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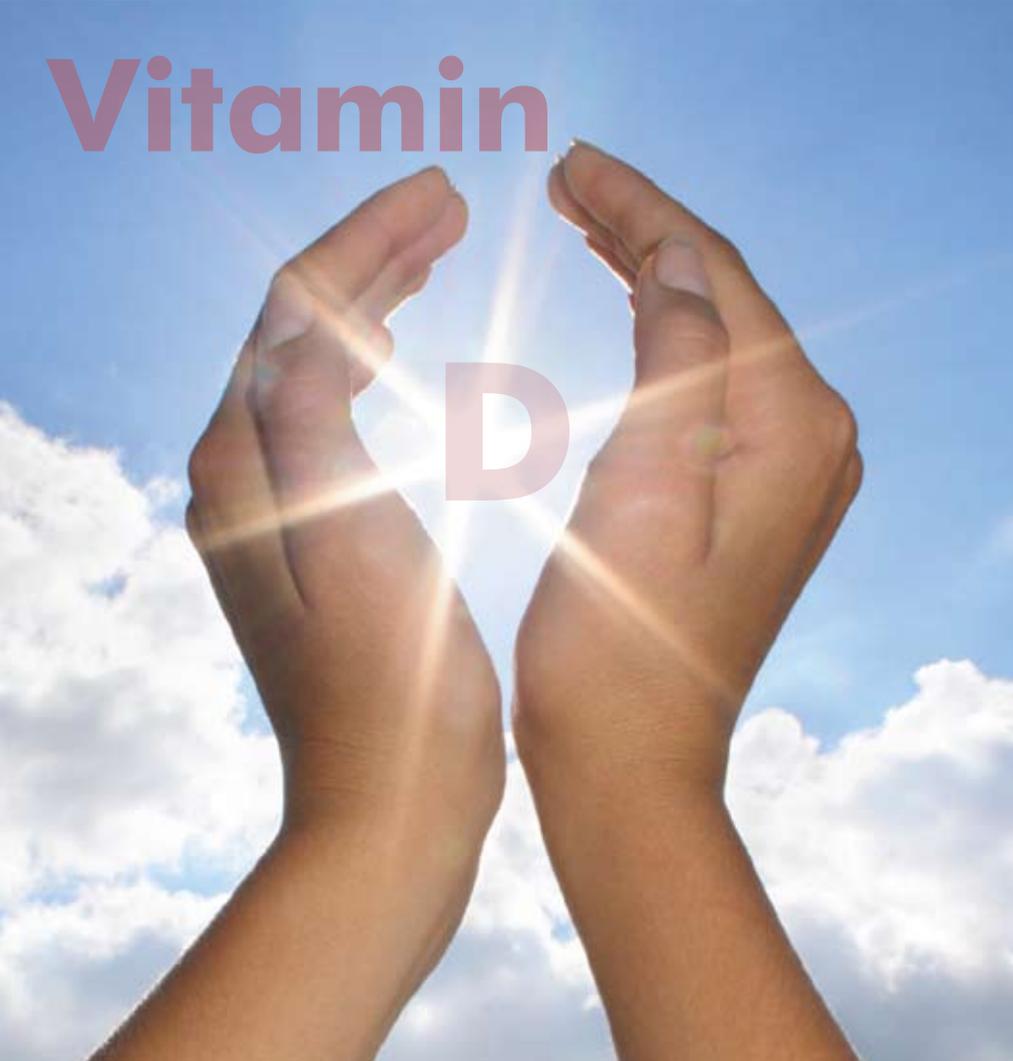
Vitamin D: Merging Research into a Clinical Lipid Practice

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Assessment and Metabolism of 25(OH)D

