Looking for a Brighter Future in Heart Failure
A Role for Vitamin D Supplementation?*

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Identifying effective pharmacologic and mechanical therapies for heart failure has been an active and costly endeavor in the past several decades. Significant progress has been made, but the morbidity and mortality from this syndrome continues to be unacceptably high. Thus, it would be an exciting development if a relatively simple intervention such as vitamin D supplementation was shown to improve outcomes in heart failure.

Vitamin D is a steroid hormone that modulates gene transcription by binding a nuclear receptor found in numerous tissues, including the heart and vasculature. One of the genes regulated by vitamin D is renin. Vitamin D acts as an endogenous inhibitor of renin expression (1). Mice with genetic deficiency of either the vitamin D receptor or the 1-alpha-hydroxylase enzyme (which converts 25-hydroxyvitamin D to activated vitamin D), develop hypertension and ventricular hypertrophy (2–4). In the 1-alpha-hydroxylase knockout mice, direct administration of activated vitamin D rescues the phenotype and normalizes left ventricular mass (4). Furthermore, administration of vitamin D analogs to Dahl salt-sensitive rats reduces the degree of left ventricular hypertrophy (5). Vitamin D analogs improve not only left ventricular structure, but also functional parameters of contractility and relaxation (5,6). Pre-clinical data suggest that vitamin D therapy might also favorably influence other pathways of relevance to heart failure, including glucose tolerance, immunity, and vascular remodeling (7–9).

Individuals with heart failure have a high prevalence of vitamin D deficiency (10). Several observational studies have shown an increased risk of incident heart failure and heart failure mortality in individuals with vitamin D deficiency (11,12). These data raise the possibility that vitamin D supplementation, in individuals with vitamin D deficiency, could improve outcomes in heart failure. To date, however, there have been few efforts to test this hypothesis in randomized controlled trials.

In this issue of the Journal, Witte et al. (13) report the results of the VINDICATE (VitamIN D treating patients with Chronic heArt failurE) trial, a randomized, double-blind, placebo-controlled trial of vitamin D supplementation (4,000 IU per day) in patients with symptomatic heart failure. All participants were required to have reduced left ventricular ejection fraction (LVEF ≤45%) and low vitamin D status (25-hydroxyvitamin D <20 ng/ml). The investigators tested the hypothesis that 1 year of vitamin D supplementation would improve the primary endpoint of 6-minute walk distance, and the secondary endpoint of LVEF. Among the 163 patients who completed the trial, oral supplementation effectively raised serum vitamin D concentrations compared with placebo. The primary endpoint, distance on the 6-minute walk test, did not improve in patients randomized to vitamin D compared with placebo. However, vitamin D supplementation did appear to have a favorable effect on LVEF (measured by echocardiography), with an 8% improvement in the active arm.
The study by Witte et al. (13) is an important contribution to a field in great need for robust randomized trial data. Strengths of the study include the blinded, placebo-controlled design, the inclusion of patients on optimal medical therapy (>90% on beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), the focus on individuals with vitamin D deficiency, and the use of meaningful, easily measured endpoints (6-minute walk test and LVEF). Compared with prior vitamin D supplementation trials involving heart failure patients, the Witte et al. study was larger and had a longer follow-up period (8,14-17).

The primary endpoint analysis was negative. The authors, however, noted higher variability in the 6-minute walk test measurements than originally expected. Thus, the study was underpowered to detect clinically relevant differences in this endpoint. The high rate of attrition was also a limitation. Only 73% of the original 223 randomized participants finished the trial. Reasons for dropout are not fully described, though the authors note that participants who dropped out had similar characteristics to those who completed. Because the primary endpoint required attendance at the follow-up examination, an intention-to-treat analysis would not address the reduction in sample size.

How do we interpret the significant secondary endpoint result with LVEF? In light (no pun intended) of the previous experimental data showing beneficial effects of vitamin D on cardiac structure and function, the clinical finding of improved LVEF is intriguing. It is worth noting that the 8% increase in LVEF seen in VINDICATE is in the range of improvement observed with much more complex interventions, such as cardiac resynchronization therapy in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial: Cardiac Resynchronization Therapy) (18). In that trial, each 5% increase in LVEF from baseline was associated with a 28% to 50% reduction in the risk of heart failure hospitalization or death (18).

On the other hand, it is clear that the secondary endpoint findings in the VINDICATE study can be regarded as no more than hypothesis generating. The list of secondary findings from cardiovascular trials that have failed to hold up in subsequent prospective trials is a long one. Prior studies investigating the effects of vitamin D on cardiac structure or function have yielded mixed results, and are difficult to compare given wide variation in doses of vitamin D, endpoints, patient populations, sample size, and treatment duration (15,16,19). The present trial might be a valuable source of additional echocardiographic and biomarker data to inform the design of future studies in heart failure populations. For instance, the authors did not specifically note whether vitamin D therapy had a beneficial effect on left ventricular mass or measures of diastolic function. Furthermore, measurement of plasma renin activity, inflammatory markers, and insulin resistance at baseline and follow-up could indicate whether vitamin D supplementation directly influenced pathways that promote adverse cardiac remodeling.

Given the low cost and safety of vitamin D supplementation, we believe that the question of whether vitamin D benefits heart failure patients should be tested in larger randomized trials. Such a trial should focus on individuals who would be most likely to benefit from vitamin D supplementation (e.g., those with low vitamin D status at baseline and evidence of reduced LVEF and/or adverse cardiac remodeling). The doses of vitamin D should be high enough to ensure a sizeable increase in 25-hydroxyvitamin D concentrations, as was observed in the VINDICATE study. This is important because nonprotocol use of vitamin D supplements or multivitamins containing vitamin D has been common in other placebo-controlled studies of vitamin D (20,21). Last, the selection of endpoints for a larger trial deserves careful consideration. Although improvements in LVEF or left ventricular mass are informative, clinical endpoints clearly matter the most. Another trial with an intermediate endpoint is unlikely to change how clinicians approach the common scenario of a heart failure patient with vitamin D deficiency. In contrast, a definitive trial on this topic would have substantial implications for both patient care and public health.

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REFERENCES

2. Xiang W, Kong J, Chen S, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the...


