

Vitamin D: Bone and Beyond, Rationale and Recommendations for Supplementation

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ABSTRACT

Adequate vitamin D status is necessary and beneficial for health, although deficiency plagues much of the world's population. In addition to reducing the risk for bone disease, vitamin D plays a role in reduction of falls, as well as decreases in pain, autoimmune diseases, cancer, heart disease, mortality, and cognitive function. On the basis of this emerging understanding, improving patients' vitamin D status has become an essential aspect of primary care. Although some have suggested increased sun exposure to increase serum vitamin D levels, this has the potential to induce photoaging and skin cancer, especially in patients at risk for these conditions. Vitamin D deficiency and insufficiency can be both corrected and prevented safely through supplementation.

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Vitamin D is essential for a vast number of physiologic processes, and as such, adequate levels are necessary or advantageous for optimal health. However, deficiency of vitamin D is now recognized as a pandemic with more than half of the world's population currently at risk.^{1,2} Although vitamin D previously was thought to exert most of its benefit through calcium homeostasis and prevention of bone disease (ie, rickets, osteomalacia, and osteoporosis), it also has been shown to induce cellular differentiation, inhibit angiogenesis, and possibly reduce the invasiveness and metastatic potential of tumors.^{3,4} It seems that serum levels needed to prevent bone disease might be less than those needed for optimal health.

Because vitamin D can be synthesized by the skin after exposure to ultraviolet B light, increasing recognition of its importance has led some health care providers to recommend increased sun exposure. This article will review vita-

min D's role in health and disease (Table 1), and discuss treatment options for hypovitaminosis D.

VITAMIN D PHYSIOLOGY

There are 2 main forms of vitamin D: vitamin D₃ (cholecalciferol) and vitamin D₂ (ergocalciferol).⁵ Vitamin D₃ is formed in the skin, after exposure to ultraviolet B radiation, from 7-dehydrocholesterol that resides in cell membranes.⁶ Vitamin D₂ is obtained through irradiation of ergosterol in plants, analogous to human production from sunlight, and enters our circulation through diet.⁷ Similar to vitamin D₂, vitamin D₃ also is available from animal sources, such as cod liver oil, salmon, mackerel, and herring.^{2,8} Certain foods in the United States are fortified with vitamin D, such as milk, yogurt, cheeses, various breads, and some juice products.² Fortified milk is the most readily available dietary source, but physiologic and cultural barriers may hinder its consumption.⁹ Only a small number of foods naturally contain vitamin D, and even those fortified with vitamin D are frequently insufficient to fulfill the requirement for children or adults, unless large amounts are consumed.² For example, there is typically only 100 IU of vitamin D in an 8-ounce serving of fortified orange juice or milk or in a half teaspoon of cod liver oil.^{1,8} Three and a half ounces of farmed salmon contains approximately 100 to 250 IU of vitamin D per serving.² Therefore, one would need to

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drink at least 2 servings of juice or milk daily or a minimum of 3.5 ounces of salmon for recommended daily amounts.

After vitamin D is ingested from the diet or synthesized in the skin, it is metabolized in the liver to a biologically inactive 25-hydroxyvitamin D, 25(OH)D, which is the major circulating form of vitamin D. It is this form of vitamin D that is used to determine a person's vitamin D status.^{2,5} Through hydroxylation by 1 α -hydroxylase, 25(OH)D is subsequently converted to a biologically active form, 1,25-dihydroxyvitamin D (1,25(OH)₂D), primarily in the kidneys.¹ 1,25(OH)₂D is then able to interact with vitamin D receptors in the intestine and bone to augment intestinal calcium absorption and mobilize osteoclast activity.¹⁰ Because they express 1 α -hydroxylase, non-calcium regulating tissues, such as the prostate, colon, and breast, locally convert 25(OH)D to 1,25(OH)₂D, which has the potential to regulate up to 200 genes to facilitate cell growth and differentiation, and to possibly decrease the risk of cell transformation into a malignant state.^{1,2,11} In addition, the vitamin D receptor is present in most tissues and cells in the body, allowing 1,25(OH)₂D to be one of the most potent regulators of cellular growth in both normal and cancer cells.¹²

CLINICAL SIGNIFICANCE

- Vitamin D deficiency is a pandemic with more than half of the world's population currently at risk.
- Adequate vitamin D levels are necessary and advantageous for optimal health.
- Although ultraviolet radiation can assist in increasing vitamin D levels, skin cancer and photoaging are increasing epidemics affecting millions of individuals each year.
- Vitamin D deficiency and insufficiency can be both corrected and prevented safely through supplementation.

As stated previously, one's vitamin D status is determined by measuring 25(OH)D levels, although the cutoff value for deficiency, which has changed over recent years, remains controversial.² This is at least partially due to discrepancies in assay methodology and variability in vitamin

D concentration by geographic variability.¹³ An emerging consensus among those with an interest in vitamin D deficiency is that a 25(OH)D concentration less than 20 ng/mL is an indication of vitamin D deficiency, 21 to 29 ng/mL suggests vitamin D insufficiency, and greater than 30 ng/mL specifies sufficiency.² By using these levels, it is estimated that one billion people worldwide have either vitamin D deficiency or insufficiency.¹⁴ In the United States alone, vitamin D inadequacy has been reported in approximately 36% of otherwise young healthy adults and up to 57% of general medicine inpatients, with even higher numbers in Europe.¹⁵

Vitamin D is important in calcium homeostasis and musculoskeletal health. Without vitamin D, only 10% to 15% of dietary calcium and approximately 60% of phosphorus will be absorbed.¹⁴ The efficiency of calcium absorption is increased by 30% to 40%, and phosphorus by 80%, with the interaction of 1,25(OH)₂D to its receptor.¹⁴

