Vitamin D deficiency and chronic kidney disease risk: cause or merely association?

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One aspect of chronic kidney disease (CKD) is unquestioned: whether it is early renal impairment or once end-stage disease ensues, vitamin D concentrations are inadequate to maintain optimal mineral balance. In healthy subjects, vitamin D’s role in disease prevention runs the gamut of cancer to diabetes, with only bone health firmly established. Even its essential role in bone health is dependent on sufficient calcium intake.

The interest in vitamin D’s possible role in health maintenance is clouded by the expansive use of measuring serum 25-hydroxyvitamin D [25(OH)D] concentrations in the healthy population combined with the debate as to what constitutes a “normal” serum concentration (1). That confusion has resulted in the measurement of 25(OH)D concentrations becoming one of the most common laboratory tests in a general physician’s office. Simultaneously, vitamin D supplement use has become commonplace in the general population (2), with many subjects consuming doses of vitamin D that exceed the Institute of Medicine’s (IOM) Recommended Dietary Intake of 600 IU/d for individuals aged 1 to <70 y and 800 IU/d for those >70 y old (3).

This confluence of excessive measurement of 25(OH)D concentrations and use of vitamin D supplements has raised concerns about increased adverse outcomes in the healthy population. Whether vitamin D supplementation, together with calcium supplementation or not, is even beneficial for the prevention of osteoporotic fractures remains controversial (4). Treatment has been associated with an increased risk of nephrolithiasis. What is less well known is how often excessive vitamin D intake with and without calcium supplementation produces more subtle symptoms such as constipation, nausea, fatigue, volume depletion, and altered mental state, and how often it induces hypercalcemia and hypercalciuria.

In renal patients who are most in need of careful management of the CKD-associated bone and mineral disorder (CKD-MBD), vitamin D supplementation has become worldwide clinical practice. In line with this practice, the recently updated Kidney Disease Improving Global Outcomes guidelines on CKD-MBD suggests that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (5). Because no randomized controlled trials with hard endpoints on the effects of vitamin D or its derivatives have ever been conducted in patients with CKD, it remains uncertain whether nutritional vitamin D supplementation improves the progression of CKD, the incidence of fractures or cardiovascular events, other hard outcomes, or quality of life (6, 7).

In this issue of the Journal, an analysis of the Korea National Health and Nutrition Survey (KNHANES) carried out between 2008 and 2015 examined a possible role of vitamin D deficiency in kidney function (8). The authors examined data on 33,210 healthy individuals. The analysis demonstrated an association of low serum 25(OH)D concentrations with glomerular hyperfiltration, a putative contributor to the risk of CKD. The 25(OH)D concentration, below which there was a higher prevalence of hyperfiltration, was 10 ng/mL. The relative risk of hyperfiltration was significantly higher in subjects with 25(OH)D concentrations <10 ng/mL than in those with concentrations ≥30 ng/mL. A concentration <10 ng/mL is considered profound vitamin D deficiency; the appropriate 25(OH)D concentrations for healthy subjects is ≥20 ng/mL as per the IOM and >30 ng/mL per the US Endocrine Society (3). In the KNHANES data set, the population’s mean (±2 SD) 25(OH)D concentration was 17.9 (±13.0) ng/mL, with 8% of the study participants <10 ng/mL. This suggests that the majority of the Korean population surveyed had vitamin D insufficiency or deficiency, whatever the optimal target definition used, and thus was reasonably representative of healthy individuals elsewhere.

The KNHANES study was motivated by numerous previous reports as summarized by Teumer et al. (9). These include an association between vitamin D deficiency and an increased risk of adverse clinical outcomes in patients with CKD. Included in their assessment were observational studies on an association between vitamin D status and renal function. Some of them suggested a beneficial effect, and others suggested no association, mixed results, or even a harmful effect. The KNHANES finding of

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Abbreviations used: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-associated bone and mineral disorder; eGFR, estimated glomerular filtration rate; IOM, Institute of Medicine; KNHANES, Korea National Health and Nutrition Survey; 1,25diOHD, 1,25diOH vitamin D; 25(OH)D, 25-hydroxyvitamin D.

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an inverse association between serum 25(OH)D concentrations and estimated glomerular filtration rate (eGFR) adds another piece of evidence to this issue. On the positive side, the study has a large sample size, and the starting hypothesis relies on biological plausibility. On the negative side, glomerular filtration rate has been estimated, not measured with one of the gold standard methods, and therefore is less reliable, especially in people whose kidney function is in the normal range. Moreover, information on medication use was lacking. Most importantly, observational studies cannot provide confounding, the observed association could be only indirect, due to factors not included in the analysis.

Teumer et al. (9) recently conducted a Mendelian randomization study that can partly overcome the problem of proving causality. These investigators examined the association of serum 25(OH)D with kidney function, using several large cohorts that included a total of >200,000 individuals, and selecting single-nucleotide polymorphisms previously reported to be associated with 25(OH)D concentration (9). They found a negative impact of 25(OH)D and also of 1,25-dihydroxy vitamin D (1,25-dioH) concentrations on eGFR, lending support to the results of the KNHANES study. However, the clinical significance of the observed link between 25(OH)D and eGFR is uncertain because only 1,25-dioH exerts significant biological activity (10). Because CKD causes a decrease in 1,25-dioH synthesis and circulating concentrations, and this could confound positive or negative associations between 25(OH)D or 1,25-dioH and kidney function, Teumer et al. (9) performed a subgroup analysis, stratifying individuals in 2 groups with eGFR greater than or less than 60 mL·min⁻¹·1.73m⁻². Whereas 1,25-dioH continued to have positive impacts on eGFR in either subgroup, 25(OH)D exerted a negative impact in the non-CKD population but a positive impact on kidney function in the patients with CKD. This finding is in agreement with the KNHANES data, although it does not provide definitive proof (8).

Whether these observations likely represent a cause to maintain healthy serum 25(OH)D concentrations or are only a surrogate parameter for healthy 1,25-dioH concentrations or negative associations between 25(OH)D or 1,25-dioH and kidney function is uncertain because only 1,25-dioH exerts significant biological activity (10). Based on knowledge, the findings clearly do not suggest that increasing one’s intake of vitamin D will afford protection against the development of renal disease or its progression other than maintaining a diet rich in those foods known to be naturally a good source of vitamin D. To do otherwise may add further to inappropriately frequent measurements of 25(OH)D concentrations and uncertain benefit of promoting vitamin D supplements in the general population’s pursuit of better health. We need to understand better for whom vitamin D supplementation will improve health outcomes.

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