Chronic Kidney Disease–Mineral and Bone Disorder
Personal Perspective after the 2017 KDIGO CKD-MBD Guideline Update

By Markus Ketteler

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Although a reasonable number of high-quality studies were published between 2009 and 2017, significant gaps in the knowledge base about the optimized treatment approaches for patients with features of CKD–MBD still exist. Nevertheless, I would like to briefly feature three developments that were stimulated by the recent KDIGO CKD–MBD update publication that may improve the treatment of patients in the future, at least from my subjective point of view:

- Diagnosis and management of osteoporosis in CKD patients
- Fibroblast growth factor-23 (FGF23) as a biomarker
- Role of nutritional vitamin D in CKD

Osteoporosis in CKD
Among the most prominent changes in the 2017 guideline update were recommendations about the clinical handling of suspected osteoporosis in patients in all stages of CKD. First, dual-energy X-ray absorptiometry for determining bone mineral density became recommended as a reasonable diagnostic test for assessing fracture risk, if the results may qualify FGF23 as a longitudinal marker of CKD severity and cardiovascular consequences. In this context, further insights about the power of available medications to substantially lower FGF23 blood levels (e.g., calcimimetics, phosphate binders) may thus have an impact on treatment modalities if FGF23 lowering can be proved to associate with improved patient-meaningful outcomes in randomized controlled trials.

Management of vitamin D status
The current recommendations about vitamin D deficiency and insufficiency from the original KDIGO CKD-MBD 2009 guidelines remain oriented toward targets for the normal population as published by most osteoporosis societies and the Institute of Medicine (6). The latter position paper recommended a range of 25-hydroxy-vitamin D levels between 20 and 60 ng/mL as necessary to achieve, and it emphasized the importance of vitamin D for bone health while remaining cautious about the so-called pleiotropic effects on cancer and cardiovascular disease protection, infectious diseases, or autoimmunity. Nevertheless, this unresolved issue triggered a few new study approaches that demonstrated the potentially beneficial effects of high-dose vitamin D3 supplementation with regard to endothelial function and vascular stiffness (7, 8). As reported at the recent ERA-EDTA Congress 2019 in Budapest, the VITALE study found that high-dose vitamin D3 treatment was associated with a lowered risk of symptomatic fracture (1% vs. 4% in low dose, odds ratio = 0.24, p = 0.02) in kidney transplant recipients, although other major study endpoints (cardiovascular events, diabetes incidence, cancer, death) were not reached (9). Further, the results of treatment studies in which extended-release calciferol was used revealed that levels of 25-hydroxy-vitamin D between 50 and 80 ng/mL—even higher than those recommended by the Institute of Medicine (IOM)—are required to effectively control secondary hyperparathyroidism in CKD patients not using dialysis (10–12).

Recently, however, two large randomized controlled trials (ViDa [n = 5108], VITAL [n = 25,871]) failed to demonstrate beneficial effects on cardiovascular and cancer endpoints by high-dose vitamin D3 supplementation in the normal population (13–15). Both trials potentially suffered from the fact that most patients were not in a state of vitamin D deficiency at baseline (actually levels at both baseline and the end of study were within the IOM recommended range in the two trials). A recent subgroup analysis of VITAL (VITAL-DKD) in patients with type 2 diabetes mellitus (n = 1,312) reported no significant difference in the change of estimated glomerular filtration rate with vitamin D supplementation (16). Nonetheless, follow-up periods of 3 or 5 years may still be too short to enable credible conclusions to be reached. It is hoped that further post hoc analyses of subgroups with impaired kidney function may become available from these trials, enabling an informative view on vitamin D supplementation in CKD patients.

Perspective
Guideline publications are always a chance and a challenge. Unanswered questions still need to be pragmatically addressed, and if this is preliminarily done by balanced expert opinion, it will be of great help for the practitioner. When research questions are raised, knowledge gaps may be subsequently closed one by one. In about 3 years from now, the CKD-MBD field will have yet again to be reappraised concerning the accumulated evidence so that...
ever more sustainable advice can be generated for clinical decision-making.

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References