Table 1 Effects of Vitamin D^{33,35,43,45-47,49,52,56-58,60,65,68,72}

| | |
|--------------------|---|
| Bone | Decreases the risk of osteoporotic fractures |
| Falls | May retard sarcopenia and decreases the risk of falls |
| Pain | Decreases neuropathic pain in type 2 diabetes mellitus |
| Autoimmune disease | Decreases the risk of multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus |
| Cancer | Decreases the risk of colorectal cancer and leukemia Decreases the total cancer incidence and mortality Decreases digestive system cancer incidence and mortality |
| Heart disease | Decreases the incidence of breast cancer Decreases the risk of myocardial infarction Decreases vascular calcification |
| Mortality | Decreases total mortality |
| Cognitive function | Increases cognitive function Improves depression and seasonal affective disorder |

EPIDEMIOLOGY AND HIGH-RISK POPULATIONS

Certain populations are at higher risk for vitamin D deficiency. Hispanics, blacks, and those with a higher body mass index have higher rates of vitamin D deficiency.¹⁶ As a group, obese individuals have lower levels of 25(OH)D when compared with non-obese individuals.¹⁷ The increase in serum vitamin D₃ was 57% less in obese than in non-obese individuals 24 hours after a single suberythemal dose of ultraviolet B. Because vitamin D is fat soluble and readily stored in adipose tissue, it is possible that subcutaneous fat in obese individuals sequestered more of the vitamin D₃ synthesized in the skin. When these same individuals were challenged with a single oral dose of 50,000 IU vitamin D₂, body mass index was inversely associated with peak serum vitamin D₂ concentrations. Therefore, an obese individual might require more vitamin D to have the equivalent 25(OH)D increase as a lean individual. Given that 69 million Americans are labeled as obese or extremely obese, vitamin D deficiency in this population is particularly worrisome.¹⁸

Although darker skin protects against skin cancer and photoaging, it can lead to a higher risk of vitamin D defi-

ciency. The National Health and Nutrition Examination Study reported that 4.2% of white women compared with approximately 42% of African American women of child-bearing age had a serum 25(OH)D level < 15 ng/mL, possibly because of increased melanin concentration.¹⁹ Furthermore, regardless of race, women using oral contraceptives had a higher mean 25(OH)D level than non-users. This might be attributed to the increased concentration of vitamin D binding protein from the estrogen component of oral contraceptives.²⁰

Various other conditions have been reported to be associated with hypovitaminosis D, including poor dietary intake, chronic renal and liver disease, and drugs that accelerate vitamin D clearance or impair its activation, such as rifampin, certain anticonvulsants, and glucocorticoid therapy.²¹ The elderly, housebound, and nursing home residents are particularly vulnerable to deficiency. Maternal vitamin D status chiefly determines the vitamin D status of a fetus and newborn infant.²² Because this nutritional status is important for the formation of tooth enamel, fetal skeletal development, and possibly general fetal growth and development, vitamin D requirements during pregnancy are higher than for the general population. Therefore, it has been suggested that health care professionals recommend additional supplementation and should consider assessing 25(OH)D levels in pregnant women.²³

VITAMIN D AND DISEASE

Bones

Vitamin D deficiency results in an abnormal calcium-phosphorus product leading to diminished mineralization of the collagen matrix, causing rickets in children and osteomalacia, osteoporosis, and an increased fracture risk in adults.¹⁴ Nutritional rickets can lead to bone pain and deformities, motor development delay, or convulsions.²⁴ Although rickets are rare in the United States, osteoporosis affects 1 in 3 women and 1 in 12 men.²⁵ Fractures of the wrist, hip, and vertebrae are the 3 main manifestations of osteoporosis and in at-risk populations causes excess mortality, a considerable economic burden, and a decrease in quality of life.²⁵

As a person ages, the risk of developing an osteoporotic fracture increases. For example, 1 in every 2 women and 1 in every 4 men aged more than 50 years will experience an osteoporotic fracture at some point in their remaining lifetime.²⁶ As a result, in the elderly, vitamin D levels have been suggested to be the best predictor of fracture risk.²⁷ In a study of more than 500 individuals with hip fractures, 95% were found to be vitamin D deficient.²⁸ A study of 82 patients with minimal trauma fracture found that all except 2 individuals had vitamin D levels less than 30 ng/mL.²⁹ The most valid vitamin D trials have suggested that achievement of vitamin D sufficiency could reduce common osteoporotic fractures by 50% to 60%.³⁰ In addition to vitamin D deficiency, age, and gender, risk factors for osteoporotic fractures include Asian or Caucasian ethnic origin, low body weight, low dietary calcium intake, cigarette smoking,

excessive alcohol consumption, long-term immobilization, low estrogen levels, glucocorticoid therapy, and low bone mineral density.³¹ Because 25(OH)D concentrations decline with age, even increased supplementation is necessary in the majority of older individuals.³² The declining concentrations are due to a decrease in the absorption of calcium, production of vitamin D by the skin, and possible decrease in vitamin D absorption with aging.³² A randomized trial demonstrated that 800 IU/d, or 100,000 IU orally every 4 months, of vitamin D₃ for 5 years in patients aged 65 to 85 years reduced fracture risk by one third at common osteoporotic sites and might reduce mortality.³³

Falls

Skeletal muscles require vitamin D for maximum function, with deficiency causing muscle weakness.³⁴ 1,25(OH)₂D binds to its receptor in muscle tissue allowing de novo protein synthesis, muscle cell growth, and improved muscle function.³⁴ Furthermore, vitamin D deficiency is believed to be one of many factors contributing to the development of sarcopenia, the degenerative loss of muscle with aging, and may be an independent risk factor for postural sway and falls.³⁵⁻³⁷ A 22% reduction in fall risk has been found in individuals receiving vitamin D treatment compared with those with placebo or calcium alone, with this benefit most noticeably established in women (Table 3).³⁵ Falls resulting from neuromuscular dysfunction are the largest single cause of injury-related deaths in elderly people and lead to 40% of all nursing home admissions.³⁸ Vitamin D supplementation directly improves neuromuscular function leading to a decrease in the number of falls, and therefore a decline in the number of fractures.³⁸ In addition, vitamin D has been found to correlate with choice reaction time, a measurement reflecting neuroprotective mechanisms such as central processing, cognition, and motor response.³⁸ Vitamin D replacement can lead to a considerable increase in choice reaction time, and consequently less falls.³⁹