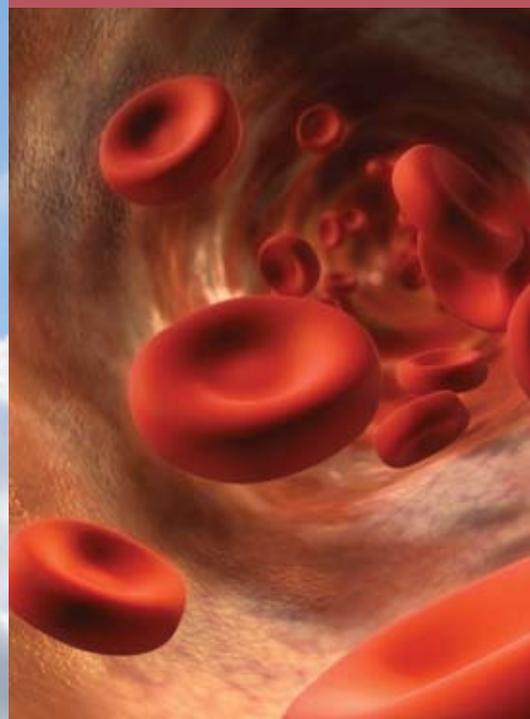
Vitamin

D



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Vitamin D: Merging Research into a Clinical Lipid Practice

Skeletal effects of low vitamin D have been recognized for a long time. However, evidence of the association between low levels of 25 hydroxyvitamin D [25(OH)D] and higher risk of cardiovascular disease is accumulating. Most recently, Giovannucci, et al., in a prospective nested case-control study involving 18, 225 men free of cardiovascular disease at baseline, followed for 10 years, showed that serum levels of 25(OH)D less than 30 ng/mL are associated with an increased risk for myocardial infarction (MI). Men with 25(OH)D of at least 30 ng/mL had approximately half the risk of MI, independent of other cardiovascular risk factors.¹ Another recently published study from the researchers with the Ludwigshafen Risk and Cardiovascular Health Study in Austria and Germany looked at vitamin D levels in 3,258 patients scheduled for coronary angiography and followed them for 7.7 years. Low Vitamin D levels were associated with a hazard ratio of 2.08 in comparison with those patients with normal levels. The hazard ratio for cardiovascular death was 2.22.² Findings published online by the American Heart Association based on National Health and Nutrition Examination Survey (NHANES) data indicated a

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strong graded association between low vitamin D levels and peripheral artery disease (PAD) with the incidence of PAD rising by 35% for each 10 ng/mL decline in serum 25(OH)D levels, even after adjusting for CVD risk factors.³ Deficiency in 25(OH)D is associated with hypertension, obesity, glucose intolerance, and metabolic syndrome.^{4,5} Vitamin D is likely to exert its effect on the risk for cardiovascular disease via vascular smooth muscle cell proliferation, inflammation, vascular calcification, the renin-angiotension system, and blood pressure.^{1,5} Vitamin D deficiency has also been linked to other non-skeletal chronic illnesses including autoimmune diseases, colon, prostate and breast cancer, polycystic ovarian syndrome (PCOS), Multiple Sclerosis and Type 1 diabetes mellitus in children.⁵

In addition to increasing risk for chronic illness, low vitamin D status adversely affects muscle performance and may contribute to perceived myalgias. Vitamin D receptors are present in human muscle tissue. Vitamin D mediated effects via alterations of intracellular calcium status are also likely to affect muscle function.⁶ Vitamin D deficiency has been associated with proximal muscle weakness, loss of muscle mass, and increased risk of falling.^{6,7} One study showed that 93% of persons 10–65 years of age who were admitted to a hospital emergency room with muscle aches and bone pain were deficient in vitamin D.⁵ Muscle weakness, myalgias and arthritic symptoms in patients with vitamin D deficiency or

insufficiency can pose a challenge when treating patients with statins and other lipid medications that affect muscle myocytes.

