

ALTERNATIVE VIEWPOINTS

Vitamin D and Cardiovascular Disease: A Second Look

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Nemerovski and colleagues have contributed an excellent review of vitamin D and its role in multiple etiologies of cardiovascular disease.¹ Their comprehensive work deserves commendation for its scope and pertinence. There are, however, some equally pertinent cardiometabolic consequences of vitamin D deficiency that were not addressed in their review; namely, the role of vitamin D in obesity and myopathy-related statin intolerance. There were also inconsistencies between their clinical definitions for vitamin D “insufficiency” (less than 30 ng/mL) and those reported in recent literature.

Ahmed and colleagues have recently documented an association between vitamin D insufficiency (defined as <32 ng/mL) and statin-induced myalgia, as well as the benefit of supplementing vitamin D in deficient patients (defined as <20 ng/mL) with concomitant statin intolerance.² In their investigation, the mean vitamin D level of patients with statin-induced myalgia was significantly lower than the asymptomatic population (28.6 versus 34.2 ng/mL, $p < 0.0001$).² Furthermore, 92% of patients with statin-induced myalgia and vitamin D deficiency achieved resolution of muscular symptoms following vitamin D supplementation.² Additional research confirming Ahmed and colleagues’ results has been accepted for presentation to the American College of Clinical Pharmacy 2009 Annual

meeting. Data from the West of Scotland Coronary Prevention Study indicates that less than 75% compliance with statin therapy results in a 33% greater risk of myocardial infarction (MI), however it is estimated that statin compliance rarely exceeds 65%.^{3,4} In a more recent study by Perreault and colleagues evaluating statin adherence and coronary artery disease event rates, patients who were less than 60% compliant with statin therapy did not incur the same cardiovascular benefit.⁵ This data implicates statin non-compliance as an important source of cardiovascular morbidity and mortality. Therefore, the maintenance of vitamin D sufficiency in statin-treated patients to avoid myalgia-related non-compliance (and ultimately discontinuation) is a clinical intervention that can improve treatment efficacy and patient outcomes, further linking vitamin D to cardiovascular disease (CVD).

Obesity has reached pandemic proportions in today’s world, increasing the risk of developing CVD and worsening preexisting CVD.⁶ An interesting concept that was not mentioned in this review is the role that obesity plays in relation to circulating vitamin D concentrations. In a prospective trial conducted by Parikh and colleagues, obesity and circulating vitamin D concentrations were negatively correlated. Vitamin D levels were significantly lower in obese patients than in non-obese patients (23.5 ng/mL versus 31 ng/mL, $p < 0.0001$).⁷ Therefore, the increased CVD risk that obese patients incur may be complicated by concomitant vitamin D insufficiency. This provides an impetus for increased screening recommendations, particularly in obese patients or those at high risk for CVD.²

Nemerovski and colleagues presented convincing data that patients achieve positive clinical outcomes when 25(OH)-D

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concentrations exceed 24 ng/mL.¹ However, the authors later recommend that treatment for sub-normal vitamin D concentrations be reserved for those patients with concentrations <20 ng/mL. We find this recommendation to be conservative in light of their own findings and those of other investigations. It has been previously noted, albeit with some debate, that optimal levels of vitamin D concentrations fall within 30–50 ng/mL or higher.⁸ Patients 60 years of age and older may particularly benefit from concentrations of at least 30 ng/mL.⁹ Based on these findings and those of Ahmed and colleagues, we suggest supplementation: (1) in patients with 25(OH)-D concentrations <30 ng/mL and (2) in statin-treated patients complaining of myalgia with 25(OH)-D concentrations <32 ng/mL.^{2, 8, 9} Although we concur with the dosing recommendations made by Nemerovski and colleagues for adequate chronic supplementation (800–2000 International Units daily), the efficacy and timeliness of “burst dosing” with weekly or bi-weekly administration of 50,000 International Units for 8 to 12 weeks cannot go without consideration. Dr. Michael F. Holick, who has long been at the front of the vitamin D movement, suggested that the chronic low doses, like those recommended by Nemerovski and colleagues, are best used as preventive measures to avoid deficiency, while burst dosing is the preferred treatment for correction of vitamin D deficiency.¹⁰ Following burst dosing for rapid correction, we feel chronic low dose therapy is essential for continued prevention.

References

1. Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE. Vitamin D and cardiovascular disease. *Pharmacotherapy* 2009;29(6):691–708.
2. Ahmed W, Khan N, Glueck CJ, et al. Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients. *Transl Res* 2009;153(1):11–6.
3. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia: West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333(20):1301–7.
4. Avorn J, Monette J, Lacour A, et al. Persistence of use of lipid-lowering medications: a cross-national study. *JAMA* 1998;279:1458–1462.
5. Perreault S, Dragomir A, Blais L, et al. Impact of better adherence to statin agents in the primary prevention of coronary artery disease. *Eur J Clin Pharmacol* 2009;16. doi:10.1007/s00228-009-0673-0.
6. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. *Circulation* 2006;113(6):898–918.
7. Parikh SJ, Edelman M, Uwaifo GI, et al. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* 2004;89(3):1196–9.
8. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr* 2005;135:317–22.
9. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: A review. *Altern Med Rev* 2005;10(2):94–111.
10. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357(3):266–81.

Authors' Reply

We appreciate the comments provided by Riche and colleagues and are pleased to learn that others are as interested in this topic as we are. The article by Ahmed et colleagues¹ relating statin-induced myalgias to vitamin D deficiency is interesting and informative. Vitamin D supplementation may be a simple, safe, and cost-effective approach to help keep patients on a very important class of drugs. Further study of this association with a placebo controlled trial in a larger number of patients may provide the long sought after solution to statin-induced myalgia that other supplements, such as coenzyme Q₁₀, have failed to provide.²

Although the data linking obesity to vitamin D deficiency was not specifically discussed in our review paper, we recognize that obesity is a risk factor for vitamin D deficiency, as discussed at the introduction of our review,³ and appreciate the additional reference provided.⁴

The observation by Riche and colleagues that our recommendations for supplementation are conservative is correct. We acknowledge that the level for optimal health might well be above 30 ng/mL and supplementation up to this level or higher is indeed reasonable. The minimum for strictly cardiovascular benefits was based upon the available prospective trials where lower thresholds were studied. We anxiously await the results of a large NIH funded study Vitamin D and Omega-3 Trial (VITAL), which will begin enrollment in 2010. This trial is designed to test whether vitamin D supplementation (2000 IU/day) given over 5 years can reduce the risk of developing heart disease or stroke in people who have no prior history of these diseases.⁵

In terms of dosing regimens, our recommendation of 800 to 2000 IU daily was not meant to exclude other dosing regimens, but rather to give a reasonable estimate of the range that would be required in most people for long-term management. Large bolus doses will replete

a patient's vitamin D stores more rapidly than chronic daily dosing. The rate at which vitamin D repletion should be carried out should be individualized, based on the severity of the deficit, the patient's clinical circumstances and individual characteristics.

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References

1. Ahmed W, Khan N, Glueck CJ, et al. Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients. *Transl Res* 2009;153:11–6.
2. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol* 2007;49:2231–7.
3. Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE. Vitamin D and cardiovascular disease. *Pharmacotherapy* 2009;29:691–708.
4. Parikh SJ, Edelman M, Uwaifo GI, et.al. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* 2004;89:1196–9.
5. The Vitamin D and Omega-3 Trial (VITAL). Available from: <http://www.vitalstudy.org>. Accessed August 3, 2009