Vitamin D deficiency and insufficiency, defined by circulating concentrations of 25-hydroxyvitamin D [25(OH)D], have garnered increasing attention in clinical medicine and research. The vitamin D receptor regulates diverse biologic systems, including calcium and bone metabolism, renin-angiotensin activity, inflammation, and muscle functioning (1,2). Lower serum concentrations of 25(OH)D are associated with many chronic diseases across a range of cohort studies (3,4). Serologic testing for 25(OH)D and empirical therapy with vitamin D supplements have increased substantially worldwide, with significant costs. Large clinical trials are now underway to determine whether vitamin D supplementation can improve cardiovascular outcomes, bone, and cancer outcomes in the general population (5).

Nephrologists have long recognized disturbances in vitamin D metabolism among patients who have CKD. In contrast to substrate 25(OH)D deficiency found in the general population, the primary metabolic defect in CKD is a decline in 1,25-dihydroxyvitamin D [1,25(OH)2D], the biologically potent form of vitamin D. Causes of reduced 1,25(OH)2D in CKD are multifactorial, including reduced functional renal mass and inhibition of 1-α hydroxylase by fibroblast growth factor-23, phosphate excess, and metabolic acidosis (6,7). Treatment with 1,25(OH)2D or related analogs has been the mainstay of vitamin D therapy in ESRD patients; however, vitamin D substrate (cholecalciferol and ergocalciferol) can also stimulate pathways responsive to the vitamin D receptor in CKD through localized production of 1,25(OH)2D in nonrenal sites, stimulation of 1-α hydroxylase activity in residual kidney tissue, or both (8). Therefore, there is growing interest in whether vitamin D supplementation can improve patient outcomes in CKD.

In this issue of CJASN, Hewitt et al. (9) take an important step forward by conducting a clinical trial of cholecalciferol supplementation on skeletal muscle function in chronic dialysis patients. The loss of muscle function (sarcopenia) is a frequently overlooked but important consequence of kidney failure, with serious clinical and quality-of-life implications (10). In the current study, 60 chronic dialysis patients who had serum 25(OH)D concentrations≤24 ng/ml were randomly assigned to receive 50,000 IU oral cholecalciferol or matching placebo weekly for 8 weeks and then monthly for 4 months. A total of 21 patients in the cholecalciferol group (70%) and 24 patients in the placebo group (80%) returned for scheduled 6-month follow-up evaluations. Over the 6-month follow-up period, cholecalciferol significantly increased serum 25(OH)D and 1,25(OH)2D concentrations compared with placebo. However, there were no differences between the treatment groups in the primary study outcomes of upper- and lower-extremity muscle strength. Similarly, there were no differences in secondary study outcomes of 6-month serum levels of parathyroid hormone, bone alkaline phosphatase, and C-reactive protein, and there were no differences in end-of-study pulse wave velocity, BP, or quality of life.

Hewitt et al. (9) should be commended on several important aspects of their study that can help inform future clinical trials in nephrology. First, by conducting an interventional trial, Hewitt et al. (9) minimized the potential for confounding, the primary limitation of observational studies of vitamin D. Second, Hewitt et al. (9) selected a primary study outcome, skeletal muscle performance, that is clinically important while minimizing attention on parathyroid hormone, a common but clinically ambiguous outcome of vitamin D studies. Third, the study used broad entry criteria with minimal exclusions and simplified treatment and monitoring procedures to enhance generalizability and increase participant retention. Of 70 subjects who met study eligibility criteria, 60 subjects participated in the trial. Fourth, the study took advantage of frequent scheduled contacts for in-center hemodialysis patients to directly administer the study medication and increase compliance.

The obvious weaknesses of the study are the small sample size and loss of some participants during follow-up. The small sample size enables the study to exclude only large effects of cholecalciferol on skeletal muscle function in dialysis patients; small or moderate effects with potential clinical importance remain possible. Although physical activity interventions can substantially improve muscle strength in general and geriatric study populations, medications alone are unlikely to produce such large changes. The inclusion of baseline physical performance values in the analysis could have increased study power. In addition, it is important to recognize that loss to follow-up in a
study of repeated measurements can lead to bias. For example, preferential loss of relatively weaker patients in the cholecalciferol treatment group would increase 6-month mean values of muscle function in that group independent of a true treatment effect. Interim measurements of study outcomes can mitigate this problem to some extent.

The study was not designed to investigate potential independent or joint effects of supplemental and activated vitamin D therapies. It is possible that effects of cholecalciferol treatment on skeletal muscle function were blunted among study participants who were concomitantly receiving oral calcitriol. Possible independent, synergistic, or antagonistic effects of supplemental and activated vitamin D therapies in CKD are best evaluated in larger clinical trials using a factorial design.

What are appropriate next steps forward? A larger trial with longer follow-up could detect possible subtle effects of cholecalciferol on skeletal muscle function in chronic dialysis patients. Broadening the study population to include nondialysis CKD patients would also be important, because skeletal muscle may be more amenable to intervention at an earlier stage of disease and residual kidney function may play an important role in cholecalciferol response. Alternatively, the effects of vitamin D therapies on skeletal muscle function could be determined within the context of a considerably larger, long-term randomized trial of clinical outcomes among CKD patients. Such a trial could address the choice of vitamin D therapy by evaluating supplement and activated vitamin D treatments separately and combined. Most importantly, a large-scale, long-term trial of clinical outcomes would determine the overall net benefits and risks of vitamin D therapies on CKD patient health, while evaluating effects of vitamin D interventions on other relevant pathways. Such data are conspicuously absent from the current literature.

Disclosures
None.

References

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Effects of Cholecalciferol on Functional, Biochemical, Vascular, and Quality of Life Outcomes in Hemodialysis Patients,” on pages 1143–1149.