Assessment and Metabolism of Vitamin D

The major sources of vitamin D for humans are from exposure to sunlight, diet, and dietary supplements. Solar ultraviolet B (UVB) radiation penetrates the skin and converts vitamin D precursors to Vitamin D3. Vitamin D from the skin and diet is metabolized in the liver to 25(OH)D. Circulating serum 25(OH)D is the best functional measure of vitamin D status.^{5,6} An adaptive hormone, 1,25-dihydroxy-vitamin D, goes up and down with calcium intake. Furthermore, as 25(OH)D is a weak steroid, when 25(OH)D levels are low, the body compensates by increasing the amount of the potent steroid 1,25-dihydroxy-vitamin D. Thus, a common cause of high 1,25-dihydroxy-vitamin D is low 25(OH)D or vitamin D deficiency. Therefore, 25(OH)D is the most accurate test to assess for deficiency.

Serum 25(OH)D concentrations vary by season and one measurement may not adequately reflect a person's vitamin D status over the course of a year.¹² Providers should consider using information on predictors of vitamin D deficiency such as skin exposure, skin pigmentation, and age, in addition to estimates of vitamin D intake when making decisions about repeated screening.¹²

vitamin D.⁵ Anticonvulsants, glucocorticoids, cimetidine, antituberculosis agents, HAART (highly active antiretroviral therapy) may lower 25(OH)D levels by either preventing vitamin D absorption or accelerating the catabolism through p450 interactions. Thiazide diuretics and some statins have been found to increase 25(OH)D levels.^{5,15} The

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

(reprinted with permission from Thorne Research)⁸

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

Definition, Causes and Prevalence of Vitamin D

Deficiency

Most experts agree that a 25(OH)D serum level less than 20 ng/mL indicates deficiency and 21–29 ng/mL is considered insufficiency.^{5,7} The optimal range of serum 25(OH)D level is still the subject of debate but is assumed to be 32–50 ng/mL or higher.⁸ Grant and Holick have summarized in Table 1 the consensus of scientific understanding related to serum 25(OH)D levels.

According to these consensus definitions, vitamin D deficiency is now recognized as a pandemic.⁷ It is estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.⁵ Of the many causes of vitamin D deficiency, reduced skin synthesis is one of the major contributors. Season, latitude and time of day significantly affect D3 synthesis with little or no D3 produced from November to February in those residing above about 35 degrees north latitude. Sunscreen SPF 8 reduces D3 synthesis by 92.5% and SPF 15 by 99%.⁵ Darker skin pigmentation requires 3–6 times as much sunlight exposure to attain the same concentration of D3 as lighter skin.¹¹ The deficiency from photoproduction declines with aging. Decreased bioavailability of D3 occurs in obesity with sequestration of D3 in body fat. Reduction of fat absorption in diseases such as cystic fibrosis, Crohn's disease, and with medications that reduce cholesterol absorption, bile sequestrants as well as orlistat can impair the body's ability to absorb

recent report that atorvastatin therapy for 12 months significantly increased 25(OH)D levels in patients with acute ischemic heart disease suggests that some of the anti-inflammatory pleiotropic effects of statins may be mediated through increases in vitamin D levels.^{15,16}

Repletion of Vitamin D

The current recommended daily allowance (RDA) for vitamin D in the United States is 200 IU/day for children and adults up to age 50 years, 400 IU/day for age 51–70 and 600 IU/day over age 70. Emerging research on the non-skeletal benefits of vitamin D has made these guidelines obsolete and extraordinarily low compared with endogenous production during sun exposure. Recent well-controlled studies offer some provisional information on how much vitamin D is required to maintain or improve vitamin D status.⁹ Various studies have shown that the greatest physiologic effects have occurred in daily doses of 2000 IU or higher.^{10,11} Doses between 1000–2000 IU daily for adults are likely needed in the absence of solar exposure to maintain levels of 30–50 ng/mL 25(OH)D.^{8,9,10} Holick's, et al., data showed that serum levels of 25(OH)D increased by 1 ng/mL for every 100 IU vitamin D3.¹⁵ Cannel, et al., found that 1000 IU/day of vitamin D3 (cholecalciferol) will usually result in about a 10 ng/mL elevation of 25(OH)D when given

