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MEETING REPORT

The pathophysiology of the chronic kidney disease–mineral bone disorder: synopsis of a symposium at the Sun Valley Musculoskeletal Biology Workshop

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In view of the recent scientific progress and the important challenge presented to the musculoskeletal field by the chronic kidney disease–mineral bone disorder (CKD–MBD) syndrome, the organizers of the 43rd Sun Valley Musculoskeletal Workshop included a symposium on the topic. Chronic kidney disease (CKD) is very common[1] and is associated with high rates of cardiovascular morbidity and mortality, making it one of, if not the greatest, the cardiovascular disease risk factors. In the ongoing REGARDS trial, the incidence of recurrent cardiovascular disease associated with a reduced kidney function was 39%, compared with 19% in a comparator group comprising subjects at high risk due to standard cardiovascular risk factors, diabetes, smoking and metabolic syndrome.[2] These risk factors were not additive to the risk associated with CKD, indicating that CKD brings specific risk to the pathogenesis of cardiovascular disease. Three CKD-associated novel risk factors have been identified: vascular calcification, phosphorus and fibroblast growth factor 23 (FGF23). Hyperphosphatemia caused by CKD stimulates vascular calcification, and increases FGF23 secretion, placing most of the cardiovascular risks specifically associated with CKD within the realm of the CKD–MBD syndrome.[3,4] In recognition of the causality of the mineral and bone disorders produced by CKD in cardiovascular disease, CKD–MBD was named as a syndrome in 2006.[5] The CKD–MBD has recently been shown to be a uniform complication of early kidney disease.

Recent studies have characterized the early CKD–MBD beginning in stage 2 CKD as the onset of vascular calcification, the development of renal osteodystrophy and an increased secretion of FGF23, dentin matrix protein 1, DMP1 and sclerostin by skeletal osteocytes.[6,7] The onset of vascular calcification in early CKD is due to osteoblastic transition of cells in the arterial vasculature, loss of αklotho expression and loss of critical inhibitory factors such as pyrophosphate and fetuin.[6] The onset of the osteodystrophy of CKD is due to inhibition of the skeletal anabolic activity and adaptation to this by parathyroid hormone.[8] When hyperparathyroidism is established in CKD, bone biopsy generally reveals a high-turnover osteodystrophy, but suppression of parathyroid hormone secretion causes the decreased anabolic activity to manifest itself as a low-turnover osteodystrophy. Both high- and low-turnover osteodystrophies are associated with the increase in fracture risk due to end-stage CKD (ESKD), which is greater than that due to post-menopausal osteoporosis.[9] The skeletal fragility associated with ESKD is contributed to by woven (non-lamellar) bone in high-turnover osteodystrophy, confounding the relationship between bone mineral density (BMD) and strength that is the basis of the DEXA surrogate for fracture risk in osteoporosis.

Additional confounders to the use of DEXA-measured BMD in CKD are the presence of vascular calcification measured as BMD in DEXA and the lack of adjustment for short stature in pediatric CKD.[10] The poor association between DEXA-determined BMD and fracture risk in CKD led the KDIGO foundation not to recommend its routine performance in stages 3–5 CKD in its 2009 guidelines. More recent studies have challenged these guidelines and found reasonable association between the low BMD measured by DEXA and the fracture risk in older adults with early CKD stage 3 not differing from the general population.[11] Other forms of skeletal imaging such as peripheral quantitative computed tomography are somewhat better than DEXA in associating with fracture risk due to the measurement of cortical BMD and endosteal circumference, but whether this is sufficient for peripheral quantitative computed tomography to become the DEXA equivalent specific for CKD remains to be determined. Peripheral quantitative computed tomography

does offer the additional opportunity to measure muscle frailty and abnormalities in muscle that correlate with muscle strength. The relationship between muscle strength, falls and fractures is important, and this area of investigation with imaging techniques is in need of additional study, but frailty becomes an important factor as CKD progresses.[12] Recent studies with peripheral quantitative computed tomography have shown that CKD causes a progressive cortical bone deficit related to parathryroid hormone, and an impairment of the functional muscle bone unit, suggesting that frailty contributes significantly to fracture risk in ESKD.[13]

The role of FGF23 in the CKD–MBD is complex. First, its secretion by skeletal osteocytes is stimulated very early in CKD when other biomarkers of the syndrome (Ca, Pi, parathyroid hormone and calcitriol) are normal,[7] and it is responsible for the maintenance of Pi homeostasis in early CKD. FGF23 is a skeletal hormone that regulates renal tubular Pi transport by binding to FGF receptors on tubular epithelial cells in the presence of the co-receptor αklotho, activating signal transduction through the MAP kinase and Erg1 pathways that regulate vesicular traffic between endosomes containing NaPi2a and NaPi2c phosphate transporters and the brush border apical membrane. In addition, FGF23 inhibits the 1-α-hydroxylase and stimulates the 24-hydroxylase decreasing the calcitriol production and increasing the vitamin D and calcitriol catabolism. This causes the near-uniform prevalence of vitamin D deficiency in CKD. How the osteocyte is stimulated by very early CKD to increase FGF23 secretion may have been clarified by the recent discovery of the endocrine function cleaved klotho (cklotho).[14] Cklotho stimulates FGF23 secretion and its production by renal tubules could be a mechanism of osteocyte signaling. However, the function of increased FGF23 is soon impaired in CKD due to the inhibition of transmembrane αklotho expression, which also decreases circulating αKlotho (cklotho) levels in CKD stages 3–5 and produces FGF23 resistance. Much remains to be discovered as to how this new endocrine axis between the kidney and the skeleton functions in CKD.[15] The development of hyperphosphatemia and loss of αklotho signal continuous secretion of FGF23, which accumulates to massive levels as CKD progresses. FGF23 in this situation strongly associates with and may directly stimulate cardiac myocyte hypertrophy and left ventricular hypertrophy.[16] This may be a major contributor to cardiovascular disease and mortality risk in CKD.[17]

αKlotho was discovered as an anti-aging hormone[18,19] and subsequently as a co-receptor for FGF23. It is a single-pass transmembrane protein with a high expression in the choroid plexus, parathyroid and renal distal and proximal tubule epithelium, along with a lower-level expression more widely such as in the vasculature, where its deficiency may contribute to the vascular calcification in CKD.[6,20,21] Cleavage of its extracellular domain by ADAM10 or 17 produces the cKlotho discussed above. αKlotho, in addition to its co-receptor functions to mediate the action of FGF23 on phosphate transport, has autocrine/paracrine effects on the tubular epithelium producing phosphaturia.[22] αKlotho is also a sialidase and glucuronidase and controls phosphate and calcium homeostasis by affecting the residence of transport functions in the apical membranes of the proximal and distal tubules.[22–24] In addition, cKlotho inhibits Pit1, the putative phosphate sensor/transport protein implicated in stimulation of vascular calcification. αKlotho deficiency increases cardiac remodeling, which can be inhibited by αKlotho administration or genetic overexpression. Thus, much more study of αKlotho deficiency and replacement needs to be accomplished to bring this exciting potential to the clinic.

Conflict of Interest

The authors declare no conflict of interest.

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