Vitamin D Part II

Depression and cardiovascular disease.

By Heidi Fritz, ND

INTRODUCTION

This article is the second in a series of reviews of the non-classical applications of vitamin D. Briefly, vitamin D3 is also known as cholecalciferol in the pre-hormone state, or as calcitriol (1,25-dihydroxyvitamin D3 [1,25(OH)2D3]) in its activated form. See Part I for more on nomenclature, physiology, and implications for immune function. This part reviews the clinical applications of vitamin D for depression, diabetes, and cardiovascular disease.

CLINICAL APPLICATIONS: DEPRESSION

Observational evidence has repeatedly demonstrated an inverse association between vitamin D levels and depression. Wilkins et al. (2006) found that after adjusting for age, race, gender, and season of vitamin D determination, vitamin D deficiency defined as <20ng/ml was strongly associated with presence of an active mood disorder (odds ratio 11.69; 95% confidence interval, 2.04-66.86; P=0.022). A more recent analysis found that 25(OH)D levels were 14% lower in subjects with both minor depression and Major Depressive Disorder (MDD) compared to healthy controls (P<0.001 for both), in a population with an average 25(OH)D level 21 ng/ml, well within the traditionally accepted normal range; depression severity was also significantly associated with decreased serum 25(OH)D levels (P=0.03) (Hoogendijk 2008). A cross-sectional analysis by Jorde et al. (2008) found that subjects with 25(OH)D ≥40nmol/L scored significantly higher on the Beck Depression Inventory (BDI) compared to those <40, supporting a role for vitamin D insufficiency in the etiology of depression in certain subjects.

Vitamin D has been hypothesized to act by 1) increasing serotonin in the brain, 2) protecting the brain against neurotoxins, and 3) downregulating glucocorticoid receptors in the brain (Shipowick 2009). Other studies show that neurons inputting on the pineal gland (site of melatonin synthesis) are probably affected by vitamin D, since they are immunoreactive to a vitamin D dependent calcium binding protein (Lansdowne 1998).

Five trials exist for vitamin D and depression and/ or seasonal affective disorder (SAD); of these, four show significant positive effects (Shipowick 2009, Jorde 2008, Dumbille 2006, Gloth 1999, Lansdowne 1998). Three trials showed benefit for symptoms of depression associated with winter (SAD), and one showed benefit for depression in overweight or obese subjects. Dosing schedules used varied considerably. These are summarized in Table 1.

DIABETES AND CARDIOVASCULAR DISEASE

Observational evidence has established an association between low vitamin D status, occurrence of cardiovascular events, cardiometabolic disorders, hypertension, and mortality (Forman 2007, Dobnig 2008, Melamed 2008). Parker et al. (2010) found a 43% reduced risk of cardiometabolic disorders among those with the highest levels of 25(OH)D.

A prospective cohort study including 3,258 subjects with symptoms of myocardial ischemia found that patients in the lower two quartiles of 25(OH)D (median, 7.6 and 13.3ng/ml, respectively) were at higher risk of death from any cause (all-cause mortality) (HR 2.08, 95% CI 1.60-2.70; and HR 1.53, 95% CI 1.17-2.01, respectively), and at higher risk of death related to cardiovascular causes (HR 2.22, 95% CI 1.57-3.13; and HR 1.82, 95% CI, 1.29- 2.58, respectively) compared with patients in the highest quartile (median,

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Table 1. Trials of Vitamin D for Depression