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over 3–4 months.¹⁵ As an example, a patient with an initial level of 10 ng/mL would generally require 3000 IU/day for several months to achieve a level of 40 ng/mL.¹⁵ Steady state is reached in approximately 90 days.^{9,14}

Vitamin D3 (cholecalciferol) is the form photosynthesized in mammals. Skin exposure without sunscreen can provide adequate amounts of vitamin D3. Vitamin D does not naturally exist in significant amounts in the human food chain. Oily fish contain about 100–500 IU/serving. Milk is fortified with 400 IU/quart (refer to Table 2). It is very difficult to consume adequate vitamin D from the diet unless consuming oily fish very frequently; albacore tuna and sockeye salmon have the greatest amounts. Fish oil capsules and cod liver oil do not provide adequate amounts of Vitamin D.

Vitamin D2 (ergocalciferol), the plant-based form, is added to certain foods and multiple vitamins and is the only form available by prescription in the United States. Only 20–40% of vitamin D2 is metabolized into the active form of 1,25diOHD. Toxicity and overdose have been related to vitamin D2 intake but not D3 intake.¹¹ Doses of more than 50,000 IU daily of Vitamin D2 raise levels of 25(OH)D to more than 150 ng/mL and were associated with hypercalcemia and hyperphosphatemia.⁵ Doses of up to 10,000 IU vitamin D3 daily for 5 months do not cause toxicity.⁵ Symptoms of hypersensitivity and toxicity are similar and include anorexia, weakness, nervousness, pruritus, nausea, polyuria and polydipsia.¹¹

Recently Holick, et al., demonstrated vitamin D2 was as effective as D3 in sustaining both (25OH)D and 1,25(OH)D and improving bone health and suggested that more than 1000 IU vitamin D2 or D3 is necessary to maintain 25(OH)D levels above 30ng/mL when sun exposure is inadequate.¹³

Table 2. Source of Vitamin D and a Comparison of Advantages and Disadvantages (reprinted with permission from Thorne Research)⁸

Source	Amount Obtained	Advantages	Disadvantages
Fish, fatty, cold ocean	100–500 IU/serving		Fish stocks are being depleted, fish contain mercury
Milk	400 IU/quart		Milk associated with increased risk of hip fracture and other diseases such as prostate cancer and acne vulgaris
Orange Juice	400 IU/quart	Source of vitamin C; can reduce HDL-LDL ratio	
Bread	In process of being developed	Whole grain cereals reduce the risk of chronic disease	
Solar UVB	0 (winter in north) to 10,000 IU per day	The natural way, maintains 25(OH)D longer compared to ingested vitamin D	Not always available, risk of melanoma, skin cancer, especially with intermittent exposure and sunburn
Artificial UVB	10-minute tanning session yields 2000 to 4000 IU	Generally available	Lamps may be high in UVA, a likely risk factor for melanoma
Supplements	200–1000 IU per day	Convenient, inexpensive	May contain vitamin A (retinol), which in high amounts may increase risk of hip fracture and birth defects

Application in a Clinical Lipid Practice

In our lipid clinic, located at a northern latitude above 35 degrees with inadequate sun exposure throughout the winter months, we obtain serum 25(OH)D on all patients with any complaints of generalized myalgias, joint pain, weakness or fatigue during any time of year. We use this as part of our workup of secondary causes of myalgias. With new data showing the association of vitamin D deficiency with increased cardiovascular risk, we are including it as part of our initial assessment of our high risk cardiovascular patients. We have frequently seen vitamin D levels in the deficient and insufficient ranges since we started regular screening.

