Vitamin D and Cardiovascular Health

Carl J. Lavie, MD; James J. DiNicolantonio, PharmD; Richard V. Milani, MD; James H. O'Keefe, MD

Case Presentation

A 56-year-old black female patient with significant coronary heart disease (CHD) after several percutaneous intervention procedures for acute coronary syndromes was seen in the office for routine follow-up. She is 5 ft 5 in tall and weighs 265 pounds. She had recently gained 25 pounds after losing nearly 100 pounds following bariatric surgery. Her blood pressure, which was previously controlled with her therapy for hypertension, which included a β-blocker, an angiotensin-converting enzyme inhibitor, a calcium blocker, and a diuretic, was 160/90 mm Hg. Her fasting glucose was 168 mg/dL, with a hemoglobin A_{1C} of 8.4% on therapy for type 2 diabetes mellitus. She was experiencing severe myalgias, which made it difficult for her to exercise, so she discontinued her atorvastatin. Her fasting lipid profile was as follows: total cholesterol, 264 mg/dL; high-density lipoprotein, 42 mg/dL; triglycerides, 220 mg/dL; and low-density lipoprotein, 178 mg/dL. Her 25-hydroxyvitamin D [25(OH)D] level was severely low at 8 ng/mL.

There have been several nutrient fads over recent decades, including beta carotene, selenium, folic acid, and vitamins E and C, all of which failed to show benefit in multiple large, randomized, controlled trials and thus did not stand the test of time, at least in terms of major cardiovascular event reduction.[1,2] Without question, vitamin D increases absorption of calcium, magnesium, and phosphorus and mobilizes calcium and phosphorus from bone. It is also clear that vitamin D deficiency adversely affects the musculoskeletal system, predisposing to rickets in children and osteomalacia and osteoporosis in adults. The potential role of vitamin D in the pathogenesis of statin-induced myopathy and myalgias is debatable, although currently it appears reasonable to use vitamin D supplementation in patients with such symptoms, especially if they also have deficient or even mildly reduced vitamin D levels.[3] Indeed, musculoskeletal pain is generally the first and most common subjective complaint in individuals who are vitamin D deficient.[4]

The potential roles of vitamin D deficiency on risk of cancer development, especially colorectal cancer, risk of numerous cardiovascular diseases, and all-cause mortality rates are being studied.[2] Clearly, vitamin D deficiency is now recognized to be highly prevalent in the United States and worldwide, affecting up to 50% of the general population, although the exact cutoff values used to define vitamin D deficiency and its severity are not firmly established (Table 1). Regardless, an extremely low level of <10 ng/mL, as in the case outlined above, represents a vitamin D deficiency that is likely to have pathological implications for both the musculoskeletal and cardiovascular systems. The major risk factors for developing vitamin D deficiency are listed in Table 2. In our patient, darkly pigmented skin, obesity, indoor lifestyle, and physical inactivity all likely played a role in her severely reduced vitamin D level.

There is increasing evidence that vitamin D plays a substantial role in determining the risk of various cardiometabolic conditions, particularly metabolic syndrome/type 2 diabetes mellitus and systemic hypertension, and epidemiological studies suggest that CHD risk may also be increased. Vitamin D may increase risk for atherosclerosis, CHD, and other cardiovascular diseases through several potential mechanisms

From the John Ochsner Heart and Vascular Institute, Ochsner Clinical School, University of Queensland School of Medicine, New Orleans, LA (C.J.L., R.V.M.); Department of Preventive Medicine, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge (C.J.L.); and Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City (J.J.D., J.H.O.).

Correspondence to Carl J. Lavie, MD, FACC, FACP, FCCP, Medical Director, Cardiac Rehabilitation Director, Exercise Laboratories, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, University of Queensland School of Medicine, 1514 Jefferson Hwy, New Orleans, LA 70121–2483. E-mail clavie@ochsner.org

(*Circulation.* 2013;128:2404-2406.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.002902**

(Figure).[2] Chronic vitamin D deficiency increases the levels of parathyroid hormone and can cause secondary hyperparathyroidism, which may mediate many adverse cardiovascular effects, especially for those individuals with concomitant renal disease. Vitamin D also plays a role in regulating the renin-angiotensin-aldosterone system, and vitamin D deficiency upregulates the renin-angiotensin-aldosterone system and predisposes to hypertension, as well as hypertrophy of smooth muscle cells in the vascular tree and the left ventricle. Vitamin D also affects mechanisms related to metabolic syndrome/type 2 diabetes mellitus. A recent randomized, placebo-controlled trial showed that supplementing obese adolescents who had vitamin D deficiency with 4000 IU/d of vitamin D_3 improved insulin sensitivity and the leptin/adiponectin ratio.[5]

Low levels of vitamin D also may increase inflammation, both directly and via increases in parathyroid hormone. Additionally, there is evidence that vitamin D deficiency may predispose to depression,[6] a known cardiovascular risk factor,[7,8] and abnormalities in cognitive function. Although a causal link between vitamin D and major cardiovascular diseases and mortality has not yet been established, numerous major epidemiological studies, which we recently reviewed,[2] have found highly significant correlations between low levels of vitamin D and cardiovascular disease, CHD, and mortality.

