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Vitamin D in congestive heart failure[1,2]

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Congestive heart failure (CHF) is a disease in which the heart can no longer meet the demands the body. CHF can be caused by hypertension, myopathy, diabetes, coronary artery disease, or defective heart valves (1).

A nutritional intervention, such as vitamin D supplementation, is a nonpharmacologic strategy that may help prevent the development and progression of CHF. In one recent clinical trial, Witte and Clark (2) randomly assigned patients with CHF (mean age: 75 y) to receive either a placebo or a cocktail of micronutrients that included vitamin D (10 μg/d; 400 IU/d). Those who received the nutrient cocktail showed a significant improvement in left ventricular function and quality of life, but there was no effect on immune system signaling molecules (ie, cytokines).

In the current issue of the Journal, Schleithoff et al (3) report on a clinical trial conducted in men with CHF (mean age: 55 y) who were randomly assigned to receive a placebo or vitamin D (50 μg/d; 2000 IU/d). The authors found no effect of vitamin D on either left ventricular function or 15-mo survival rates. However, serum concentrations of tumor necrosis factor α, an inflammatory cytokine, decreased with vitamin D treatment; in contrast, concentrations of interleukin 10, an antiinflammatory cytokine, increased. These changes suggest that vitamin D has protective effects on the heart itself and on the atherosclerosis that may precipitate CHF (4, 5).

The article by Schleithoff et al is important because it offers 2 insights about vitamin D. First, the article confirms previous evidence that vitamin D supplementation affects immune-modulating cytokines in desirable ways. Second, it points to a higher dose requirement for achieving this. The study by Witte and Clark (2) used vitamin D at 10 μg/d (400 IU/d), and this dose did not affect cytokine concentrations. Another study by Mahon et al (6) produced modest responses with 25 μg vitamin D/d (1000 IU/d). With the use of 50 μg vitamin D/d (2000 IU/d), Schleithoff et al produced more substantial effects on inflammatory cytokine concentrations. A pattern is emerging: higher doses of vitamin D have greater effects on regulatory molecules of the immune system.

The authors did not mention the rationale for selecting the administered doses in any of the 3 reports involving vitamin D and cytokine responses. The doses used were the multivitamin dose of vitamin D (1), the limit for a nonprescription dose (6), and the upper limit for vitamin D (3). The selection of dose in all these studies was not based on objective evidence. A conventional diet alone cannot ensure adequate concentrations of vitamin D, which means that supplements are often necessary. Despite that, no study—let alone a clinical study of CHF patients—has ever included a dose-finding phase to determine how much additional vitamin D may be required to produce the desired outcome with any degree of plausibility.

Many aspects of vitamin D biology make it a satisfying area for investigation. The mechanistic basis for many potential clinical effects of vitamin D on health stems from the realization that many tissues throughout the body possess the ability to generate the biologically active molecule 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] and to use it as a local, paracrine signaling molecule. Among the effects pertinent to cardiovascular health is the shift toward an antiinflammatory response, as shown by Schleithoff et al (3). In addition, vitamin D improves muscular function (7), moderates blood pressure (8), and probably improves both glucose tolerance (9) and the odds of developing juvenile diabetes (10). Each of these vitamin D–related mechanisms targets an underlying cause of CHF, whether it is hypertension, myopathy, diabetes, or coronary artery disease (1).

It was ambitious for Schleithoff et al to have expected to see improvements in cardiac function or greater survival rates in a small study of relatively short duration and at a late stage in the disease. Nonetheless, it is to their credit to have used a dose that was high in the context of traditional nutrition, to have shown the protocol to be safe, and to have produced desirable changes to cytokine profiles.

Vitamin D is unique in the field of nutrition because of the range of its pleiotropic effects. CHF is a chronic disease involving many body systems and is the long-term consequence of several major risk factors, most of which may be moderated with improved vitamin D nutrition (3, 6–10). To expect a therapeutic response to a modest dose of this one nutrient in patients with CHF is surely too much to ask. The more realistic question raised by Schleithoff et al (3) and Witte and Clark (2) is whether the use of an appropriate dose of vitamin D, as one part of a nutritional strategy, could help in the primary prevention or treatment of CHF.

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REFERENCES

1. Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev 2000;5:167–73.
2. Witte KK, Clark AL. Chronic heart failure and multiple micronutrient supplementation: realistic hope or idealistic conjecture? Heart Fail Monit 2005;4:123–9.
3. 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;83:754–9.
4. Torre-Amione G. Immune activation in chronic heart failure. Am J Cardiol 2005;95:3C–8C.
5. Potteaux S, Esposito B, van Oostrom O, et al. Leukocyte-derived interleukin 10 is required for protection against atherosclerosis in low-density lipoprotein receptor knockout mice. Arterioscler Thromb Vasc Biol 2004;24:1474–8.
6. Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT. Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. J Neuroimmunol 2003;134:128–32.
7. Weishaar RE, Simpson RU. The involvement of endocrine system in regulating cardiovascular function: emphasis on vitamin D3. Endocr Rev 1989;10:351–65.
8. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D_3 and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab 2001;86:1633–7.
9. Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens 1995;8:894–901.
10. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001;358:1500–3.

The American Journal of Clinical Nutrition