



BRIEF ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS

## Q: Does vitamin D deficiency play a role in the pathogenesis of chronic heart failure? Do supplements improve survival?

**VICTOR HAJJAR, MD**

Department of Hospital Medicine, Cleveland Clinic

**JEREMIAH P. DEPTA, MD**

Department of Internal Medicine, Cleveland Clinic

**MARIA M. MOUNTIS, DO**

Section of Heart Failure and Transplant, Heart and Vascular Institute, Cleveland Clinic

**A:** Vitamin D deficiency may play a role in the pathogenesis of chronic heart failure, but whether giving patients supplements to raise their vitamin D levels into the normal range improves their survival is not clear.

### ■ ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND OTHER DISORDERS

In the mid-17th century, Whistler and Glisson independently described rickets as a severe bone-deforming disease characterized by growth retardation, bending of the spine, deformities of the legs, and weak and toneless muscles. Histologically, rickets is characterized by impaired mineralization of the cartilage in the epiphyseal growth plates in children. In 1919, Sir Edward Mellanby identified vitamin D deficiency as the cause.

Osteomalacia, another disease caused by vitamin D deficiency, is a disorder of mineralization of newly formed bone matrix in adults. Vitamin D, therefore, has well-known roles in maintaining bone health and calcium and phosphorus homeostasis.

In addition, vitamin D deficiency has been shown in recent years to be associated with myocardial dysfunction.<sup>1,2</sup>

doi:10.3949/cjcm.77a.08078

### ■ VITAMIN D METABOLISM IS COMPLEX

Vitamin D's metabolism is complex and involves many organ systems (FIGURE 1).

In skin exposed to ultraviolet B light, the provitamin 7-dehydrocholesterol is converted to vitamin D<sub>3</sub> (cholecalciferol). Vitamin D<sub>3</sub> is also obtained from dietary sources. However, many scientists consider vitamin D more a hormone than a classic vitamin, as adequate exposure to sunlight may negate the need for dietary supplements.

The active form of vitamin D is synthesized by hydroxylation in the liver and kidney. In the liver, hepatic enzymes add a hydroxyl (OH) group to vitamin D<sub>3</sub>, changing it to 25-hydroxyvitamin D<sub>3</sub>. In the kidney, 25-hydroxyvitamin D<sub>3</sub> receives another hydroxyl group, converting it to the biologically active metabolite 1,25-dihydroxyvitamin D<sub>3</sub> (calcitriol). This renal hydroxylation is via 1-alpha-hydroxylase activity and is directly under control of parathyroid hormone (PTH), and indirectly under control of the serum concentrations of calcium.

Interestingly, a number of different organ cells, including cardiomyocytes, also express 1-alpha-hydroxylase and therefore also convert 25-hydroxyvitamin D<sub>3</sub> to 1,25-dihydroxyvitamin D<sub>3</sub>. Unlike the renal hydroxylation, this extrarenal process depends on cytokine activation and on serum levels of 25-hydroxyvitamin D<sub>3</sub>.<sup>3</sup> Low levels of 25-hydroxyvitamin D<sub>3</sub> lead to alterations in cellular control over growth, differentiation, and function.

The active form of vitamin D is transported protein-bound in the blood to various target organs, where it is delivered in free form

Vitamin D  
may be more  
of a hormone  
than a vitamin

to cells. Specific nuclear receptor proteins are found in many organs not classically considered target organs for vitamin D, including the skin, brain, skeletal muscles, cardiomyocytes, vascular endothelial cells, circulating monocytes, and activated B and T lymphocytes. Vitamin D plays a significant role in the autocrine and paracrine regulation of cellular function, growth, and differentiation in various organs.<sup>3</sup>

### ■ MOST HEART FAILURE PATIENTS HAVE LOW VITAMIN D LEVELS

More than 40% of men and 50% of women in the United States have low vitamin D levels (< 30 ng/mL [75 nmol/L])—and low levels in adults are associated with both coronary artery disease and heart failure.<sup>4</sup> Most patients with heart failure have low levels.<sup>5,6</sup> Therefore, screening for vitamin D deficiency in patients with heart failure is appropriate and encouraged.

