Cardiovascular disease (CVD) is the major cause of morbidity and mortality in patients with CKD (1,2). There is clear evidence that in patients with CKD on dialysis, the major cause for mortality, morbidity, and hospitalization is relentless CVD (3). This excess cardiovascular risk is also evident in patients with CKD not yet on dialysis (4,5). The cardiovascular risk factors in the population of patients with CKD can be separated somewhat arbitrarily into traditional risk factors such as hypertension, hyperlipidemia, diabetes mellitus, and family history and a group of risk factors more prevalent in patients with kidney disease, which have been grouped into what is called nontraditional risk factors such as positive calcium and phosphorus mineral balance, secondary hyperparathyroidism, renal osteodystrophy, vascular calcification, vitamin D insufficiency, and more recently described, elevated levels of fibroblast growth factor 23 (FGF23) (6). This collection of abnormalities has also been labeled as the CKD-mineral bone disorder (CKD-MBD) syndrome, with vascular calcification representing one of the most significant risk factors. The majority of patients with CKD overlap these traditional and nontraditional risk factors and have some features of all of them. Patients on dialysis almost uniformly have vascular calcification at the start of dialysis, and the condition progressively worsens with time on renal replacement therapy. The relationship between CKD and CVD is thought to be mediated in part by inflammatory cytokines (7,8). Markers of inflammation such as the inflammatory cytokines TNF-α, IL-6, and C-reactive protein promote and accelerate atherosclerosis and are associated with a rapid decline in renal function and an increased risk of death (7–9). These markers contribute to a cascade of events that produce an injury pattern to the intimal layer of blood vessels, which in all likelihood leads to ischemic cardiovascular events such as myocardial infarction, stroke, and peripheral vascular events (8,10).

An independent body of evidence links mineral and bone disorders with CVD in patients with CKD. Vascular calcification represents a hallmark clinical condition that is strongly associated with CVD (11). However, the blood vessel injury associated with vascular calcification does not typically lead to classic ischemia but rather to disorders of compliance and stiffening of the arterial tree. There is a strong body of evidence demonstrating that mineralization of the blood vessels actually occurs in situ, with production of hydroxyapatite crystals occupying the media of blood vessels in a pattern that might be termed vascular ossification (12). Sudden cardiac death and arrhythmias are much more common cardiac events in dialysis patients who have a very high prevalence of vascular calcification. The enhanced cardiovascular risk may be more related to these CKD risk factors in the dialysis patient than is classic ischemia.

FGF23, a phosphaturic hormone produced in the osteocyte, a transformed osteoblast with neuroendocrine cell characteristics, has been strongly associated with mortality in patients with ESRD on dialysis (4,6), in patients with CKD where it is also linked to progression toward renal failure (10), and more recently, in patients with AKI (13). FGF23 has also been elegantly linked to the development of left ventricular hypertrophy, vascular dysfunction, and vascular calcification (14).

The connection between inflammatory cytokines on the one hand and FGF23 as a representative MBD toxin on the other hand has previously been unclear. In this issue of CJASN, Mendoza et al. (15) demonstrate, for the first time, a strong statistical association, using a logistic regression analysis, between ascending quartiles of FGF23 levels and the highest quartile for inflammatory cytokines derived from the very large Chronic Renal Insufficiency Cohort database. In contrast, parathyroid hormone (PTH) and phosphate were not significantly associated with inflammation, highlighting this unique feature of the connection between FGF23 and risk factors for ischemic CVD. This very large database facilitated the analysis of multiple variables including renal function, vitamin D levels, serum phosphate, PTH, body mass index, age, race, sex, smoking, use of statin drugs, and urinary microalbumin/creatinine ratios, demonstrating the independent association of FGF23 and inflammatory cytokines. Although a link to dysregulation of klotho was not identified, the authors correctly point out that a reliable in vivo klotho measurement is not yet available and that links to elevated FGF23 levels and to depressed levels of klotho thought to be present in CKD are at present theoretical and must await a suitable assay to be properly tested in patients. Another potential link between FGF23 and inflammation is in a connection with elevated leptin.
levels noted in both CKD and obesity (16,17). Leptin is strongly associated with inflammation, and leptin injection in mice stimulated the production of FGF23, thus raising the possibility that leptin is a mediator between these two arms of the CVD risk triangle (17). This hypothesis, however, remains to be tested in humans.

Although FGF23 and inflammation are both independently associated with CVD, which comes first in the CVD spiral is unclear from the data presented. Nevertheless, the cross-sectional design of the study places limits on the interpretation of the directionality of the connection and of course on the causality. However, this connection most certainly represents a missing piece in a complex pathophysiological puzzle. Previously, associations with multiple seemingly independent variables and cardiovascular risk were highlighted (1,2,4). Traditional cardiovascular risk factors and ischemic risks are clearly evident in our CKD patients. Nontraditional MBD risk factors are also highly prevalent in this population. What can be surmised from the work presented in the current paper is that both these sets of risk factors coexist in the patient with CKD. Finding the connecting piece allows us to go forward and begin the process of identifying modifiable variables that can be targeted. Lowering FGF23 levels with dietary modifications such as low protein and/or low phosphate intake can now be tested in patients with CKD. Rather than depending on long-term outcome data, measurements of the effects of such interventions on inflammatory cytokine levels could readily identify and isolate interventions that might be useful clinically. Ultimately, the aim of this line of reasoning and future research is to apply an intervention grounded with physiological evidence that can alter the natural history of CKD and CVD, reducing the strikingly high cardiovascular mortality in our patients with CKD.

Disclosures
None.

References

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