What Is the Role of Vitamin D Supplementation on Vascular Health in CKD?

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The importance of synthesis of 1,25 dihydroxyvitamin D or 1,25(OH)2D (calcitriol) in the kidney is well documented, and alterations in vitamin D metabolism, ubiquitous in patients with CKD, are a key feature of CKD mineral and bone disorder (CKD-MBD). The progressive decrease in calcitriol synthesis with CKD, and subsequent development of secondary hyperparathyroidism (SHPT), is an active process primarily mediated by the counter-regulatory effects of increasing levels of the phosphaturic hormone, fibroblast growth hormone 23.

Availability of 1-α hydroxylase (also known as CYP27B1), a key enzyme involved in the conversion of 25-hydroxyvitamin D (25(OH)D) to 1,25(OH)2D, is reduced as kidney mass declines. This enzyme is highly dependent on the substrate 25(OH)D, and reduced availability of this substrate in patients with CKD also has an important role in 1,25(OH)2D deficiency and SHPT. Reduced sun exposure, impaired skin synthesis of vitamin D, and dietary restrictions contribute to the high prevalence of 25(OH)D deficiency in CKD.

There is a growing body of evidence showing that vitamin D is pivotal to good health in the CKD population. The biologic effects of vitamin D extend beyond calcium metabolism in experimental and epidemiologic data. Observational studies report vitamin D deficiency is associated with hypertension, cardiovascular disease and mortality, in both the general population (1) and patients with CKD (2), and therefore may be a potentially modifiable cardiovascular risk factor. One meta-analysis reported increased mortality in patients with CKD with a relative risk of 0.86 (95% confidence interval, 0.82 to 0.91) per 10 ng/ml decrease in 25(OH)D levels (2); another suggested vitamin D replacement confers a 27% (95% confidence interval, 8 to 56%) risk reduction in cardiovascular mortality when administered to patients with CKD (3). Vitamin D deficiency has been implicated in endothelial dysfunction and in vitro studies demonstrate treatment with vitamin D analogs abrogates osteogenic processes and inhibits mineralization in vascular smooth muscle cells (4), as well as having anti-inflammatory effects (5).

Active vitamin D therapy (calcitriol or vitamin D analogs) has been the predominant treatment for SHPT in patients with CKD for many decades. This therapy inhibits parathyroid hormone (PTH) secretion via the vitamin D receptor and, in addition to tissues involved in mineral homeostasis, this receptor has been identified in many organs including vascular smooth muscle, endothelial cells, and cardiac tissue.

Nutritional vitamin D supplementation with vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) has not been as extensively or systematically investigated in the CKD population, and clinical trial evidence of its effect on cardiovascular risk or outcomes in patients with CKD is lacking. Recent studies have reported the effectiveness of calcifediol, a vitamin D prohormone, to treat SHPT (6). Calcifediol, also called calcidiol or 25(OH)D, is converted to calcitriol by CYP27B1 and inhibits the catabolism of both 25(OH)D and 1,25(OH)2D, thus increasing levels of both. Few studies, however, have assessed benefits of calcifediol beyond mineral metabolism in patients with CKD.

Numerous experimental studies have supported the potential effect of vitamin D on vascular tone, including altered vascular oxidative stress and smooth muscle function, and multiple clinical trials have explored the effects of vitamin D therapy (nutritional and active vitamin D) on surrogate markers of cardiovascular risk in patients with CKD, including several studies involving assessment of vascular stiffness. Vitamin D induces concentration dependent increases in endothelial nitric oxide production (7), and small observational and case control studies report an improvement in endothelial function with vitamin D supplementation (8). There is inconsistent evidence to date, however, to suggest that vitamin D improves indicators of vascular function and arterial stiffness, and this may relate to the heterogeneity in study designs (9). With conflicting literature, more evidence is needed to examine the hypothesis that vascular tone could be the physiologic mechanism by which vitamin D confers cardiovascular protection in CKD.

In this issue of the Clinical Journal of the American Society of Nephrology (CJASN), two randomized controlled trials (RCTs) are presented exploring the effects of vitamin D therapy on vascular function. Although both had only moderate-sized study cohorts and relatively short follow-up periods, both studies are extremely well conducted clinical trials, novel and unique in their study designs, and provide further understanding on the pleiotropic effects of vitamin D on numerous tissues, including endothelial and vascular smooth muscle cells.

Firstly, Levin et al. (10) report a double-blind placebo-controlled trial to assess the effectiveness of vitamin D
supplementation on pulse wave velocity (PWV). PWV, a marker of arterial stiffness, is affected by endothelial and smooth muscle function, fibrous tissue and calcification, and is an independent predictor of cardiovascular disease and mortality. Levin et al. (10) compared fixed doses of oral calcifediol (5000 IU), calcitriol (0.5 μg) or placebo, administered three times weekly for 6 months, in 119 patients with CKD stages 3b and 4. Study medication was given irrespective of 25(OH)D levels and all study participants received renin-angiotensin-aldosterone system blockers. Despite randomization, there was an imbalance in baseline PWV measurements, with higher readings in the placebo arm, although adjustments were made in the analyses for this discrepancy. In the 87 participants who completed the study, a decrease in PWV was observed in the calcifediol group, with no change in the calcitriol group and an increase in those on placebo. Although potentially underpowered on the basis of the investigators’ initial sample size calculation, with a moderately high attrition rate for a 6-month study, Levin et al. (10) report that PWV was significantly different between combined vitamin D groups (mean change, −0.4; 95% confidence interval, −1.2 to 0.4 m/s) and placebo (mean change, +1.1; 95% confidence interval, −0.1 to 2.2 m/s).