Low vitamin D levels carry a poor prognosis. Pilz et al<sup>5</sup> measured baseline 25-hydroxyvitamin D<sub>3</sub> levels in 3,299 patients referred for elective coronary angiography and followed them prospectively for a median of 7.7 years. Even after adjustment for cardiac risk factors, patients who had low 25-hydroxyvitamin D<sub>3</sub> levels were more likely to die of heart failure or sudden cardiac death than patients with normal levels.

Boxer et al<sup>7</sup> found an association between low 25-hydroxyvitamin D<sub>3</sub> levels and low exercise capacity and frailty in patients with systolic heart failure.

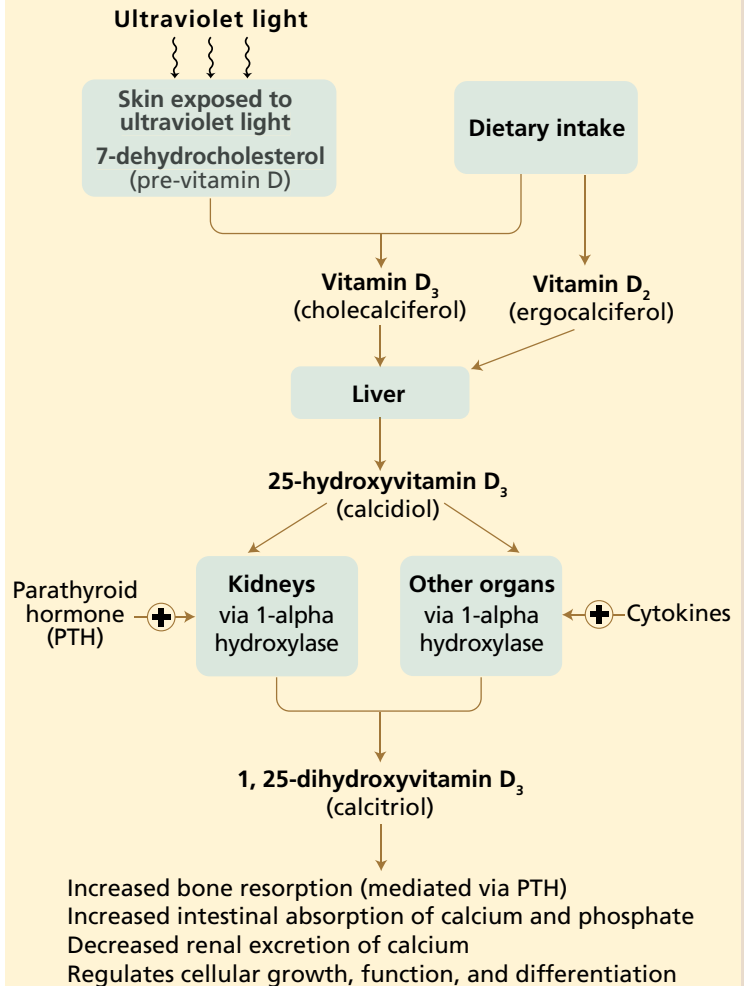
### ■ LOW VITAMIN D CONTRIBUTES TO THE PATHOGENESIS OF HEART FAILURE

In recent years, ideas about the pathophysiology of heart failure have expanded from a purely hemodynamic view to a more complex concept involving inflammatory cytokines and neurohormonal overactivation.<sup>8</sup>

Animal studies first showed vitamin D to inhibit the renin-angiotensin-aldosterone system, activation of which contributes to the salt and water retention seen in heart failure.<sup>4,9</sup>

In addition, vitamin D has a number of effects that should help prevent hypertension,

## Synthesis and effects of vitamin D



**FIGURE 1**

an important risk factor for heart failure. It protects the kidney by suppressing the renin-angiotensin-aldosterone system, prevents secondary hyperparathyroidism and its effects on vascular stiffness, prevents insulin resistance, and suppresses inflammation, which protects vascular endothelial cells.<sup>10</sup>

