_3$. McAlindon et al[232] observed that a higher intake of vitamin D and higher blood levels of 25(OH)D decreased progression of osteoarthritis in men and women by more than 60%. Krall et al[233] found that calcium and vitamin D supplementation was associated with a reduced risk of tooth loss in elderly patients. More recently, Dietrich et al[137] reported that low serum levels of 25(OH)D may be associated with periodontal disease, independent of BMD.

Experimental evidence also exits for an immunomodulatory role of VDR ligands in attenuating rejection of rat aortic allografts[154,188] and both vascular and nonvascular transplants.[155] Treatment of nonobese diabetic mice with a vitamin D analogue KH1060 in combination with cyclosporine achieved 100% early graft success of xenogenic islets.[234] In addition, VDR ligands have been used experimentally to attenuate bone loss after organ transplantation.[235] Nagpal et al[188] postulate that the mechanism by which vitamin D prevents transplantation-induced osteoporosis may be comparable to the mechanism by which it suppresses secondary hyperparathyroidism brought on by immunosuppressive agents such as corticosteroids and/or cyclosporine; the mechanism appears to involve pregnane X receptor–enhanced CYP24 gene expression.[74]

## VITAMIN D DOSING, SUPPLEMENTATION, AND UV IRRADIATION AND/OR SENSIBLE SUN EXPOSURE

Supplementation with vitamin D has been estimated to prevent vitamin D deficiency in approximately 98% of the general population.[1,16,236] Vitamin D supplementation and exposure to sunlight or simulated sunlight have been shown to increase serum 25(OH)D levels in elderly patients [11,84,87,89,90,92,94,97,102,107,237-240] (Figure 3).

The Institute of Medicine's adequate intake for the United States and Canada is 200 IU/d for all children and adults younger than 51 years, 400 IU/d for people aged 51 to 70 years, and 600 IU/d for those older than 70 years.[21,236] A report by the Scientific Committee for Food, established by the European Commission, indicated that adults 65 years and older should receive 400 IU/d of vitamin $D_3$ and suggested that the requirements of all adults, including those with inadequate sunlight exposure, would be met by this dietary intake.[241] This recommendation is consistent with that of the US Food and Drug Administration's daily recommended value of 400 IU/d (10 µg/d) of vitamin $D_3$ regardless of age.[242] Because it has been suggested that amounts up to 1000 IU/d of vitamin $D_3$ may be needed to maintain a healthy 25(OH)D level of more than 30 ng/mL (75 nmol/L),[5,28,243,244] an intake of 400 IU/d may represent a minimum. This is especially true in the winter or for children and adults not exposed to sunlight.

Vitamin D toxicity has not been reported from long-term exposure to sunlight[1,4] and has only been observed from dietary intake when daily doses exceed 10,000 IU.[245,246] Doses of 4000 IU/d for 3 months and 50,000 IU/wk for 2 months have been administered without toxicity.[11,247,248]

## TREATMENT OF SEVERE VITAMIN D DEFICIENCY

Although severe vitamin D deficiency (25[OH] levels <10 ng/mL [25 nmol/L]) is much less common than inadequacy, it does occur, especially in elderly house-bound people. The best method for treating vitamin D deficiency is an oral dose of 50,000 IU/wk of vitamin $D_2$ for 8 weeks, then checking 25(OH)D levels.[1,11] In some cases, another once-weekly 8-week course of 50,000 IU of vitamin $D_2$ may be necessary to boost 25(OH)D levels into the desired range of more than 30 to 50 ng/mL (75-125 nmol/L). For

patients prone to developing vitamin D deficiency, after correcting the deficiency, giving patients 50,000 IU every 2 weeks will sustain them in a vitamin D–suffcient state. Alternatively, 1000 IU of vitamin $D_3$ intake should be maintained. Cutaneous exposure to sunlight or artificial UV-B such as a tanning bed is also helpful, especially if the patient is prone to vitamin D deficiency.[76,165,238-240,248,249] Exposure to direct sunlight typically of no more than 5 to 10 minutes on the arms and legs between the hours of 10 AM and 3 PM during the spring, summer, and fall will prevent vitamin D inadequacy.[1,16,65]

## CONCLUSION

Vitamin D is important for calcium and phosphorus homeostasis and musculoskeletal health. In children, severe vitamin D deficiency (25[OH]D, <10 ng/mL [24.9 nmol/L]) manifests as rickets, and vitamin D inadequacy (25[OH]D, 10-29 ng/mL [24.9-72.4 nmol/L]) can impair or retard attainment of peak bone mass. In adults, inadequate vitamin D can result in secondary hyperparathyroidism, decreased BMD, osteoporosis, osteomalacia, and increased risk of fragility fractures.[250-252]

Vitamin D inadequacy is a global problem, especially among elderly patients and patients with osteoporosis. Risk factors for low vitamin D include lack of exposure to sufficient sunlight, inadequate dietary intake and supplementation, and other factors, including obesity, age, medication use, sunscreen use, covering all skin with clothing, and skin pigmentation. Fortunately, vitamin D supplements are widely available and relatively inexpensive.

