Pioneering studies in the 1970s demonstrated that CKD leads to substantial perturbations in the vitamin D endocrine system and, as a result, bone loss (1–4). In particular, in CKD, renal production of 1,25-dihydroxyvitamin D (1,25(OH)2D) from 25-hydroxyvitamin D (25(OH)D) is markedly reduced, leading to low circulating 1,25(OH)2D concentrations. Insufficient 1,25(OH)2D contributes to the development of secondary hyperparathyroidism and osteitis fibrosa. Moreover, 1,25(OH)2D treatment lowers circulating parathyroid hormone (PTH) concentrations and reigns in excessively high bone turnover (5,6).

More recently, it has become clear that insufficient 1,25(OH)2D may contribute to a wide variety of non-bone health problems. The vitamin D receptor (VDR) is present in virtually all cells. 1,25(OH)2D complexes with the VDR and coreceptors to regulate transcription by binding to vitamin D response elements, which are present in the promoter region of hundreds of human genes. Through this mechanism, 1,25(OH)2D regulates cell proliferation and differentiation, immune cell function, and a number of tissue-specific processes.

Interestingly, the effect of 1,25(OH)2D may be greatest on the organ that produces it in greatest quantity—the kidney. In animals, 1,25(OH)2D and its analogs potentiate the transcription of renin in the juxtaglomerular apparatus and exert direct prosurvival effects on podocytes, preventing damage and apoptosis (7–13). In diverse kidney injury models, 1,25(OH)2D and its analogs reduce albuminuria, glomerulosclerosis, and loss of GFR (7–9). Importantly, these effects appear to be synergistic with those of renin-angiotensin inhibitors, suggesting that 1,25(OH)2D may offer a useful addition to standard CKD care (9).

Still unknown is the degree to which 1,25(OH)2D deficiency affects the human kidney in vivo and—more importantly—whether vitamin D–related treatments can improve kidney health. Short-duration clinical trials have consistently demonstrated that treatment with 1,25(OH)2D or an analog reduces urine albumin excretion (14,15). Over the short term, treatment with 1,25(OH)2D or an analog also lowers estimated GFR. In the PRIMO (Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity) trial, this effect, combined with an imbalance of baseline GFR, may have contributed to an excess progression to ESRD (six patients versus one patient over 48 weeks) (16). Whether continued treatment with 1,25(OH)2D or an analog leads to progressive GFR loss or long-term renoprotection, as with renin-angiotensin system inhibitors, remains to be determined.

“Nutritional” forms of vitamin D, such as cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2), are an interesting and promising alternative treatment to 1,25(OH)2D. These agents require metabolism to 25(OH)D and then 1,25(OH)2D to tightly bind the VDR. Because the conversion of 25(OH)D to 1,25(OH)2D is tightly regulated, nutritional vitamin D supplementation leads less to toxicity, particularly hypercalcemia, than does 1,25(OH)2D treatment. Moreover, tissue-specific production of 1,25(OH)2D from 25(OH)D may most effectively enhance beneficial paracrine effects of 1,25(OH)2D.

Observational studies of circulating 25(OH)D offer an important tool to gauge the degree to which nutritional vitamin D supplementation may affect health. Circulating 25(OH)D concentration largely reflects the total intake of cholecalciferol and ergocalciferol through cutaneous synthesis and dietary consumption. In this issue of CJASN, Fernández-Juárez et al. report a cohort study testing associations of circulating 25(OH)D concentration with CKD progression and death among 103 people with type 2 diabetes and a urine albumin/creatinine ratio ≥300 mg/g (17). The authors report that 25(OH)D $<15$ ng/ml was associated with substantial increases in the risk of the primary composite outcome (≥50% increase in serum creatinine, ESRD, or death; adjusted hazard ratio, 2.88; 95% confidence interval, 1.84 to 7.67) and the risk of a more limited renal outcome (≥50% increase in serum creatinine or ESRD; adjusted hazard ratio, 3.79; 95% confidence interval, 1.20 to 12.02), compared with 25(OH)D ≥15 ng/ml. A remarkable feature of the report is the magnitude of association, which is substantially larger than that observed in prior studies of 25(OH)D and CKD progression, which have observed smaller (18,19) or null associations (20,21). Together, these studies suggest a large range of potential renal benefit from vitamin D supplementation.