The first studies to show a connection between cardiovascular homeostasis and vitamin D status were in animal models more than 20 years ago. These studies showed that 1,25-dihydroxyvitamin D<sub>3</sub> acts directly on cardiomyocyte vitamin D receptors, which are widely distributed throughout the body in several tissue types.<sup>11</sup>

Excess PTH levels associated with low vitamin D levels may play a role in cardiovascu-

TABLE 1

**Recommended daily vitamin D intake for men and women**

AGE (YEARS) <sup>a</sup>	ADEQUATE INTAKE (IU) <sup>b</sup>	TOLERABLE UPPER INTAKE (IU) <sup>c</sup>
14–18	200	2,000
19–50	200	2,000
50–70	400	2,000
> 70	600	2,000

<sup>a</sup> Recommendations are the same for pregnant or lactating women.

<sup>b</sup> "Adequate intake" refers to the recommended daily intake of vitamin D to maintain bone and calcium in healthy individuals and assumes that vitamin D is not synthesized by exposure to ultraviolet light. A recommended daily allowance has not been established due to insufficient evidence.

<sup>c</sup> "Tolerable upper intake" refers to the maximum daily intake associated with the fewest adverse effects.

INSTITUTE OF MEDICINE, FOOD AND NUTRITION BOARD. DIETARY REFERENCE INTAKES: CALCIUM, PHOSPHORUS, MAGNESIUM, VITAMIN D, AND FLUORIDE. WASHINGTON, DC: NATIONAL ACADEMY PRESS, 1997.

**Vitamin D receptors are found in many organs, not just bone**

lar disease by leading to cardiomyocyte hypertrophy and interstitial fibrosis of the heart.<sup>12</sup> Animal studies have found that vitamin D suppresses cardiac hypertrophy.<sup>13</sup> Vitamin D also plays a role in cardiomyocyte relaxation and may abrogate the hypercontractility associated with diastolic heart failure.<sup>2,14</sup>

Currently, it is unclear whether vitamin D deficiency is a causative risk factor for heart failure or simply a reflection of the poor functional status of patients with heart failure that leads to decreased exposure to sunlight. This debate will continue until further randomized clinical trials address this association.

**VITAMIN D AND HEART TRANSPLANTATION**

One would expect that patients with end-stage organ failure would be at high risk of vitamin D deficiency because of limited sunlight exposure. However, few studies have evaluated the role of this vitamin in heart transplant recipients.

Stein and colleagues<sup>15</sup> measured serum 25-hydroxyvitamin D<sub>3</sub> immediately after transplantation in 46 heart and 23 liver transplant recipients. Levels were low in both types of

transplant recipients, but liver transplant recipients had significantly lower levels than heart transplant patients. This could be explained by malabsorption and impaired synthesis of 25-hydroxyvitamin D<sub>3</sub> in end-stage liver disease.

Also, an important point is that osteoporosis is prevalent in postcardiac transplant patients and likely related to the immunosuppressive agents these patients must take.<sup>16</sup> In theory, increasing the body's stores of vitamin D during the pretransplant period could lower the rate of bone loss and osteoporosis after cardiac transplantation.

Further investigation is needed to determine whether restoring adequate levels of vitamin D at the time of or after transplantation prevents graft rejection or improves survival.

**VITAMIN D SUPPLEMENTATION AND SURVIVAL IN HEART FAILURE**

Vitamin D requirements vary, depending in part on sun exposure and age, from 200 to 600 IU per day (TABLE 1). Currently, experts believe these recommendations are outdated and estimate that optimal amounts are closer to 1,000 IU daily.<sup>17,18</sup> Further studies are needed to update the current guidelines on the optimal amount of vitamin D intake.