Two recent studies of vitamin D and cardiovascular diseases are of note.[9,10] The Copenhagen City Heart Study[9] assessed 10 170 men and women in 1981 to 1983, analyzed these patients for major cardiovascular diseases during a 29-year follow-up, and demonstrated that lower levels of vitamin D were associated with 64% higher risk of myocardial infarction, 57% higher risk of early death, and 81% higher risk of fatal CHD events. The authors also analyzed 17 population-based prospective studies, assessing the data with and without the Copenhagen City Heart Study, which was the largest study. Regardless of whether the Copenhagen City Heart Study was included, there was an ≈40% higher risk of CHD and death in the lowest quartile of 25(OH)D levels.

The Whitehall study[10] performed a 13-year follow-up of 5409 mostly older men (mean age, 77 years), showing that higher concentrations of 25(OH)D were inversely and linearly correlated with both vascular and nonvascular mortality. After statistical adjustment, doubling of 25(OH)D concentrations was associated with 20% and 23% reductions in vascular and nonvascular mortality, respectively. They also performed a meta-analysis of 12 prospective studies with 4632 vascular deaths and 18 prospective studies with 11 734 deaths from all causes, demonstrating that those in the top quartile of 25(OH)D compared with the bottom quartile had 21% and 28% lower vascular and total mortality, respectively. Although the Copenhagen City Heart Study,[9] the Whitehall study,[10] and accompanying meta-analyses from both studies support the importance of 25(OH)D in cardiovascular diseases and vascular and nonvascular mortality,[2,9,10] a large-scale, randomized, controlled trial is underway.[11]

At present, vitamin D supplementation appears to be indicated for a sizable proportion of the general population. Although the Institute of Medicine suggests that North Americans need on average 600 IU of vitamin D daily and those >70 years of age may require as much as 800 IU/d,[12] considering that the average US adult consumes only 230 IU daily, has minimal sun exposure, and uses sunscreens heavily when in the sun to prevent skin damage and skin cancers,[13] many experts have suggested that higher doses (in the range of 800–2000 IU daily) may be needed. These higher doses are difficult to obtain without routine supplementation, especially in areas with extreme winter climates and in higher altitudes.[2]

Sunlight is the most potent source of vitamin D, with ≈3000 IU of vitamin D_3 obtained during 5 to 10 minutes of midday, midyear exposure of arm and legs for a light-skinned white person.[2,14] In addition, to maintain a normal vitamin D level, many people may need daily supplementation of 1000 to 2000 IU of vitamin D_3 or 50 000 IU of

Table 1. Current Vitamin D Status

Serum 25-Hydroxyvitamin D, ng/mL	Vitamin D Status
≤10	Severe deficiency
10–20	Deficiency
20–30	Mild to moderate deficiency
≥30	Sufficient
40–50	Ideal
50–150	Indeterminate data*
>150	Toxicity
Institute of Medicine definitions	
<12	At risk of deficiency
12–19	At risk of inadequacy
20–50	Sufficient
>50	Possibly harmful

*Some data suggest increased falls, fractures, certain cancers, and even cardiovascular risk at values >50 ng/mL.

Adapted with permission from Lavie et al.[2] Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Table 2. Major Risk Factors for Vitamin D Deficiency

Aging
Increased distance from the equator
Shorter days related to nonsummer seasons
Indoor lifestyle
Darkly pigmented skin
Institutionalized/housebound
Sunscreens and cover-up clothing
Air pollution
Smoking
Obesity
Physical inactivity
Genetic factors
Malabsorption
Renal disease
Liver disease
Certain medications: Glucocorticoids, antirejection medications, human immunodeficiency virus medications, certain antiepileptic drugs

Reproduced from Lavie et al[2] with permission from the publisher. Copyright © 2011, Elsevier.