Pain

Severe vitamin D deficiency, particularly with 25(OH)D levels less than 12 ng/mL, leads to osteomalacic myopathy characterized by severe muscle weakness and pain, with rapid resolution of symptoms after vitamin D replacement.⁴⁰ Nonspecific musculoskeletal pain has been well documented to occur before the onset of osteomalacia bone pain in European immigrants and residents of Saudi Arabia, with women particularly at risk.⁹ In one study, it was determined that all outpatients with persistent, nonspecific musculoskeletal pain, not meeting criteria for fibromyalgia, seem to be at risk for severe hypovitaminosis D, as one study found 90% of the study group deficient in 25(OH)D.⁹ Deficient levels of vitamin D have recently been discovered in US service members who have returned from Iraq or Afghanistan presenting with chronic musculoskeletal pain.⁴¹ As a result, it has been suggested that testing for hypovitaminosis D should be undertaken in those with per-

sistent, nonspecific musculoskeletal pain.⁹ A suggested mechanism of this pain is that there is insufficient calcium phosphate to mineralize the expanding collagen matrix of bone resulting in a rubbery matrix that is inadequate for support, but instead hydrates and expands.⁴² This creates an outward pressure under the thoroughly innervated periosteal covering.⁴² Vitamin D repletion in vitamin D-deficient type 2 diabetic persons with neuropathic pain results in a significant reduction in pain, allowing it to be a potential analgesic.⁴³ There is evidence that vitamin D is a neurotropic substance that modulates neuronal differentiation and growth and neuromuscular function, yet its role in diabetic neuropathic pain is uncertain.⁴³ It has been hypothesized that vitamin D insufficiency may impair nociceptor function and potentiate nerve damage, resulting in pain at a threshold of serum 25(OH)D concentration higher than that in the nondiabetic population.⁴³

Autoimmune Diseases

Autoimmune diseases caused or exacerbated by vitamin D deficiency have been a topic of much discussion since the identification of vitamin D receptors in cells involved in the immune response, and because of the discovery that activated dendritic cells produce vitamin D hormone.⁴⁴ In a recent large prospective study, it was established that women who used supplemental vitamin D, mainly from multivitamins, had a 40% lower risk of multiple sclerosis than women who did not take supplementation.⁴⁵ Magnetic resonance imaging demonstrated that low vitamin D levels precede the occurrence of high lesion activity and that high vitamin D status precedes low lesion activity.⁴⁵ Disease severity of systemic lupus erythematosus has been shown to be correlated with lower vitamin D levels.⁴⁴ Whether lower vitamin D levels cause disease or are a consequence of the disease or its treatment is not clear. Deficiency could be due to many factors in these patients, such as chronic steroid use leading to altered vitamin D metabolism, renal involvement from systemic lupus erythematosus causing decreased hydroxylation of 25(OH)D, or formation of anti-vitamin D antibodies in a subset of patients with systemic lupus erythematosus.⁴⁴

Data from the Iowa Women's Health Study found that greater intake of vitamin D may be associated with a lower risk of rheumatoid arthritis in older women.⁴⁶ Supplemental vitamin D demonstrated a stronger inverse association with rheumatoid arthritis development than did dietary vitamin D.⁴⁶ Vitamin D treatment also has been shown to improve and prevent type 1 diabetes mellitus, with these effects attributed to the immunomodulatory actions of vitamin D.⁴⁷ One study found that treating children with 2000 IU/d vitamin D through the age of 1 year resulted in an 80% decreased risk of developing type 1 diabetes throughout the following 20 years.¹² Those children deficient by age 1 year had a 5-fold increase in developing type 1 diabetes.¹² Recent evidence in the pathogenesis of type 2 diabetes suggests that alterations in vitamin D status may affect insulin sensitivity, beta-cell function, or both, given the discovery

of vitamin D receptors in beta cells and the vitamin D-dependent calcium-binding proteins in pancreatic tissue.⁴⁷ Vitamin D is essential for normal insulin release in response to glucose and for maintenance of glucose tolerance, whereas deficiency results in decreased insulin secretion without altering glucagon secretion.⁴⁷ One study found that serum levels of 25(OH)D less than 20 ng/mL result in decreased beta-cell function, whereas insulin sensitivity is as much as 60% higher in persons with a 25(OH)D serum level of 30 ng/mL compared with those with levels \leq 10 ng/mL.⁴⁸

Cognitive Function

Increasing evidence supports a role for vitamin D in brain development and function, including neuroprotection by vitamin D in vitro, quantification of vitamin D receptors in the brain, and down-regulation of vitamin D receptors in hippocampal cells in Alzheimer's disease.⁴⁹ Neuroprotection may be conferred through immunomodulation, neuronal calcium regulation, antioxidative mechanisms, enhanced nerve conduction, and detoxification mechanisms.⁵⁰ In one study of older adults without functional disability, it was found that vitamin D deficiency was associated with worse performance and low mood on 2 measures of cognitive function.⁴⁹ Furthermore, a retrospective review of older adults presenting with memory problems found a positive, significant correlation between serum 25(OH)D concentration and Mini Mental Status Exam results suggesting a potential role for vitamin D in cognitive function of older adults.⁵¹ A cross-sectional study of patients with Alzheimer's disease found that those with sufficient vitamin D levels had significantly higher Mini Mental Status Exam scores than those with insufficient vitamin D levels.⁵²

Additional studies have found that depression and seasonal affective disorders have improved with vitamin D supplementation, although until recently a consistent correlation between vitamin D levels and depression had not been found.⁴⁹ In a large population-based study, it was found that both depression and depression severity are strongly associated with lower serum 25(OH)D and higher parathyroid hormone levels, although further studies are needed to determine if this is a cause or consequence of depression.⁵³

Cancer

Observations demonstrating longer survival for patients diagnosed with certain malignancies during summer months than winter months, as well as higher cancer mortality with increasing distance from the equator, have led investigators to study the association of hypovitaminosis D and cancer.^{54,55} Further studies have been undertaken and completed as a result of reports that demonstrated that 1,25(OH)₂ is antiproliferative and can promote cell differentiation, induce apoptosis, inhibit telomerase expression, and suppress tumor-induced angiogenesis.⁸