The standard recommendation for treatment of vitamin D deficiency is 50,000 IU of vitamin D2 (ergocalciferol) once weekly for 8 weeks and repeat for another 8 weeks if 25(OH)D <30ng/mL.⁵ We have utilized this recommendation to treat with prescription D2 but found that levels of 25(OH)D increased very slowly and many times needed renewal

We are finding improved 25(OH)D levels with vitamin D3 supplements within 8 weeks. Once levels of 32–50 ng/mL of 25(OH)D are achieved, 1000-2000 IU daily of vitamin D3 is usually needed for maintenance in the absence of sun exposure or inability to maintain adequate 25(OH)D levels.

for another 6–8 weeks. As an alternative, we have managed patients with vitamin D deficiency with over-the-counter vitamin D3 (cholecalciferol) 5,000 IU daily for 8 weeks and continue an additional 8 weeks if levels do not rise above 30 ng/mL. We are finding improved 25(OH)D levels with vitamin D3 supplements within 8 weeks. Once levels of 32–50 ng/mL of 25(OH)D are achieved, 1000-2000 IU daily of vitamin D3 is usually needed for maintenance in the absence of sun exposure or inability to maintain adequate 25(OH)D levels. Doses are adjusted based on serum 25(OH)D levels for patients who are overweight, obese or darker in pigmentation who may need increase in D3 dose. Our goal is to maintain levels of 25(OH)D between 35–90 ng/mL. For patients with past history of vitamin D deficiency/insufficiency, we plan to assess at least once yearly during winter months. Generally, we find many patients have significant improvement in symptoms, including reduction in myalgias, muscle fatigue and cramping as well reduction in generalized fatigue.

Case Study

SH, a 57-year-old man presented to our lipid clinic with history of “abnormal cholesterol” and an interest in obtaining a second opinion regarding the need for lipid-lowering therapy. His major risk factor included age over 55. There is a family history of hyperlipidemia, but no premature cardiovascular disease. He also reports a family history of statin intolerance and a personal history of muscle aches and fatigue and has concerns about starting a statin due to potential muscle side effects. An initial evaluation in April 2008 revealed body weight 169.5 pounds, height: 65 inches. Initial labs from this primary care physician’s office included total cholesterol 246, triglycerides 96, LDL-C 174, and HDL-C 53. He made positive changes in his



diet and a subsequent evaluation 3 weeks later with NMR lipoprofile revealed LDL particle concentration of 1508 nmol/L, small LDL p 896 nmol/L, LDL particle size 21.1nm (Pattern A), LDL-C 149, HDL-C 54, triglycerides 102, and total cholesterol 223. He was noted to have severe Vitamin D deficiency [25(OH)Vitamin D was 16 ng/mL]. He was started on 5000 IU units vitamin D3 over the counter. Two months later (June 2008), he reported substantial improvement in fatigue and muscle aching and follow up 25(OH)D testing revealed his serum level to be 47 ng/mL. He also had an intentional 12 pound weight loss in this time frame due to dietary changes and a walking program. A follow up

lipid panel at the same time revealed LDL-C 138, HDL-C 57, triglycerides 88, total cholesterol 213, LDL Particle 1322 nmol/L, small LDL p 815nmol/L. He was also noted to have high LpPLA2 244 (optimal <200) and a carotid intimal media thickness (CIMT) scan revealed evidence of small plaque. He was started on low-dose statin and to date has had no issues of tolerance.

We suggest patients and colleagues utilize Web resources such as the National Institute of Health Office of Dietary Supplements (ods.od.nih.gov/factsheets/vitamind.asp) to keep current with vitamin D research. We also recommend www.vitamindcouncil.org. The AMA's Council on Science and Public Health is writing a report on vitamin D that is due to be released at the AMA's June 2009 annual meeting. The Endocrine Society is creating a clinical practice guideline on vitamin D deficiency and approach to treatment that is expected to be released by the end of 2008.

Vitamin D deficiency is an important parameter to assess in patients with risk for cardiovascular disease. Future research will be needed to determine whether supplementation with Vitamin D will have a beneficial effect on reducing morbidity and mortality. Regardless of direct cardiovascular benefit, treatment of Vitamin D deficiency may lead to improvement in myalgias and other symptomatology that may allow for improved tolerance of proven therapies such as lipid-lowering agents.

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