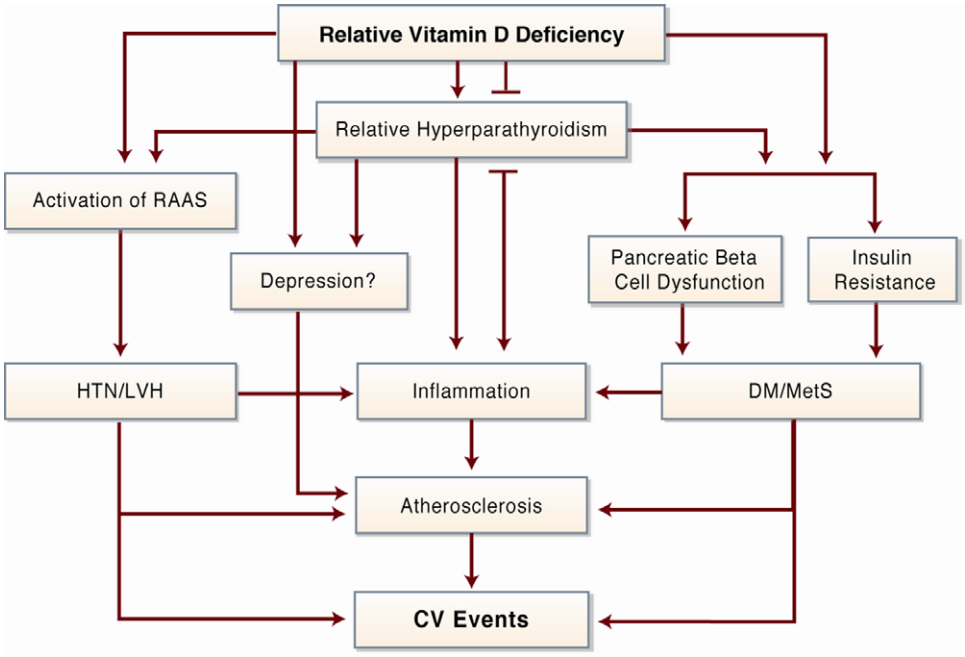

Figure. Potential mechanisms for cardiovascular (CV) effects of vitamin D deficiency. DM indicates diabetes mellitus; HTN, hypertension; LVH, left ventricular hypertrophy; MetS, metabolic syndrome; and RAAS, renin-angiotensin-aldosterone system. Reproduced from Lavie et al[2] with permission from the publisher. Copyright © 2011, Elsevier.

either vitamin D_2 or D_3 every 2 weeks (Although vitamin D_3 is more potent, it is usually not available in this dose).[15] For patients with significant vitamin D deficiency, as in the patient presented here, this high dose should be started once or twice weekly for 2 to 3 months, followed by maintenance therapy (routine sunlight exposure, 800–2000 IU of vitamin D_3 daily, or 50 000 IU of vitamin D_2 or D_3 every 2 weeks).

Case Resolution

After receiving 50 000 IU oral vitamin D_2 twice weekly for 10 weeks, followed by 50 000 IU twice monthly, our patient had resolution of her myalgias, which allowed her to resume a more physically active lifestyle. She was also able to restart her atorvastatin (40 mg/d initially and then 80 mg/d), which she tolerated. She subsequently noted marked improvements in her CHD risk factor profile.

Disclosures

Dr DiNicolantonio is employed by a company that sells Vitamin D products, but he does not share in any profits from these sales. Dr O'Keefe has a major ownership interest in CardioTabs, a nutraceutical company that sells nutritional supplements, including some that contain vitamin D.

References

1. Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J Am Coll Cardiol*. 2009;54:585–594.
2. Lavie CJ, Lee JH, Milani RV. Vitamin D and cardiovascular disease: will it live up to its hype? *J Am Coll Cardiol*. 2011;58:1547–1556.
3. Gupta A, Thompson PD. The relationship of vitamin D deficiency to statin myopathy. *Atherosclerosis*. 2011;215:23–29.
4. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc*. 2010;85:752–758.
5. Belenchia AM, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. *Am J Clin Nutr*. 2013;97:774–781.
6. Hoang MT, Defina LF, Willis BL, Leonard DS, Weiner MF, Brown ES. Association between low serum 25-hydroxyvitamin D and depression in a large sample of healthy adults: the Cooper Center longitudinal study. *Mayo Clin Proc*. 2011;86:1050–1055.
7. Lavie CJ, Milani RV, O'Keefe JH, Lavie TJ. Impact of exercise training on psychological risk factors. *Prog Cardiovasc Dis*. 2011;53:464–470.
8. O'Keefe JH, Patil HR, Lavie CJ. Can vitamin D deficiency break your heart? *Mayo Clin Proc*. 2012;87:412–41; author reply 413.
9. Brøndum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-Hydroxyvitamin D levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. *Arterioscler Thromb Vasc Biol*. 2012;32:2794–2802.
10. Tomson J, Emberson J, Hill M, Gordon A, Armitage J, Shipley M, Collins R, Clarke R. Vitamin D and risk of death from vascular and non-vascular causes in the Whitehall study and meta-analyses of 12,000 deaths. *Eur Heart J*. 2013;34:1365–1374.
11. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, Zaharris E, Macfadyen JG, Danielson E, Lin J, Zhang SM, Buring JE. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials*. 2012;33:159–171.
12. Institute of Medicine of the National Academies. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; November 30, 2010.
13. Moore C, Murphy MM, Keast DR, Holick MF. Vitamin D intake in the United States. *J Am Diet Assoc*. 2004;104:980–983.
14. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr*. 2006;84:18–28.
15. O'Keefe JH, Lavie CJ, Holick MF. Vitamin D supplementation for cardiovascular disease prevention-Letter to the Editor. *JAMA*. 2011;306:1546–1547.