Many studies have looked at vitamin D and cancer incidence. A recent meta-analysis found that a serum 25(OH)D level greater than 33 ng/mL was associated with a 50% lower risk of colorectal cancer incidence compared with those with levels less than 12 ng/mL.⁵⁶ Garland et al⁵⁷ projected that 50% of North American colon cancer incidence could be prevented by maintaining a lifelong serum 25(OH)D level greater than 34 ng/mL, and that breast cancer incidence could be reduced by 30% with lifelong maintenance of 25(OH)D greater than 42 ng/mL. A 60% decrease in all-cancer risk was revealed in a trial of postmenopausal women receiving calcium plus 1000 IU of vitamin D daily compared with the placebo arm.⁵⁸ A further study of patients referred to coronary angiography found that low levels of 25(OH)D are associated with an increased risk of fatal cancer, suggesting that vitamin D supplementation may be promising in the prevention or treatment of cancer.⁵⁹ In the Health Professionals Follow-Up Study, it was discovered that adequate levels of vitamin D are associated with a 17% reduction in total cancer incidence, a 29% reduction in total cancer mortality, and a 43% and 45% reduction of digestive-system cancer incidence and mortality.⁶⁰ The strongest inverse relationship in this study was found between low vitamin D and risk for all oral or pharyngeal cancers, with a relative risk of 0.30.⁴⁷ In addition, it was found that adequate levels of vitamin D are associated with a reduced risk of developing leukemia.⁶⁰ These data followed a case report in which adequate vitamin D intake, without further treatment, was associated with clinical remission of chronic lymphocytic leukemia for at least 16 years.^{60,61}

Patients with colorectal cancer with a mean prediagnosis 25(OH)D level of 40 ng/mL have been found to have a considerable decrease in mortality.⁶² In recent years, it has been suggested that decreased levels of 25(OH)D contribute to melanoma progression and pathogenesis because of melanoma's responsiveness to the antiproliferative and pro-differentiation effect of 1,25(OH)₂.^{63,64} Another recent review of randomized controlled trials using supplementation with vitamin D found that although those given vitamin D were no more likely to be diagnosed with cancer than those given placebo, they were less likely to die of the cancer.⁶⁵

Heart Disease

Ecologic studies have suggested that ultraviolet light and vitamin D also might have a role in cardiovascular disease.^{66,67} In a recent cohort study, it was found that low levels of vitamin D were an independent risk factor for myocardial infarction in men.⁶⁸ More specifically, levels of 25(OH)D greater than 30 ng/mL decreased the risk of myocardial infarction by 50% in the population studied.⁶⁸ As a potential mechanism, vitamin D affects blood pressure through the reticular activating system, vascular calcification, smooth muscle cell proliferation, and inflammation.⁶⁸ Experimental and clinical data have found that vitamin D deficiency directly promotes the development of hypertension, whereas vitamin D supplementation has led to reductions in blood pressure.⁶⁹ Because of

its potent effects on vascular endothelial cells, vitamin D seems to confer cardioprotection.⁷⁰ Data from the Third National Health and Nutrition Examination Survey demonstrated a significant association between low vitamin D levels and increased cardiovascular disease risk factors, and another study suggested that moderate to severe vitamin D deficiency is a risk factor itself for developing cardiovascular disease.^{69,71} Another study found that higher serum 1,25-vitamin D levels were associated with lower amounts of vascular calcification and suggested that 1,25-vitamin D may directly inhibit vascular calcification.⁷² Further studies found that increased serum parathyroid hormone with lower vitamin D levels was independently associated with calcific aortic stenosis in patients with significant coronary artery disease without renal disease, suggesting that dysregulation of calcium metabolism might be involved in aortic stenosis pathogenesis.⁷³ In patients who are undergoing hemodialysis and have secondary hyperparathyroidism, it was found that intravenous calcitriol significantly reduced myocardial hypertrophy.⁷⁴ This might be due to the effect of calcitriol on myocardium, calcitriol affecting the renin-angiotension system, or the direct effect of parathyroid hormone on heart muscle.⁷⁴

Mortality

Whether because of the panoply of vitamin D effects or a singular effect, there seems to be sufficient evidence to conclude that vitamin D supplementation decreases total mortality.⁶⁵ In addition to the previously cited study, a recent meta-analysis of 18 randomized trials on vitamin D ascertained that individuals assigned to the vitamin D arms had a 7% reduction in mortality from any cause.⁷² Another recent study of patients referred for coronary angiography who were followed for more than 7 years found that those with baseline 25(OH) vitamin D levels in the lower 2 quartiles had higher all-cause and cardiovascular mortality than those in the higher quartiles.⁷⁵

TREATMENT CONSIDERATIONS

Ultraviolet Radiation

Although increasing sun exposure may increase vitamin D levels, for many individuals, especially those with fair skin, this can occur at the price of increased risk. Ultraviolet radiation from the sun not only causes photoaging but also is an environmental carcinogen, with acute and chronic exposure increasing the risk for skin cancer.^{8,76} At present rates in the United States, 1 in 5 people will develop a skin cancer during their lifetime.⁷⁷ There are 3 major types of skin cancer: basal cell carcinoma is the most common, followed by squamous cell carcinoma, and last, melanoma, the most fatal form.⁷⁸ Approximately 1,200,000 non-melanoma skin cancers develop each year in the US population, 80% of which are basal cell cancers.⁷⁹ Cutaneous melanoma is the most rapidly increasing cancer in white populations,

whereas the majority are caused, at least in part, by excessive exposure to sunlight.⁸⁰

Although for melanoma and basal cell carcinoma, epidemiologic and experimental evidence suggests a role for acute sun exposure, the evidence for chronic sun exposure as a causal role for squamous cell carcinoma is vast. In the latter case, areas of the body where skin cancer develops appear to be related to the amount of sun exposure received in those sites.⁸¹ Therefore, the risk for squamous cell carcinoma is related to cumulative ultraviolet exposure.⁷⁷ Although squamous cell carcinoma uncommonly causes death, it is a leading cause of mortality among transplant recipients.⁸² Occurrence on sun-exposed areas such as the face in any individual can be disfiguring.⁸³

