Vitamin D

Applications in autoimmunity and infectious disease.

By Heidi Fritz, ND

INTRODUCTION

Vitamin D3, also known as cholecalciferol or "the sunshine vitamin," is a pre-hormone with an array of physiological activities within the body upon conversion to its active form. Vitamin D is well known for its role within the skeletal system with respect to calcium absorption and deposition. However, a recent review of clinical trials also identified evidence supporting a potential role for vitamin D in immune regulation, mood stabilization, cancer prevention, psoriasis, type II diabetes, and cardiovascular disease. This paper reviews the application of vitamin D in autoimmunity and infectious disease, and summarizes the current evidence around target blood levels. Subsequent articles to follow will cover additional non-classical clinical applications.

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Heidi Fritz, ND, MA (CAND)
Research Associate
Canadian College of Naturopathic Medicine
Bronte Naturopathic Clinic

1255 Sheppard Avenue East
Toronto, Ontario, Canada M2K 1E2
905-876-3047 ext 204
hfritz@ccnm.edu

PHYSIOLOGY

Vitamin D undergoes a series of metabolic conversions within the body. In addition, because there is more than one form of the pre-hormone (ergocalciferol or D2, and cholecalciferol or D3), nomenclature around "vitamin D" can be confusing. Cholecalciferol is the naturally occurring form in humans, and is synthesized by UVB light in the skin (Hughes 2009). It is commonly measured in micrograms or international units (IU); 1mcg is equivalent to 40 IU. Calcidiol [25(OH)D3] is made from cholecalciferol in the liver, and is the accepted serological marker of vitamin D status (Cannell 2006). Canadian units of measure for circulating 25(OH)D are nmol/L; 1nmol/L is equivalent to 0.40ng/L (Hoogendijk 2008). Calcitriol or 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] is the biologically active form of vitamin D3, a hormone, that is converted from the intermediate calcidiol in the kidney by 1α-hydroxylase (Cutolo 2008).

Serum 25(OH)D concentrations >25nmol/L (>10ng/ml) have traditionally been considered adequate, since this is the level required to prevent rickets; there is a growing consensus, however, that levels >75nmol/L (>30ng/ml) may be more appropriate given the range of vitamin D's extraskeletal benefits (Hughes 2009).

Vitamin D activity is mediated by the vitamin D receptor (VDR), which has been identified in many tissues throughout the body, including skin, cells of the immune system, vascular endothelial cells and cardiomyocytes, and neurons in the eye and brain, especially the substatia nigra and hypothalamus (Berk 2007, Cutolo 2008, Jorde 2008, Kulie 2009). The discovery that some of these peripheral tissues can also convert vitamin D to its active form, 1,25(OH)2D3 has led to an explosion in vitamin D research and interest in its range of potential applications.

IMMUNE MODULATION

Circulating 25(OH)D levels have been inversely associated with a host of autoimmune conditions, including multiple sclerosis (MS), type I diabetes (DM I), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) (Adorini 2008). Epidemiological evidence shows a strong increase in MS prevalence with higher latitudes, and increased adult incidence associated with spring births (Grant 2006). Kulie et al report that in one study, for every 10nmol/L increase in 25(OH)D levels, the risk of MS was reduced by 19%, suggesting a protective effect of higher vitamin D levels (2009).

Hyppönen et al found similar protective effects in type I diabetes (2001). Vitamin D supplementation during the first year of life was associated with an 88% decreased risk of type I diabetes, rate ratio RR 0.12 (95% Cl 0.03-0.51) for regular supplementation versus no supplementation. Conversely, children suspected of having rickets during the first year of life had three times the risk RR 3.0 (1.0-9.0), compared with those without such a suspicion.

The mechanism for vitamin D's effect in these immune mediated conditions is through the vitamin D receptor (VDR), which has been identified in many cells of the immune system including macrophages, dendritic cells, T cells, and B cells. 1,25(OH)2D3 enhances innate immunity by upregulating expression of antibacterial proteins such as cathelicidin, β-defensin, and receptors such as Toll-like receptor 2 and CD14 following injury, as well as enhancing phagocytosis by macrophages (Adorini 2008, Cutolo 2008, Yamshchikov 2009).

With respect to adaptive immunity, vitamin D promotes tolerance by inducing tolerogenic properties in dendretic cells; inducing and enhancing regulatory T cells over effector T cells; and inhibiting B cell proliferation and antibody production (Adorini 2008). Vitamin D shifts the immune response toward Th2 by inhibiting Th1 cytokines such as interleukin-1 (IL-1) and interferon-γ (IFN-γ), while enhancing Th2 cytokines such as IL-5 and IL-10; this shift is potentially therapeutic in a host of autoimmune conditions (Adorini 2008, Cutolo 2008).