The best laboratory test to assess vitamin D levels is the serum 25-hydroxyvitamin D<sub>3</sub> concentration. A level between 20 and 30 ng/mL (50–75 nmol/L) is considered insufficient, and a level below 20 ng/mL (50 nmol/L) represents vitamin D deficiency.<sup>4,5,11</sup>

Vitamin D insufficiency is typically treated with 800 to 1,000 IU of vitamin D<sub>3</sub> daily, whereas deficiency requires 50,000 IU of vitamin D<sub>3</sub> weekly for 6 to 8 weeks, followed by 800 to 1,000 IU daily.<sup>19</sup> The goal of therapy is to increase the serum 25-hydroxyvitamin D<sub>3</sub> level above 30 ng/mL.<sup>19</sup>

Currently, it is unknown if vitamin D supplementation improves survival in heart failure. We recommend testing for vitamin D deficiency in all patients with heart failure and treating them as described above. For heart failure patients that are not deficient, daily intake of 800 to 1,000 IU of vitamin D is reasonable. Our review underscores the need

for more studies to evaluate the efficacy of vitamin D replacement in improving survival in patients with heart failure.

### KEY POINTS

- Screening for vitamin D deficiency in patients with heart failure is appropriate and encouraged.
- Vitamin D deficiency is common in pa-

### REFERENCES

1. Nibelink KA, Tishkoff DX, Hershey SD, Rahman A, Simpson RU. 1,25(OH)<sub>2</sub>-vitamin D<sub>3</sub> actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. *J Steroid Biochem Mol Biol* 2007; 103:533–537.
2. Tishkoff DX, Nibelink KA, Holmberg KH, Dandu L, Simpson RU. Functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. *Endocrinology* 2008; 149:558–564.
3. Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest* 2005; 35:290–304.
4. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008; 102:1540–1544.
5. Pilz S, März W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab* 2008; 93:3927–3935.
6. Zittermann A, Schleithoff SS, Koerfer R. Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev* 2006; 11:25–33.
7. Boxer RS, Dauser DA, Walsh SJ, Hager WD, Kenny AM. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. *J Am Geriatr Soc* 2008; 56:454–461.
8. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr* 2006; 83:754–759.
9. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator

of the renin-angiotensin system. *J Clin Invest* 2002; 110:229–238.

- In theory, achieving adequate levels of vitamin D would have a beneficial effect on patients with heart failure.
- Randomized controlled trials are needed to determine if vitamin D supplementation confers a survival benefit in patients with heart failure who have deficient vitamin D levels. ■

of the renin-angiotensin system. *J Clin Invest* 2002; 110:229–238.

10. Pilz S, Tomaschitz A, Ritz E, Pieber TR, Medscape. Vitamin D status and arterial hypertension: a systematic review. *Nat Rev Cardiol* 2009; 6:621–630.
11. Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE. Vitamin D and cardiovascular disease. *Pharmacotherapy* 2009; 29:691–708.
12. Rostand SG, Drüeke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 1999; 56:383–392.
13. Wu J, Garami M, Cheng T, Gardner DG. 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes. *J Clin Invest* 1996; 97:1577–1588.
14. Green JJ, Robinson DA, Wilson GE, Simpson RU, Westfall MV. Calcitriol modulation of cardiac contractile performance via protein kinase C. *J Mol Cell Cardiol* 2006; 41:350–359.
15. Stein EM, Cohen A, Freeby M, et al. Severe vitamin D deficiency among heart and liver transplant recipients. *Clin Transplant* 2009; (Epub ahead of print).
16. Shane E, Rivas M, McMahon DJ, et al. Bone loss and turnover after cardiac transplantation. *J Clin Endocrinol Metab* 1997; 82:1497–1506.
17. Norman AW, Bouillon R, Whiting SJ, Vieth R, Lips P. 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007; 103:204–205.
18. Vieth R, Bischoff-Ferrari H, Boucher BJ, et al. The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr* 2007; 85:649–650.
19. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int* 2005; 16:713–716.

ADDRESS: Victor Hajjar, MD, Department of Hospital Medicine, A13, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail hajjarv@ccf.org.