Despite some negative studies, the preponderance of evidence from RCTs supports a reduction in the risk of vertebral[100] and nonvertebral[92,107] fractures with vitamin D (given in combination with calcium in most trials), especially in populations with low vitamin D status and low calcium intake at baseline. Similarly, results of a meta-analysis of RCTs suggest that vitamin D can reduce the risk of falls.[143]

Many lines of research support the concept that inadequate vitamin D may be involved in the pathogenesis and/or progression of several disorders, including cancer, hypertension, cardiovascular disease, neuromuscular diseases, osteoarthritis, diabetes, and other autoimmune diseases (Table 2). Some of the mechanisms by which vitamin D exerts its noncalcemic effects include apoptosis, antiangiogenesis, antiproliferation, prodifferentiation, and immunomodulation (Figure 5) (Table 2).[150,178-188,253]

However, the current level of evidence for associations of vitamin D with nonmusculoskeletal conditions is generally weaker than that for its calcemic and musculoskeletal effects (falls and fractures). The reported nonmusculo-

skeletal associations have come primarily from observational studies in humans or laboratory experiments (in vivo and in vitro). As indicated in Table 2, randomized, placebo-controlled, double-blind clinical trials (or meta-analyses of these trials) are considered to provide the highest level of evidence because randomization and blinding minimize the risk of bias in estimating treatment effects.[254,255] Even among observational studies, evidentiary value varies, with prospective cohort studies (such as the Framingham Study, the Nurses' Health Study, or the Study of Osteoporotic Fractures) yielding the most clinically useful information, whereas bench research and expert opinion provide the least. All types of non-RCT studies are subject to the risk of several biases, which are minimized by the design of RCTs: the qualitative and quantitative differences between observational and trial findings about hormone replacement therapy for postmenopausal women are probably the most noteworthy recent demonstration of the limitations of observational data.[256,257] However, results from nontrial studies are important because they identify associations and suggest hypotheses that can be tested more rigorously in RCTs. The presence of VDR in tissues other than bone and muscle suggests the possibility of important effects of vitamin D; however, the available supporting data are sometimes conflicting and generally represent a low level of evidence. The putative nonmusculoskeletal effects of vitamin D may become better understood if appropriate trials are conducted, but at present inferences about such effects must be made with caution.

Despite evidence of its profound importance to human health, vitamin D inadequacy is not widely recognized as a problem by physicians and patients. These observations highlight the need for greater awareness among researchers, clinicians, and patients of the high prevalence of vitamin D inadequacy and more aggressive screening for vitamin D inadequacy with a serum 25(OH)D determination, particularly among high-risk populations such as elderly patients and patients with osteoporosis.

Finally, we should not forget the important role that sensible sun exposure has in providing both young and old people with their vitamin D requirement. It is well documented that excessive exposure to sunlight, especially the number of sunburning experiences, is related to increased risk of squamous and basal cell carcinoma.[258,259] These skin cancers, if detected early, are usually easily treated and often cured. Melanoma, however, is one of the most aggressive and deadly forms of skin cancer. This is because melanocytes are neurocrest cells and when they become malignant they express the Slug gene, which is responsible for its quick exit from skin metastasizing to various organs, making it difficult to detect and treat.[260] However, it should be appreciated that most melanomas occur on the least sun-

exposed areas.[16,261,262] Furthermore, Kennedy et al[259] reported that lifetime sun exposure appeared to be associated with a lower risk of malignant melanoma, despite the fact that lifetime sun exposure did not diminish the number of melanocytic nevi or atypical nevi. Furthermore, Berwick et al[263] reported that sun exposure is associated with increased survival in patients with melanoma, and Chang et al[264] reported that a history of increased sun exposure was associated with reduced risk of non–Hodgkin lymphoma. These observations are consistent with the suggestion of Apperly[163] that sun exposure seems to provide an immunity for most deadly cancers, even though it is associated with increased risk of relatively benign skin cancer. No substantiated scientific evidence exists to suggest that sensible suberythemal sun exposure significantly increases risk of any type of skin cancer and certainly not melanoma. The negative publicity regarding sun exposure during the past 30 years has resulted in a vitamin D deficiency pandemic. The important role that sensible sun exposure has in providing vitamin D for the world's population needs to be reevaluated. Indeed, in Australia and New Zealand, where the incidence of skin cancer is the highest in the world, the New Zealand Bone and Mineral Society in collaboration with the Australian College of Dermatologists and the Cancer Council of Australia have recommended a balance between avoiding an increased risk of skin cancer and achieving enough UV radiation to maintain adequate vitamin D levels. It is hoped that this message will be heard loud and clear and that this recommendation will also be adopted worldwide.

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