Although melanoma is seen more frequently in men than in women and with increasing age, it is the most frequent cancer in women aged 25 to 29 years, and the second most frequent cancer in women aged 30 to 34 years.⁸³ Approximately 15% of melanomas prove to be fatal.⁸² Overall, the risk for melanoma is directly related to annual ultraviolet exposure.⁷⁷ Although as previously noted, acute sunburn at any age has been associated with an increased risk of melanoma.⁷⁸

Individuals found to be at an elevated risk for melanoma include those who are most sensitive to the sun with light skin, hair, and eye color, and those with the inclination for the skin to burn rather than tan when exposure to ultraviolet light.⁸⁴ The presence and number of acquired melanocytic nevi and freckling also increase the risk.⁸⁴ One study found that early life spent in high-sunlight southern states gave an increased risk of melanoma as adults, even in subjects who later moved to low-sunlight states.⁷ Migration studies to Australia have found similar results, showing that childhood migration may be more important in the risk for melanoma than the total number of years spent in Australia.⁸⁵ This has suggested that exposure in early life may be important in determining later risk for melanoma.⁸⁴

Ultraviolet radiation-induced photoaging is associated with wrinkles, blotchy pigmentation, freckling, laxity, a yellow hue, roughness, and telangiectasias.^{86,87} Short-term damage to the skin, the immediate response to ultraviolet rays, presents clinically as tanning, burning, blistering, or peeling.⁸² Histologically, the dermis becomes filled with an amorphous mass of deranged elastic fibers, blood vessels become dilated and tortuous, collagen fibers become disorganized, inflammatory cells are increased, and keratinocytes become irregular with loss of polarity.²⁰ It is important to note that those with darker skin types are less likely to develop skin cancer and photoaging, and they can require longer sun exposure to synthesize vitamin D than less darkly pigmented individuals.^{19,88}

Despite differences in vitamin D levels among more darkly pigmented populations, there has been no evidence that regular sunscreen use causes vitamin D insufficiency or deficiency in otherwise healthy adults.⁸ Because of their 1000-fold risk of sunlight-induced skin cancers, patients with xeroderma pigmentosum are advised to constantly pro-

tect themselves from the sun by wearing sun-protective clothing, minimizing daylight time outdoors, and continually using sunscreen.⁸⁹ A study of 8 patients with xeroderma pigmentosum participating in such measures, while continuing their normal diet, found 25(OH)D levels to remain in the low to mid-normal range.⁸⁹ A prospective study investigating the effect of SPF-17 sunscreen on vitamin D levels found no statistically significant difference in 25(OH)D levels between those in the sunscreen group versus those in the control group.⁹⁰ Although all participants were advised to avoid the sun mid-day and to wear sun-protective clothing, no individual was found to be vitamin D deficient or insufficient.

Treatment

Vitamin D₃ has been found to be 2 to 3 times more effective in increasing blood levels of 25(OH)D than the equivalent dose of vitamin D₂.¹³ Because vitamin D₃ is formed after exposure to ultraviolet radiation, some have advised against strict sun protection as a way to curtail deficiency.⁹¹ However, vitamin D deficiency can occur even in the presence of abundant sun exposure.¹³ Fifty-one percent of adults in Hawaii receiving at least 3 hours of sun daily for a minimum of 5 days per week had serum 25(OH)D levels less than 30.¹³ Furthermore, Levis et al⁹² found that 39% ambulatory adults studied living in south Florida, an area at subtropical latitude with year-round warm, sunny weather, were vitamin D deficient. In addition, a study conducted to assess 25(OH)D levels in more than 600 residents of southern Arizona, another region with high sun exposure, found that approximately 25% of the adult population were vitamin D deficient.¹⁶

Although cutaneous vitamin D production exists with ultraviolet exposure, its synthesis varies with factors other than time spent outdoors, such as level of skin pigmentation, season, latitude, body mass, cloud coverage, air pollution, age, and the amount of skin exposure.⁸⁹ Therefore, it might be overly simplistic to recommend a universal time frame for adequate vitamin D synthesis, without considering all of the above variables and negative effects of ultraviolet radiation.

Oral supplementation has been found to effectively and reliably increase circulating vitamin D to the recommended levels, suggesting that unnecessary intentional ultraviolet B exposure can be prevented (Table 2).⁹³ The American Academy of Dermatology recently released its position statement on vitamin D recommending "that an adequate amount of vitamin D should be obtained from a healthy diet that includes foods naturally rich in vitamin D, foods/beverages fortified with vitamin D, and/or vitamin D supplements; it should not be obtained from unprotected exposure to ultraviolet (UV) radiation."⁹⁴

Evidence has shown that supplementation can correct both vitamin D deficiency and insufficiency, except in those with gastrointestinal malabsorption as the cause.⁸ In the case of malabsorption, hypophosphatemic vitamin D-resistant states, or chronic renal insufficiency, patients

will likely require injectable or oral calcitriol along with oral supplements of vitamin D.³⁶ The Institute of Medicine currently recommends that all children and adults up to the age of 50 years receive 200 IU vitamin D per day, adults aged 51 to 70 years receive 400 IU vitamin D per day, and those aged more than 71 years receive 600 IU vitamin D per day.⁹⁵

Postmenopausal women, obese people, and those with fat malabsorption or other risk factors might need supplementation of at least 800 to 1000 IU vitamin D per day.^{14,96} For instance, a meta-analysis of elderly individuals and fracture prevention found that 400 IU vitamin D per day failed to manipulate fracture incidence, whereas 700 to 800 IU vitamin D per day reduced all fractures by 23% and hip fractures by 26%.⁹⁷ At currently accepted levels for sufficiency, a minimum daily intake of 2600 IU of vitamin D₃ would meet the needs of 97% of United States residents at risk for bone loss.³⁰ Supplementation with 1000 IU per day can be assumed to result in a 10 ng/mL elevation of serum 25(OH)D when given over 3 to 4 months.⁹⁸ Therefore, a healthy, normal-weight individual with a 25(OH)D level of 10 ng/mL may require 2000