A reduction in PTH was observed in both the calcifediol and calcitriol groups, and 25(OH)D levels were significantly elevated with calcifediol, but not with calcitriol. These findings are consistent with known effects of these vitamin D agents because calcifediol does not induce CYP24A1 (an enzyme which readily catabolizes 25(OH)D and 1,25(OH)2D), unlike calcitriol. It is difficult to distinguish the effect of vitamin D supplementation or change in PTH levels on the improvement in PWV in this study, although participants who achieved the highest 25(OH)D levels at the end of the 6-month period were those with a significant decrease in PWV.

In the second RCT, Kendrick et al. (11) compared the effects of oral calcitriol and cholecalciferol on another surrogate marker of vascular health, flow-mediated dilation (FMD). FMD, which reflects endothelium-dependent and nitric oxide–mediated arterial function, is a noninvasive approach to examine vasodilator function in vivo. Kendrick et al. (11) assessed 128 patients, again with CKD stages 3b and 4, but with vitamin D deficiency, defined as 25(OH)D levels <30 ng/ml. In this double-blinded study, participants were randomized to receive either oral cholecalciferol (4000 IU daily for 1 month, then 2000 IU daily) or calcitriol (0.25 μg daily for 1 month, then 0.5 μg daily). Brachial FMD and endothelium-independent dilation were performed at baseline and 6 months. At study end, in the 115 participants who completed the trial, there was no difference in FMD between the two arms or changes in brachial arterial dilation to nitroglycerin, in contrast to investigators’ hypothesis that calcitriol would be more effective than cholecalciferol. There was also no change in total vascular endothelial cell expression of NFkB or in markers of inflammation. Given that many of these factors are potential mechanisms for the development and progression of left ventricular hypertrophy, the negative findings in this study may explain why recent RCTs assessing the effect of vitamin D therapy on this cardiac end point have not proved to be positive (12,13).

As expected, Kendrick et al. (11) showed a significant reduction of PTH in the calcitriol group, although not with cholecalciferol, and 25(OH)D levels increased with cholecalciferol, although not calcitriol. An increase in fibroblast growth hormone 23 was reported in both arms and, as expected, there was a reduction in albuminuria with calcitriol, consistent with prior evidence that active vitamin D reduces proteinuria (14). Of note, only two thirds of participants were taking renin-angiotensin-aldosterone system blockers in this study.

Levin et al. (10) and Kendrick et al. (11) should be commended for their important RCTs, further adding to our understanding of vitamin D and vascular health; however, there remains uncertainty about the effectiveness of vitamin D supplementation on vascular endpoints in patients with CKD, as not all results are consistent with previously published studies. Other RCTs have reported benefits of vitamin D on FMD in patients with CKD, including the Paricalcitol and Endothelial Function in Chronic Kidney Disease trial with paricalcitol (15), and another more recent trial in this month’s issue of the *Journal of the American Society of Nephrology* (16). Kumar et al. (16) studied 120 nondiabetic patients with CKD stages 3 and 4 and vitamin D deficiency (25(OH)D levels ≤20 ng/ml) and assessed the effect of cholecalciferol (300,000 IU administered at baseline and 8 weeks) compared with placebo on FMD over 16 weeks. FMD was increased with cholecalciferol but not with placebo, and changes correlated with 25(OH)D levels, findings in contrast to the RCT by Kendrick et al. (11), although the latter did not involve a placebo arm. Kumar et al. (16) also reported a benefit of vitamin D therapy on nitroglycerin-mediated dilation and on PWV, the latter finding consistent with results of the RCT by Levin et al. (10).

The RCTs in this edition of *CJASN* are timely with the recent publication of the updated Kidney Disease Improving Global Outcomes CKD-MBD clinical guidelines (17). The safety of active vitamin D therapy in patients who are predialysis, with the risk of hypercalcemia and potential promotion of vascular calcification, remains a concern as highlighted in recent RCTs (12,13). Kendrick et al. (11) also reported higher rates of hypercalcemia as well as hyperphosphatemia, with 11% of participants in the calcitriol arm commenced on phosphate binders during the study period. This concern with active vitamin D therapy has resulted in the revision of recommendations by the Kidney Disease Improving Global Outcomes CKD-MBD work group, with administration of calcitriol and vitamin D analogs now not routinely recommended in patients who are predialysis, unless for the treatment of severe and progressive SHPT (17).

The potential effect of vitamin D supplementation on vascular endothelial and smooth muscle function in patients with CKD continues to be of significant interest. Despite the excellent studies presented in this edition of *CJASN*, we remain in the dark regarding optimal thresholds for vitamin D replacement, and preferred formulations and doses to affect vascular health. However, current evidence would generally support cardiovascular benefits of improved vascular compliance and endothelial-dependent vasodilation with any vitamin D supplementation (cholecalciferol, calcifediol, or active vitamin D) in patients with CKD, with advantages on vascular health perhaps outweighing potential harms of these medications. Future clinical trials may need to focus on graduated dose increases of vitamin D supplementation and pharmacodynamic data in combination with hard cardiovascular clinical outcomes to further inform clinical practice.
Disclosures
None.

References

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See related articles, “Randomized Controlled Trial for the Effect of Vitamin D Supplementation on Vascular Stiffness in CKD,” and “Cholecalciferol, Calcitriol, and Vascular Function in CKD: A Randomized, Double-Blind Trial,” on pages 1447–1460 and 1438–1446, respectively.