Bone and the kidney: it's complex

It is increasingly recognized that organ systems within the body do not function as autonomous entities, but rather interact extensively through a series of complex signalling networks. The consequence of such crosstalk is that alterations or dysfunction in one system have knock-on effects in others. Crosstalk between the kidney and bone is one such example. Chronic kidney disease (CKD) is associated with a host of alterations in bone metabolic factors, which markedly affect mineral homeostasis and bone remodelling. As a consequence, patients with CKD have increased bone fragility and a substantially increased risk of fracture compared with that of the general population (Alem, A. M. *et al*. *Kidney Int*. **58**, 396–399; 2000). The downstream effects of renal dysfunction on mineral metabolism extend beyond alterations in bone remodelling, however. Vascular calcification also occurs as a consequence of disrupted mineral metabolism and contributes to the high cardiovascular mortality associated with CKD. In September 2012, the *International Society of Nephrology* held a Nexus symposium on 'Bone and the Kidney' to promote the exchange of insights and information between scientists and clinicians with an interest in the mineral metabolism, bone disease and vascular calcification of patients with CKD (Drueke, T. B. & Olgaard, K. *Kidney Int*. **83**, 557–562; 2013). This focus issue of *Nature Reviews Nephrology* features five Reviews written by key opinion leaders who presented at this symposium.

Secondary hyperparathyroidism is a frequently encountered complication of CKD. In this issue, Justin Silver and Tally Naveh-Many discuss the complex signalling pathways linking phosphate, vitamin D, calcium, parathyroid hormone and fibroblast growth factor (FGF)-23, and describe how secondary uraemic hyperparathyroidism induces pathogenic remodelling processes in bone. In his Review, Makoto Kuro-o describes the pathogenic role of the FGF–Klotho endocrine axis in relation to abnormal mineral metabolism and premature ageing. Similarities in the phenotypes of mice lacking *Klotho* and humans with CKD have led to the proposal that CKD represents a premature ageing-like syndrome caused by hyperphosphataemia. Kuro-o proposes that the cytotoxic effects of phosphate might be attributable to calciprotein particles, which cause oxidative stress and tubular injury. Further evaluation is necessary to elucidate the role of these particles in CKD-related pathology, but Kuro-o suggests that phosphate restriction in early stages of CKD—when serum FGF-23 levels start to rise—could attenuate calciprotein particle formation and the progression of tubular damage.

The finding that patients on dialysis—even children—exhibit accelerated medial vascular calcification, lends support to the suggestion that CKD is a syndrome of premature ageing. In her Review, Catherine Shanahan describes similarites between the mechanistic processes that promote vascular calcification in patients with CKD and those that associate with cardiovascular mortality in elderly individuals. Uraemic toxins are thought to have a central role in these processes, promoting oxidative stress, prelamin A accumulation and DNA damage, leading to premature senescence and cellular ageing.

Until findings from ongoing mechanistic studies translate to new diagnostics and therapies, clinicians must use available approaches to assess and treat bone and vascular pathology. In their Review, Hartmut Malluche and colleagues discuss methods to evaluate bone quality in patients with CKD. The authors argue that loss of bone mass alone is insufficient to explain the increased occurrence of fractures associated with CKD, and suggest that changes in bone quality are important. Malluche and colleagues explain how integrating the study of bone quality into the clinical workup and management of patients with CKD will improve understanding of the bone abnormalities that occur with loss of kidney function. Studies of the metabolic, bone remodelling, structural and vascular changes that occur in CKD have revealed important differences between CKD-associated bone disease and osteoporosis, suggesting that osteoporosis treatments might not always be appropriate for patients with CKD. In the final Review of this issue, Susan Ott describes the currently available osteoporosis medications and the evidence for or against their use in patients at various stages of CKD.

As described by Ott, achieving simultaneous control of calcium, phosphate and parathyroid hormone levels in patients with CKD is challenging and therapy should be guided by the underlying disease pathology. It is for this reason that in addition to further clinical research into the long-term safety and efficacy of available osteoporosis medications in patients with CKD, further understanding of the pathological mechanisms of bone disorders in CKD is essential. It is only through combined efforts to improve understanding of the complex relationships between bone, kidney and the vasculature, that the efficacy of existing therapeutics will be improved and the development of new modalities to prevent, or reverse, CKD-associated bone disease will be possible.

doi:10.1038/nrneph.2013.184

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Competing interests
The author declares no competing interests.