The study by Fernández-Juárez et al. has important strengths, including the measurement of 25(OH)D at three time points near study baseline to improve ascertainment of long-term 25(OH)D exposure, frequent regular follow-up for the primary study outcome, a reasonably long median follow-up of 32 months, and a large number of events observed. Of course, as with other studies in the field, this study also has limitations that must be considered when interpreting
and applying results. These include the focus on a single biomarker, limits to external validity, and potential confounding due to the observational design.

Circulating 25(OH)D is a valuable biomarker because it largely reflects cholecalciferol and ergocalciferol intake, is modifiable with supplementation, and has favorable measurement characteristics, including relatively high circulating concentrations and a long circulating T1/2 of approximately 4 weeks. However, 25(OH)D is also affected by genetic factors (22), regulatory hormones including PTH and fibroblast growth factor-23 (FGF-23), and common CKD treatments. For example, in stage 3–4 CKD, treatment with VDR agonists substantially reduces 25(OH)D concentration by inducing its catabolism (23). Biomarkers of vitamin D metabolism are therefore interrelated. Fernández-Juárez et al. did not measure FGF-23 or 1,25(OH)2D, and it is possible that these biomarkers, PTH, or vitamin D treatments partially explain the observed association of low 25(OH)D with study outcomes. More importantly, it should be recognized that supplementation with cholecalciferol and ergocalciferol is likely to affect more than just 25(OH)D.

The study from Fernández-Juárez et al. derives from a multicenter clinical trial in Spain. Similarities between participants due to geographic proximity may help reduce bias and improve internal validity, which can help identify important relationships. As a trade-off, homogeneity also limits external validity. In community-based populations, associations of 25(OH)D with nonrenal clinical outcomes have been reported to vary by race/ethnicity and by polymorphisms in the VDR gene (24,25). Results may therefore not necessarily extrapolate to more geographically or racially diverse populations. In addition, 25(OH)D assays vary in quality and calibration. Without careful calibration to an accepted standard, such as that provided by the National Institute of Standards and Technology, and without careful statistical analyses focused on identifying a suitable 25(OH)D threshold associated with disease risk, readers should not assume that the 25(OH)D threshold used in this study (15 ng/ml) is a proven therapeutic target.

Like the observational studies that preceded it, the most important limitation of the study by Fernández-Juárez et al. is its observational design, which can lead to confounding. Physical inactivity, diets low in dairy and oily fish, adiposity, heavy proteinuria, and other unfavorable health habits and conditions lead to low 25(OH)D concentrations. It could be these characteristics, rather than insufficient 25(OH)D itself, that adversely affect the kidney. Observational studies of 25(OH)D are therefore insufficient on their own to change practice.

Clinical trials are necessary to determine the effects of vitamin D supplementation on CKD and other health outcomes. As with 1,25(OH)2D trials, trials of vitamin D supplementation to date have been of short duration. In addition, these trials have mostly focused on vitamin D– and bone-related outcomes, such as circulating 25(OH)D and PTH concentrations, and must have been small in size. Larger, longer trials are needed. Observational studies are critical to designing such trials. For example, observational studies, including that by Fernández-Juárez et al., suggest that the association of circulating 25(OH)D with CKD progression may be largest among people with diabetes, who tend to have greater urine albumin excretion and a faster rate of GFR loss (17,19). On the basis of this observation and others, one ongoing clinical trial (NCT01684722) has enrolled 1320 participants with type 2 diabetes to test the effects of cholecalciferol on urine albumin excretion and estimated GFR over at least 2 years of follow-up.

It is important to note that a single clinical trial rarely answers an important scientific question. Any given trial has a limited target population, a limited nature or dose of intervention(s), and a discrete primary outcome. Given the compelling evidence now supporting potential beneficial effects of vitamin D–related interventions on the kidney and other health outcomes, additional trials in this field are warranted (26).

How should the expanding literature on circulating 25(OH)D concentration, including the article by Fernández-Juárez et al., affect clinical practice? It is quite reasonable to be excited about the prospects of vitamin D as a potential new tool to improve kidney health. However, it remains premature to measure 25(OH)D concentrations or prescribe vitamin D–related therapies for the purpose of improving kidney or other nonbone outcomes. Instead, vitamin D–related therapies should be guided by our knowledge of how CKD affects the vitamin D endocrine system and bone health. In the future, the table may turn, with focus directed instead on the effect of the vitamin D endocrine system on CKD.

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