Table 2 Recommended Supplementation Alternatives^{36,99-108}

| Food and Drugs | International Units Per Serving |
|--|---------------------------------|
| Cod liver oil, 1 tablespoon | 1360 |
| Mackerel, 3.5 ounces | 345 |
| Sardines, 1.75 ounces | 250 |
| Tuna fish, 3 ounces | 200 |
| Quaker Nutrition for Women Instant Oatmeal (Quaker Oats, Chicago, Ill) | 154 |
| Orange Juice-Vitamin D fortified, 8 ounces | 100 |
| Milk-Vitamin D fortified, 8 ounces | 98 |
| Margarine, fortified, 1 tablespoon | 60 |
| Nature Made Vitamin D (Nature Made, Mission Hills, Calif) | 1000 |
| Centrum Multivitamins (Wyeth, Madison, NJ) | 400-500 |
| One-A-Day Multivitamins (Bayer, Garden Grove, Calif) | 400-800 |
| VIActiv Multivitamins (McNeil Nutritionals, Ft. Washington, Penn) | 400 |
| Weil Nutritional Supplement Vitamin D (Weil Lifestyle, Phoenix, Ariz) | 1000 |
| Ergocalciferol-oral | 400-800 daily |
| Ergocalciferol-oral | 50,000 twice weekly for 5 wks |
| Ergocalciferol-IM | 500,000 1 time |
| FOSAMAX PLUS D (Merck, Whitehouse Station, NJ) | 5600 once weekly |
| Os-cal 500 + D (GlaxoSmithKline, Pittsburgh, Penn) | 200 |
| Os-cal 500 + Extra D (GlaxoSmithKline, Pittsburgh, Penn) | 400 |

Table 3 Populations Who Might Benefit from 25(OH)D Screening^{97,98}

- Older individuals with low bone mass
- Individuals at risk for falls
- Homebound elders
- Those with muscle weakness
- Pregnant women or those thinking of becoming pregnant
- Obese individuals

IU vitamin D per day to achieve a serum level of 30 ng/mL.⁹⁸ In addition, the dose of vitamin D required to repair vitamin D deficiency differs significantly from vitamin D-sufficient patients requiring only maintenance.³⁶ Unlike the previously stated dosages to maintain sufficiency, vitamin D deficiency can be treated with 50,000 IU of vitamin D₂ twice weekly for 5 weeks or a single intramuscular dose of 500,000 IU vitamin D₂.³⁶

Although serum 25(OH)D is the best indicator of vitamin D status, clinical measurement has posed some difficulty because individual results are highly laboratory dependent.⁹⁹ On the basis of between laboratory bias and assay variability, an evaluation of 25(OH)D measurement suggested that a single laboratory result could vary by as much as 20% from the real value.⁹⁹ As a result, it has been proposed that clinicians consider using 35 to 40 ng/mL as a therapeutic goal to ensure a sufficient vitamin D status.⁹⁹ Overall, it has been proposed that every individual at risk, regardless of absent physical symptoms, be screened for deficiency by obtaining a 25(OH)D measurement at least twice yearly.⁹⁹

CONCLUSIONS

Vitamin D deficiency remains an evolving, worldwide health concern contributing to a multitude of disease entities, whereas vitamin D sufficiency is proving to be essential for overall health and well-being. Although ultraviolet radiation serves as an option to assist in increasing serum vitamin D levels, less harmful and more reliable alternatives exist. Because ultraviolet radiation-induced skin cancer and photoaging are an increasing problem, we recommend vitamin D supplementation over deliberate sun exposure to ensure adequate vitamin D levels, especially in fair-skinned individuals. Mounting evidence has shown that it remains vital for physicians and health professionals to counsel their patients and ensure adequate intake to avoid the harmful effects of vitamin D deficiency.

References

1. Holick MF. Sunlight, UV-radiation, vitamin D and skin cancer: how much sunlight do we need? *Adv Exp Med Biol.* 2008;624:1-15.
2. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr.* 2008;87:1080S-1086S.
3. Oronez-Moran P, Larriba MJ, Pendas-Franco N, et al. Vitamin D and cancer: an update of in vitro and in vivo data. *Front Biosci.* 2005; 10:2723-2749.