Description	Dose	Outcomes	Reference
Prospective trial: 9 women with 25(OH)D <40ng/ml were given vitamin D	5,000 IU/d x 8 weeks with initial assessment in January - March	There was an average 27 ng/mL increase in 25(OH)D. Three subjects achieved concentrations >40, and in these three subjects, the BDI-II score after 8 weeks decreased to normal (<14) or within a point of normal (14). Overall, there was an average decrease in 10 points on the BDI.	Shipowick 2009
RCT: 441 overweight or obese subjects (BMI>28) were randomized to one of two doses of vitamin D or placebo.	20,000 or 40,000 IU vitamin D3/wk x 1 year	In the vitamin D groups, but not in the placebo group, there was a significant improvement in Beck Depression Inventory-II scores after 1 year compared to baseline (P<0.05), and this was accompanied by a doubling in 25(OH)D levels in the high dose treatment group.	Jorde 2008
RCT: 2,117 women ≥70 years were randomized to receive vitamin D or placebo.	800 IU vitamin D3/d + calcium (1,000mg)	Using the mental component score (MCS) of the SF-36 questionnaire as assessed during the late fall/winter, there was no significant change in the treatment group.	Dumbille 2006
RCT: 15 subjects with seasonal affective disorder (SAD) were randomized to vitamin D or phototherapy.	100,000 IU vitamin D3 (schedule not specified)	All patients receiving vitamin D improved on the Hamilton Depression scale, the SIGH-SAD, and the SAD-8 depression scale, while there was no change in the phototherapy group. Vitamin D status improved in both groups, though more so in the vitamin D group (74% vitamin D group, P<0.005 and 36% phototherapy group, P<0.01). Improvement in 25-OH D was significantly associated with improvement in depression scale scores (R2=0.26; P=0.05).	Gloth 1999 [Abst]
RCT: 44 healthy subjects were given one of two doses of vitamin D and vitamin A, or vitamin A only (control).	400 IU VitD + 9,000 IU VitA OR 800 IU VitD x 5 days in late winter	Vitamin D3 significantly enhanced positive affect (P<0.001 between groups), and there was a non-significant reduction in negative affect with treatment using the Positive and Negative Affect Schedule (PANAS).	Lansdowne 1998

28.4ng/ml) (Dobnig 2008). Similar results with respect to all-cause mortality have also been found in the general population (Melamed 2008). Scragg (2010) found significant associations between low serum 25(OH)D levels and increased heart rate, systolic blood pressure, and rate-pressure product, suggesting that low vitamin D status may increase cardiac work.

Although critics have pointed out that vitamin D may be a biomarker of physical activity and exposure to sunlight, the existence of mixed beneficial findings in intervention trials seems to suggest that vitamin D may be one of many causal factors contributing to these conditions. For instance, vitamin D is known to suppress renin production and regulate the renin-angiotensin system (RAS) via effects on the juxtaglomerular apparatus; endothelial cells are also vitamin D responsive (Ullah 2010, Witham 2009). A recent systematic review of vitamin D and cardiovascular outcomes from Harvard highlights "consistent reductions in cardiovascular disease (CVD) mortality among adults who received vitamin D supplements" (Wang 2010).

Results of RCTs have found benefits for supplementation with vitamin D in congestive heart failure (CHF), endothelial function, hypertension, type 2 diabetes and/ or glucose metabolism, and polycystic ovary syndrome, the last of which is often characterized by insulin resistance and so is included here.

A 2009 systematic review found that vitamin D supplementation non-significantly reduced systolic blood pressure (-3.6mmHg, 95% CI -8.0 to 0.7) and significantly reduced diastolic blood pressure (-3.1mmHg, 95% CI -5.5 to -0.6) compared to placebo (Witham 2009). This effect was only seen in patients who were hypertensive at baseline; no effect was seen in normotensive patients. Unactivated forms of vitamin D (D2, D3) were more effective than activated (calcitriol, 1-alpha calcidiol), with overall decrease in systolic BP of 6.2mmHg (95% CI -12.32 to -0.04, P=0.05) for unactivated D, compared to no significant effect for activated D. A review of the trials included here shows that the benefits of vitamin D on diabetes and

Table 2. Trials Showing Benefit from Vitamin D in Type 2 Diabetes and Cardiovascular Disease