Controlled trials have shown positive results for vitamin D in atopy, diabetes mellitus I (DM I), fibromyalgia, and multiple sclerosis (MS) (See Table 1). Uncontrolled trials have found positive results in scleroderma and IgA nephropathy. A controlled trial also found that vitamin D supplementation reduced the need for cyclosporine immunosuppressive therapy in organ transplant patients by 28 and 29% compared to controls at one and two years, respectively (Briffa 2003). Obviously such results are preliminary and ought to be interpreted with caution, however they attest to the powerful ability of vitamin D to modulate immune function, particularly the adaptive immune system.

There have been preliminary findings of anti-vitamin D antibodies in a small subset of subjects with SLE (4%), antiphospholipid syndrome (APL) (3.5%), and pemphigus vulgaris (11%) (Carvalho 2007). This was not associated with any difference in extent of disease or serum 25(OH)D levels. The clinical implications of this are not yet known.

INFECTIOUS DISEASE

A 2009 systematic review of vitamin D for infectious disease summarizes 13 controlled trials of vitamin D for the treatment or prevention of bacterial, viral, and other infections (Yamshchikov 2009). Two of four trials identified showed positive results for viral upper respiratory tract infections (URTI).

Table 1. Trials for Modulation of Autoimmunity

Condition	Trials (+/total)	Dose	Outcomes	Source
Atopy	2/2	4,000 IU D3 x 21 days 1,000 IU D2 x 1 month	Atopic dermatitis: ↑ broad spectrum antimicrobial peptide cathelicidin, which may help prevent infection secondary to dermatitis. Winter related dermatitis: ↓ IGA score in four subjects (80%) of vitD group versus 1(17%) of placebo group (P=0.04).	Hata 2008, Sidbury 2008
Diabetes mellitus I	1/1	Calcitriol 0.25µg/d q2d or nicotinamide 25mg/kg/d x 1 year	Although there was no significant difference in baseline/ stimulated C-peptide or HbA1C, the insulin dose at three and six months was significantly ↓ in the calcitriol group. Since this was not seen at 12 months, it may be a transient effect.	Pitocco 2006
Fibromyalgia	1/1	50,000 IU D3/week x 8 weeks	Although most musculoskeletal symptoms did not change, the treatment group but not the placebo group showed significant improvement in the overall fibromyalgia assessment scores (P=0.03). Patients with mild to moderate baseline 25(OH)D deficiency (10-25ng/ml) showed improvement while severely deficient patients (<10ng/ml) did not.	Arvold 2009
IgA Nephropathy	1/1	1.0µg/d Calcitriol x 12 weeks	Uncontrolled trial found a significant ↓ in proteinuria (P=0.03) and progressive ↓ in protein-creatinine ratio versus baseline; no adverse effects on renal function or blood pressure.	Szeto 2008
Multiple sclerosis	2/3	5,000 IU D3 in 20g cod liver oil + calcium/ magnesium x 1-2 years 1,000 IU D3 x 6 months 2.5µg/d Calcitriol x 48 weeks	The number of exacerbations during the study period was < 50% of that expected based on patients' history at baseline. No adverse effects. ↑ TGF-β1 after six months compared to baseline in the treatment group but not placebo. (TGF-β1 is produced by Treg cells.) An uncontrolled pilot study found an on-study exacerbation rate of 27% less than baseline.	Goldberg 1986, Mahon 2003, Wingerchuk 2005
Scleroderma	1/2	0.75µg/d Calcitriol x 6 months + 1.25µg/d Calcitriol x 3 months 1.75µg/d Calcitriol x 6 months-1 year	One study showed no significant changes in skin score, or serum markers of collagen synthesis or degradation, or lung function. A second uncontrolled study found significant clinical improvement compared to baseline. No adverse effects.	Hulshof 2000, Humbert 1993
Organ Transplant	2/2	0.5µg/d Calcitriol in donor x 6 days pre-op Then continued in recipient x 6 months post-op 0.5-1.0µg/d Calcitriol x 1-2 years	The first study found significant expansion of CD(+) CD25(+) regulatory T cells in the treated group verus control. The second study found decreased requirements for immunosuppressive therapy (cyclosporine) by 28% and 29% at one and two years respectively, compared to controls. No changes in rates of rejection were seen in either study.	Ardalan 2007, Briffa 2003

Key: IGA Investigator's Global Assessment scale; TGF-β1 transforming growth factor beta-1; Treg cells regulatory T cells. *Note: Trials included are controlled unless otherwise stated. **Note: D3 refers to cholecalciferol as differentiated from calcitriol; D2 refers to ergocalciferol.