4. Banerjee P, Chatterjee M. Antiproliferative role of vitamin D and its analogs—a brief overview. *Mol Cell Biochem.* 2003;253:247-254.
5. Lips P. Vitamin D physiology. *Prog Biophys Mol Biol.* 2006;92:4-8.
6. Holick MF. The cutaneous photosynthesis of previtamin D₃: a unique photoendocrine system. *J Invest Dermatol.* 1981;77:51-58.
7. Rapuri PB, Gallagher JC, Haynatzki G. Effect of vitamins D₂ and D₃ supplement use on serum 25OHD concentration in elderly women in summer and winter. *Calcif Tissue Int.* 2004;74:150-156.
8. Wolpowitz D, Gilchrist BA. The Vitamin D questions: how much do you need and how much should you get? *J Am Acad Dermatol.* 2006;54:301-317.
9. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc.* 2003;78:1463-1470.
10. Holick MF, Garabedian M. Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: Favus MJ, ed. *Orumer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* 6th ed. Washington DC: American Society for Bone and Mineral Research. 2006:129-137.
11. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. endoreceptor ligands. *Endocr Rev.* 2005;26:662-687.
12. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr.* 2004;80(6 Suppl):1678S-1688S.
13. Binkley N, Novotny R, Krueger D, et al. Low vitamin D status despite abundant sun exposure. *J Clin Endocrinol Metab.* 2007;92:2130-2135.
14. Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;357:266-281.
15. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc.* 2006;81:353-373.
16. Jacobs ET, Alberts DS, Foote JA, et al. Vitamin D insufficiency in southern Arizona. *Am J Clin Nutr.* 2008;87:608-613.
17. Wortsman J, Matsuo LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr.* 2000;72:690-693.
18. Obesity by the numbers. Available at: <http://www.obesityinamerica.org>. Accessed November 22, 2008.
19. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr.* 2002;76:187-192.
20. Svobodova A, Walterova D, Vostalova J. Ultraviolet light induced alteration to the skin. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2006;150:25-38.
21. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med.* 1998;338:777-783.
22. Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. *Pediatrics.* 2008;122:1142-1152.
23. Reichrath J. Vitamin D and the skin: an ancient friend, revisited. *Exp Dermatol.* 2007;16:618-625.
24. Shah D. Should routine vitamin D/calcium supplementation be advocated to prevent nutritional rickets? *Indian Pediatr.* 2008;45:219-220.
25. Writing Group on Osteoporosis for the British Menopause Society Council, Al-Azzawi F, Barlow D, Hillard T, et al. Prevention and treatment of osteoporosis in women. *Menopause Int.* 2007;13:178-181.
26. Kamel HK. Postmenopausal osteoporosis: etiology, current diagnostic strategies, and nonprescription interventions. *J Manag Care Pharm.* 2006;12(6 Suppl A):S4-S9.
27. Malavolta N, Pratelli L, Frigato M, et al. The relationship of vitamin D status to bone mineral density in an Italian population of postmenopausal women. *Osteoporos Int.* 2005;16:1691-1697.
28. Gallacher SJ, McQuillan C, Harkness M, et al. Prevalence of vitamin D inadequacy in Scottish adults with non-vertebral fragility fractures. *Cur Med Res Opin.* 2005;21:1355-1361.
29. Simonelli C, Weiss TW, Morancey J, et al. Prevalence of vitamin D inadequacy in a minimal trauma fracture population. *Curr Med Res Opin.* 2005;21:1069-1074.
30. Brown SE. Vitamin D and fracture reduction: an evaluation of the existing research. *Altern Med Rev.* 2008;13:21-33.
31. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet.* 2002;359:1929-1936.
32. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med.* 1997;337:670-676.
33. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D and calcium to prevent hip fractures in elderly women. *N Engl J Med.* 1992;327:1637-1642.
34. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr.* 2006;84:18-28.
35. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: a meta-analysis. *JAMA.* 2004;291:1999-2006.
36. Geller JL, Adams JS. Vitamin D therapy. *Curr Osteoporos Rep.* 2008;6:5-11.
37. Montero-Odasso M, Duque G. Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. *Mol Aspects Med.* 2005;26:203-219.
38. Staud R. Vitamin D: more than just affecting calcium and bone. *Curr Rheumatol Rep.* 2005;7:356-364.
39. Gallagher JC. The effects of calcitriol on falls and fractures and physical performance tests. *J Steroid Biochem Mol Biol.* 2004;89-90:497-501.
40. Prabhala A, Garg R, Dondona P. Severe myopathy associated with vitamin D deficiency in western New York. *Arch Intern Med.* 2000;160:1199-1203.
41. Roessel TR. Vitamin D deficiency in Iraq and Afghanistan veterans with chronic musculoskeletal pain. *J Occup Environ Med.* 2008;50:613-614.
42. Mascarenhas R, Morbarhan S. Hypovitaminosis D-induced pain. *Nutr Rev.* 2004;62:354-359.
43. Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. *Arch Intern Med.* 2008;168:771-772.
44. Cutolo M, Otsa K. Review: vitamin D, immunity and lupus. *Lupus.* 2008;17:6-10.
45. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology.* 2004;62:60-65.
46. Merlino LA, Curtis J, Mikuls TR, et al. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum.* 2004;50:72-77.
47. Palomer X, Gonzalez-Clemente JM, Blanco-Vaca F, Mauricio D. Role of vitamin D in the pathogenesis of type 2 diabetes mellitus. *Diabetes Obes Metab.* 2008;10:185-197.
48. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr.* 2004;79:820-825.
49. Wilkins CH, Sheline YI, Roe CM, et al. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry.* 2006;14:1032-1040.
50. Buell JS, Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing "D"ecline? *Mol Aspects Med.* 2008;29:415-422. 2008 May 13. [Epub ahead of print]
51. Przybelski RJ, Binkley NC. Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function. *Arch Biochem Biophys.* 2007;460:202-205.
52. Oudshoorn C, Mattace-Raso FU, van der Velde N, et al. Higher serum vitamin D₃ levels are associated with better cognitive test performance in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2005;25:539-543.
53. Hoogendijk WJ, Lips P, Dik MG, et al. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatry.* 2008;65:508-512.

