Can Vitamin D Supplementation Improve Physical Function and Quality of Life in Older Patients With Heart Failure?

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lthough early research on vitamin D focused on the effects of vitamin D deficiency on bone metabolism, more recent work has found a vast variety of roles for vitamin D throughout the body. Studies suggest that too little vitamin D might increase the risk for conditions as diverse as cardiovascular disease, cancer, autoimmunity disease, and depression. The optimal level of vitamin D is not known, but there is general agreement that serum 25-hydroxyvitamin D <50 nmol/L (20 ng/mL) represents deficiency. However, some researchers have suggested that levels >80 nmol/L may be required for optimal health.

Vitamin D deficiency is common in patients with heart failure, and adequate vitamin D may reduce disease progression and symptom severity through suppression of the renin-angiotensin-aldosterone system, suppression of parathyroid hormone, reduction of cardiac remodeling, and improvement in muscle strength. As an adjunct to pharmacological treatment of heart failure, vitamin D supplementation is appealing. Vitamin D can be obtained from sun exposure, over-the-counter dietary supplements, and prescription formulations. It has several potential additional benefits, including reducing the risk for falls, and few known adverse effects until high serum concentrations are reached (25-hydroxyvitamin D ≥374 nmol/L).

In this issue of *Circulation: Heart Failure*, Witham et al present the results of a randomized, double-blind, placebo-controlled trial testing the hypothesis that intermittent vitamin D supplementation improves physical function, as assessed with a 6-minute walk test, in older patients with systolic heart failure. Secondary outcomes include the timed up-and-go test, the Functional Limitation Profile, the Minnesota Living with Heart Failure questionnaire, physical activity assessed using accelerometers, and concentrations of renin, aldosterone, B-type natriuretic peptide, and tumor necrosis factor-α. There was no significant difference between the supplementation and placebo groups on the 6-minute walk test at 10 or 20 weeks. In fact, the treatment group had a slightly lower walking distance at 20 weeks compared with a slightly higher walking distance in the placebo group, although the difference was much smaller than the 30-m minimum clinically significant difference. There was a small, but statistically significant, decrease in quality of life in the treatment group. On the other hand, there was also a decrease in B-type natriuretic peptide. No significant differences were seen in other secondary outcomes.

This trial was well designed with a primary outcome that has been shown to be a good marker of physical function in older populations and secondary outcomes that measured quality of life and important physiological and biochemical markers of heart failure status. The directly observed administration of the vitamin D supplementation ensured 100% compliance with the study treatment. The study was well powered for the primary outcome, and a higher than expected percentage of participants completed the trial (96 of 105 randomly assigned). The results were robust to sensitivity analyses that adjusted for baseline imbalances, assumed a walk distance of 0 for missing observations, or examined the percentage of change in the walk distance. The trial lasted 20 weeks, long enough for many of the hypothesized effects of vitamin D to manifest and as long as, or longer than, studies that showed effects of other interventions in heart failure populations. The study population reflects the type of patients with systolic heart failure often seen in clinical practice. However, patients with heart failure with preserved systolic function, who make up a large proportion of the heart failure population, were not included in this study.

Does this mean that treatment with vitamin D cannot improve physical function and quality of life in older patients with systolic heart failure? It is certainly possible that vitamin D does not have important effects on heart failure or on heart failure in older populations. There is a history of nutritional supplement trials that showed no beneficial effect despite promising epidemiological and preclinical studies. As the authors note, these patients could be too far along the disease course for vitamin D to make a difference. The vitamin D dose could also be too low to see benefits in these patients who were deficient at baseline.

In this study, the treatment was 100 000 IU of ergocalciferol given at baseline and 10 weeks for a total dose of 200 000 IU. The 25-hydroxyvitamin D in the treatment group was 19.5 nmol/L higher at 20 weeks than baseline. However, baseline levels were low (only 20.5 nmol/L), and the post-supplementation average was 40.0 nmol/L, which is still in the deficient range. Therefore, it may not be surprising that a benefit was not observed. Commonly used treatment regimens in the United States include 50 000 IU per week for 4 weeks followed by 50 000 IU per month for 5 months, 50 000 IU per month for 6 months, and 50 000 IU 3 times per week for 6 weeks. By using these more intensive regimens,
patients achieved 25-hydroxyvitamin D \( \geq 50 \text{ nmol/L} \) in 55%, 86%, and 95% of cases, respectively.\(^6\) Even correcting frank deficiencies in vitamin D may not be enough to reap all of the potential health effects. Some authors consider levels between 50 and 75 nmol/L as “insufficient” vitamin D.\(^1\) Above 75 nmol/L, parathyroid hormone reaches its nadir and calcium absorption plateaus.\(^1\) Among patients treated for low vitamin D, those who received a total dose of \( \leq 300,000 \text{ IU} \) were 7-fold more likely to have insufficient 25-hydroxyvitamin D at the end of treatment than those who received \( \geq 600,000 \text{ IU} \).\(^6\) Although vitamin D intoxication is a serious complication of excessive supplemental intake, intoxication occurs at much higher levels of 25-hydroxyvitamin D (\( \geq 374 \text{ nmol/L} \)) than those observed in the study by Witham et al.

A previous study randomly assigned younger patients with heart failure to 2000 IU of vitamin D per day plus calcium or only calcium for 9 months.\(^7\) The mean increase in 25-hydroxyvitamin D was \( \approx 67 \text{ nmol/L} \). Although the investigators measured various biochemical and clinical markers, including B-type natriuretic peptide, left ventricular ejection fraction and end-diastolic volume, and maximum oxygen uptake, only the inflammatory markers tumor necrosis factor-\(\alpha\) and interleukin-10 were significantly different between the treatment and placebo groups. Although the 6-minute walk test was not measured in this population, the lack of effect of vitamin D on the physiological parameters does provide an argument against the explanation that the vitamin D was simply too low in the current study.

In summary, Witham et al provide convincing evidence that a regimen of 100,000 IU of vitamin D at 0 and 10 weeks does not improve the 6-minute walk test in older patients with heart failure with vitamin D deficiency. The decrease in B-type natriuretic peptide, a secondary outcome, in the treatment group is intriguing but is counterbalanced by a decrease in quality of life. This high-quality study adds to the body of knowledge about the role of vitamin D in heart failure. Future studies should focus on higher doses to raise vitamin D out of the deficient range.

### Disclosures

None.

### References


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