Three of four trials identified showed positive results for tuberculosis (TB, bacterial lung infection). Dosing schedules were highly variable, ranging from the equivalent of >8,000 to 800 IU per day over variable periods of time. Results of the trials for viral URTI showed decreased recurrence of infections in children who had experienced ≥6 respiratory or antibiotic requiring illnesses over the past six months (Rehman 1994), and decreased incidence of URTI symptoms in healthy adult women, which also coincided with increases in serum 25(OH)D (Aloia 2007). A third trial that found no significant effects overall did however find a statistical trend in favour of vitamin D with respect to all outcomes: frequency, severity, and duration of symptoms of URTI (Li-Ng 2009). Of note, in the trial by Aloia et al, of two doses of vitamin D used both significantly decreased symptoms of URTI compared to placebo (P<0.002), however the high dose group (2,000 IU/d) had even fewer reported symptoms than the low dose group (800 IU/d), suggesting that additional benefit can be derived from a higher dose (2007). A fourth trial showing no effect used a low dose, 800 IU/d (Avenell 2007).

Yamshchikov et al describe four trials for the treatment or prevention of tuberculosis (2009). Three of these reported positive results including 23% greater rate of sputum conversion (100% of treatment group vs 76.7% of placebo, P=0.002) and 22.5% greater rate of radiographic improvement (Nursyam 2006); 16% higher rate of TB symptom resolution and better weight gain in children with TB (Morcos 1998).

Yamshchikov et al also report positive outcome for trials of vitamin D for H. pylori infection and schistosomaisis (2009). Trials of vitamin D coinjection at vaccination sites of influenza vaccines showed no significant differences in hemagglutination inhibition titres against H1N1, N3N2, or influenza B antigens at one to three months compared to placebo (Kriesel 1999).

TARGET SERUM LEVELS

The scientific community is increasingly recognizing the need for higher doses than those currently recommended in order to raise serum 25(OH)D levels within the range associated with extraskeletal benefits. As stated above, many consider >75nmol/L (>30ng/ml) to be an appropriate level (Hughes 2009). Recently, a panel of 16 scientists and physicians issued a call to action urging an increase in the recommended intake of vitamin D to 2,000 IU per day, and raising the minimum serum levels to 100-150nmol/L (40 to 60ng/ml) (Garland 2009). Both these suggested serum levels are considerably higher than those traditionally used to define adequacy.

The dose of vitamin D required by some may be still higher, depending on the individual's baseline status and factors such as latitude, lifestyle, and skin pigmentation. Aloia et al investigated the dose of vitamin D3 required to raise serum 25(OH)D3 levels >75nmol/L in both black and white healthy subjects residing in New York (2008). A dose of 3,800 IU (95µg) per day was the estimated requirement to attain this blood level in those with 25(OH)D >55nmol/L at baseline, while 5,000 IU (125µg) was the requirement for those <55nmol/L. No hypercalcemia or hypercalciuria attributable to the intervention were observed.

Factors that increase risk of deficiency include skin pigmentation, area of residence and UVB exposure, increasing age, obesity (causes increased sequestration), medications that increase breakdown (glucocorticoids, anticonvulsants, highly active antiretroviral medications, some immunosuppressants), medications that decrease conversion to the active form (hydroxychloroquine), chronic kidney disease (decreased synthesis), and conditions with impaired nutrient (cholesterol) absorption (Cuotolo 2009, Kulie 2009).

SAFETY

The primary safety concern with vitamin D supplementation is hypercalcemia. This was either unobserved or very infrequently observed in the trials reviewed here. Vieth reports in a review of vitamin D safety that "Except in those with conditions causing hypersensitivity, there is no evidence of adverse effects with serum 25(OH)D concentrations <140nmol/L, which require a total vitamin D supply of 250mg (10,000 IU)/d to attain" (1999). Vieth found that "Hypercalcemia due to vitamin D intoxication per se is always accompanied by serum 25(OH)D concentrations >220nmol/L" (1999).

Vitamin D hypersensitivity and consequent hypercalcemia are associated with certain conditions. Of these, primary hyperparathyroidism is the most common.

In granulomatous disease (sarcoidosis, tuberculosis) and certain cancers (small cell lung cancer, non-Hodgkin's lymphoma), the diseased tissue converts 25(OH)D into activated 1,25(OH)2D3 at higher rates than normal, resulting in very high 1,25(OH)2D3 levels and hypercalcemia. These patients should not take vitamin D except under the care of a physician, and should have serum 25(OH)D, calcitriol and calcium checked routinely (Vieth 1999).

CONCLUSION

Vitamin D3 is a pre-hormone to calcitriol in the human body, where it powerfully regulates immune tolerance and resistance to infection. Current evidence supports target serum 25(OH)D levels ≥75nmol/L, and a prominent body of experts has even recommended upwards of 100nmol/L for the population at large. Vitamin D3 supplementation is generally safe, with reports of hypercalcemia only in certain subsets of patients or at 25(OH)D levels >220nmol/L.

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