54. Lim HS, Roychoudhuri R, Peto J, et al. Cancer survival is dependent on season of diagnosis and sunlight exposure. *Int J Cancer*. 2006;119:1530-1536.
55. Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. *Recent Results Cancer Res*. 2003;164:371-377.
56. Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. *Am J Prev Med*. 2007;32:210-216.
57. Garland CF, Grant WB, Mohr SB, et al. What is the dose-response relationship between vitamin D and cancer risk? *Nutr Rev*. 2007;65(8 Pt 2):S91-S95.
58. Lappe, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr*. 2007;85:1586-1591.
59. Pilz S, Dobnig H, Winklhofer-Roob B, et al. Low serum levels of 25-hydroxyvitamin D predict fatal cancer in patients referred to coronary angiography. *Cancer Epidemiol Biomarkers Prev*. 2008;17:1228-1233.
60. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst*. 2006;98:451-459.
61. Politzer WM. Long-term clinical remission of chronic lymphocytic leukaemia by dietary means. *South African Med J*. 2005;95:321-322.
62. Ng K, Meyerhardt JA, Wu K, et al. Circulating 25-hydroxyvitamin D levels and survival in patients with colorectal cancer. *J Clin Oncol*. 2008;26:2984-2991.
63. Nurnberg B, Schadendorf D, Gartner B, et al. Progression of malignant melanoma is associated with reduced 25-hydroxyvitamin D serum levels. *Exp Dermatol*. 2008;17:627.
64. Egan KM, Sosman JA, Blot WJ. Sunlight and reduced risk of cancer: is the real story vitamin D? *J Natl Canc Inst*. 2005;97:161-163.
65. Autier P, Gandini S. Vitamin D supplementation and total mortality. *Arch Intern Med*. 2007;167:1730-1737.
66. Zittermann A, Schleithoff SS, Koerfer R. Putting cardiovascular disease and vitamin D insufficiency into perspective. *Br J Nutr*. 2005;94:483-492.
67. Scragg R. Seasonality of cardiovascular disease mortality and the possible protective effect of ultraviolet radiation. *Int J Epidemiol*. 1981;10:337-341.
68. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men. *Arch Intern Med*. 2008;168:1174-1180.
69. Wang TJ. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117:503-511.
70. Langman CB, Brooks ER. Renal osteodystrophy in children: a systemic disease associated with cardiovascular manifestations. *Growth Horm IGF Res*. 2006;16(Suppl A):S79-S83.
71. Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2007;167:1159-1165.
72. Watson KE, Abrolat ML, Malone LL, et al. Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation*. 1997;96:1755-1760.
73. Linhartova K, Veselka J, Sterbakova G, et al. Parathyroid hormone and vitamin D levels are independently associated with calcific aortic stenosis. *Circ J*. 2008;72:245-250.
74. Kim HW, Park CW, Shin YS, et al. Calcitriol regresses cardiac hypertrophy and QT dispersion in secondary hyperparathyroidism on hemodialysis. *Nephron Clin Pract*. 2006;102:c21-29.
75. Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. *Arch Intern Med*. 2008;168:1340-1349.
76. De Gruijl FR. Skin cancer and solar UV radiation. *Eur J Cancer*. 1999;35:2003-2009.
77. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. *J Am Acad Dermatol*. 2008;58:S129-S132.
78. Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study with the Nurses' Health Study. *Int J Epidemiol*. 2006;35:1514-1521.
79. Abdulla FR, Feldman SR, Williford PM, et al. Tanning and skin cancer. *Pediatr Dermatol*. 2005;22:501-512.
80. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer- the role of sunlight. *Adv Exp Med Biol*. 2008;624:89-103.
81. Bulliard JL. Site-specific risk of cutaneous malignant melanoma and pattern of sun exposure in New Zealand. *Int J Cancer*. 2000;85:627-632.
82. Buell JF, Hanaway MJ, Thomas M, et al. Skin cancer following transplantation: the Israel Penn International Transplant Tumor Registry experience. *Transplant Proc*. 2005;37:962-963.
83. Gallagher RP. Sunscreens in melanoma and skin cancer prevention. *CMAJ*. 2005;173:244-245.
84. Gallagher RP, Lee TK. Adverse effects of ultraviolet radiation: a brief review. Vitamin D physiology. *Prog Biophys Mol Biol*. 2006;92:119-131.
85. Khat M, Vail A, Parkin M, Green A. Mortality from melanoma in migrants to Australia: variation by age at arrival and duration of stay. *Am J Epidemiol*. 1992;135:1103-1113.
86. Seite S, Fourtanier. The benefit of daily photoprotection. *J Am Acad Dermatol*. 2008;58:S160-S166.
87. Rabe JH, Mamelak AJ, McElquinn PJ, et al. Photoaging: mechanisms and repair. *J Am Acad Dermatol*. 2006;55:1-19.
88. Rouhani P, Hu S, Kirsner RS. Melanoma in Hispanic and Black Americans. *Cancer Control*. 2008;15:248-253.
89. Sollitto RB, Kraemer KH, DiGiovanna JJ. Normal vitamin D levels can be maintained despite rigorous photoprotection: six years' experience with xeroderma pigmentosum. *J Am Acad Dermatol*. 1997;37:942-947.
90. Marks R, Foley PA, Jolley D, et al. The effect of regular sunscreen use on vitamin D levels in an Australian population. Results of a randomized controlled trial. *Arch Dermatol*. 1995;131:415-421.
91. Reichrath J. Vitamin D and the skin: an ancient friend, revisited. *Exp Dermatol*. 2007;16:618-625.
92. Levis S, Gomez A, Jimenez C, et al. Vitamin d deficiency and seasonal variation in an adult South Florida population. *J Clin Endocrinol Metab*. 2005;90:1557-1562.
93. Oberszyn TM. Non-melanoma skin cancer: importance of gender, immunosuppressive status and vitamin D. *Cancer Lett*. 2008;261:127-136.
94. Position Statement on Vitamin D. Available at: <http://aad.org/>. Accessed November 22, 2008.
95. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington, DC: National Academy Press; 1999.
96. National Osteoporosis Foundation. Updated Recommendations for Calcium and Vitamin D Internet: Intake. Available at: http://www.nof.org/prevention/calcium_and_VitaminD.htm. Accessed June 11, 2008.
97. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA*. 2005 11;293:2257-2264.
98. Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. *Altern Med Rev*. 2008;13:6-20.
99. Binkley N, Krueger D. Evaluation and correction of low vitamin D status. *Curr Osteoporos Rep*. 2008;6:95-99.
100. National Institutes of Health Office of Dietary Supplements. Dietary

- Supplement Fact Sheet: Vitamin D. Available at: <http://ods.od.nih.gov/factsheets/vitamind.asp>. Accessed August 10, 2008.
101. MayoClinic.com. Vitamin D. Available at: http://www.mayoclinic.com/health/vitamin-d/NS_patient-vitamind. Accessed August 10, 2008.
 102. Merck. Fosamax Plus D. Available at: http://www.fosamax.com/alendronate_sodium/fosamax/hcp/about_plus_d/index.jsp?WT.svl=2. Accessed August 11, 2008.
 103. Oregon State University. Linus Pauling Institute Micronutrient Research for Optimum Health. <http://lpi.oregonstate.edu/infocenter/vitamins/vitaminD/>. Accessed August 11, 2008.
 104. Os-cal Products. Available at: <http://www.oscal.com/Products.aspx>. Accessed August 11, 2008.
 105. Nature Made. Available at: <http://www.lsgcal.naturemade.com/naturemade/vitamind.aspx?> Accessed August 11, 2008.
 106. Centrum: Wyeth Consumer Health Care. Available at: http://www.centrum.com/product_detail_home.aspx?productid=CENTRUM. Accessed August 12, 2008.
 107. One A Day Multivitamin. Available at: <http://www.oneaday.com/>. Accessed August 12, 2008.
 108. VIACTIVE. Available at: <http://www.viactiv.com/index.jhtml>. Accessed August 12, 2008.