Condition	Design/ Population	Dose	Outcomes	References
Congestive Heart Failure (CHF)	RCT: 123 patients with CHF were randomized to receive vitamin D + calcium or placebo + calcium for 9 months.	50mcg VitD3 + 500mg calcium or calcium alone orally x 9 mo	25(OH)D ↑ by 26.8ng/ml in the VitD group compared to 3.6ng/ml in the control group. Compared with baseline, the anti-inflammatory cytokine IL-10↑ significantly in the VitD group after nine months. Pro-inflammatory TNF-α↑ in the control group but not in the VitD group.	Schleithoff 2006
Hypertension (HTN)/ Endothelial Function (Flow Mediated Dilation, FMD)	RCT: 148 elderly women with 25(OH)D <50nmol/L were given vitamin D3 with or without calcium.	800 IU VitD3 with or without 1,200mg calcium/d orally x 8 weeks	VitD + calcium ↑25(OH)D 72% compared to calcium alone (P<0.01), ↓ systolic blood pressure (SBP) 9.3% (P=0.02), and ↓ heart rate 5.4% (P=0.02). No effects on diastolic BP.	Pfeifer 2001
	Controlled trial: 23 VitD-deficient subjects (25(OH)D <25nmol/L) were compared to a control group (mean 25(OH)D 75 nmol/L)	300,000 IU intramuscular VitD3 monthly x 3 months	FMD was significantly ↓ in 25(OH)D-deficient subjects vs. controls (P=0.001) and improved after replacement therapy (P=0.002).	Tarcin 2009
	RCT: Subjects with type 2 diabetes, mean age 64 years, and serum 25(OH)D levels <50nmol/L were given vitamin D2 or placebo.	Single dose of 100,000 IU VitD2	Treatment ↑ 25(OH)D by 15.3nmol/L compared to placebo, and significantly improved blood FMD of the brachial artery 2.3%. Diastolic BP ↓ significantly by 14mmHg compared to placebo, and did not correlate with FMD.	Sugden 2008
Diabetes, Type 2 (DM2)/ Glucose Tolerance	Uncontrolled trial: 12 women with gestational diabetes were given oral and IV calcitriol, and monitored for change in glucose tolerance by the oral glucose tolerance test (OGTT).	2mcg/m2 calcitriol IV 2 h prior to the second OGTT, followed by 0.25mcg calcitriol per day orally x 14 days	Calcitriol ↑significantly compared to baseline after IV calcitriol (from 92 to 138ng/l, P<0.001), but returned to the baseline level after 2 weeks of oral calcitriol (85ng/l). Glucose simultaneously ↓ from 5.6 to 4.8mmol/l (P<0.01) after IV treatment, but not after two weeks. Insulin levels tended to be lower after both IV and oral calcitriol.	Rudnicki 2007
	RCT: 100 healthy but centrally obese men ≥35 years were given VitD3 or placebo for 6 weeks.	120,000 IU VitD3 orally every two wk x 6 wk	VitD3 significantly improved oral glucose insulin sensitivity (OGIS) by per protocol analysis (P=0.038). There were no changes in insulin secretion, basal indices of insulin sensitivity, blood pressure or lipid profile.	Nagpal 2009
	RCT, secondary analysis: 314 non-diabetic adults ≥65 years were randomized to VitD3 + calcium or placebo for 3 years.	700 IU vitamin D(3) + 500mg calcium citrate per day orally x 3 yr	Among participants with impaired fasting glucose (IFG), the treatment subjects had a lower rise in FPG at three years vs those on placebo (0.02mmol/l vs. 0.34mmol/l, respectively, P=0.042) and a lower increase in HOMA-IR, a measure of insulin resistance (0.05 vs. 0.91, P=0.031).	Pittas 2007
	RCT: 31 hemodialysis patients received either calcitriol or placebo for 8 weeks. There was also a healthy control group of 12 subjects.	0.5mcg calcitriol per day orally x 8 wk	Hemodialysis patients treated with calcitriol had significantly ↑ basal serum insulin (7.81 versus 11.63microIU/ml) as well as elevated insulin immediately following calcitriol treatment at 30, 60, 90, and 120 min. HbA1C and fructosamine ↓ after calcitriol treatment (HbA1C 7.09% versus 5.22% P<0.001). Blood glucose ↓ significantly after calcitriol treatment at 0, 30, 60, 90, and 120 min. Several other trials have reported similar effects, as well as beneficial impact on lipids.	Turk 1992 Bonakdaran 2008, Strozecki 2004, Allegra 1994, Mak 1992

Dyslipidemia	RCT: 84 healthy, overweight or obese women were given either calcium + vitamin D or placebo; both groups restricted calories by 700kcal/d for 15 weeks.	400 IU vitamin D + 1,200mg elemental calcium per day x 15 wk	Calcium + VitD led to greater ↓ in total cholesterol:HDL and LDL:HDL (P<0.01 for both) and LDL cholesterol (P<0.05) compared to placebo. This was independent of changes in fat mass and in waist circumference. A trend toward more beneficial changes in HDL cholesterol, triacylglycerol, and total cholesterol was also observed in the calcium+D group (P=0.08).	Major 2007
	RCT: 200 healthy overweight subjects with mean 25(OH)D of 30 nmol/L received vitamin D or placebo for 12 mo while participating in a weight-reduction program.	83mcg VitD per day x 12 mo	No effects on weight loss, however, the treatment group had greater ↓ in serum triglycerides (-13.5% compared with +3.0%; P<0.001), and TNF-α (-10.2% compared with -3.2%; P=0.049). Vitamin D supplementation also ↑ LDL-cholesterol concentrations compared with placebo (+5.4% compared with -2.5%; P<0.001).	Zittermann 2009
	Uncontrolled trial: 15 haemodialysis patients with secondary hyperparathyroidism were given IV calcitriol for 8 weeks.	1mcg calcitriol IV 3x/wk x 8 wk	Calcitriol significantly ↓ serum intact PTH (476.45 versus 191.37ng/l, P<0.001) and plasma triglyceride (2.24 versus 1.80mmol/L, P=<0.05), and significantly ↑ plasma apoprotein A-I (38.13 versus 44.19 micromol/l, P<0.05).	Lin 1994 [Abst]
Polycystic Ovary Syndrome (PCOS)	RCT: 60 infertile PCOS patients received one of three treatment protocols: 1. calcium + D 2. calcium, D + metformin 3. 1,500 mg metformin.	400 IU of VitD3 + 1,000mg of calcium per day orally, with or without metformin x 3 months	The number of dominant follicles (> or = 14mm) during the 2-3 months of follow-up was higher in the calcium-vitamin D plus metformin group than in either of the other two groups (P=0.03).	Rashidi 2009

cardiovascular disease tend to be stronger in populations with demonstrated suboptimal levels or at high risk of inadequacy (obesity, elderly, kidney failure, etc), and at doses that are adequate to raise 25(OH)D levels. As well, trials using low doses such as 400 IU/d or 5mcg/d vitamin D3 often fail to show benefits in these conditions (Pan 1993, Margolis 2008).

Vitamin D as calcitriol benefits patients with renal disease, since these patients cannot adequately convert calcidiol to the activated form, calcitriol. In these patients, vitamin D improves glucose and lipid metabolism (See Table 2).

There is preliminary evidence to suggest that adequate vitamin D status may also aid weight loss. Ortega (2008) found that among overweight or obese women of childbearing age placed on a hypocaloric diet, those with 25(OH)D >50nmol/L had greater body fat losses than women with lower levels, OR 0.462 (CI 0.271-0.785; P<0.001). Caan (2007) found supplementation with low dose vitamin D and calcium reduced risk of weight gain 11% in postmenopausal women with low intake calcium at baseline.

INTERACTIONS BETWEEN CVD MEDICATIONS AND VITAMIN D

There have been reports of an association between inadequate 25(OH)D levels and statin-induced myalgia (Lee 2009). Eight of 11 statin intolerant patients in a case series of consecutive patients were found to be vitamin D deficient (<60nmol/L), of which three were <30nmol/L. Four of six patients who agreed to a rechallenge with the same statin after vitamin D replacement therapy were able to tolerate the drug.

One study examined vitamin D replacement therapy in vitamin D deficient (<32ng/mL), myalgic patients who continued statin therapy: 38 patients were given vitamin D (50,000 units/week for 12 weeks). Serum vitamin D increased from 20.4 to 48.2ng/ml (P<0.0001) and myalgia resolved in 35 (92%) (Ahmed 2009).

ACE Inhibitors have also been shown to decrease 25(OH)D levels in subjects with certain ACE polymorphisms (Pérez-Castrillón 2006).

CONCLUSION

Vitamin D inadequacy has been linked to affective disorders as well as a range of cardiovascular conditions including hypertension, cardiac events, cardiometabolic disease, and conditions characterized by dysglycemia. Although observational evidence is

limited due to possible confounding by vitamin D's positive association with outdoor activity, intervention trials have yielded positive results in these conditions. Vitamin D supplementation shows promise in the treatment of such conditions when given at doses sufficient to raise serum 25(OH)D levels to at least 50-70nmol/L or higher, higher being recommended by vitamin D experts (see Part I). Vitamin D inadequacy may also be a causal factor contributing to statin-induced myalgia.

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