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Chronic kidney disease mineral and bone disorders; controversies and directions

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The revised Kidney Disease Improving Global Outcomes (KDIGO) guidelines for Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) will soon be published. Perhaps the most important insight arising from the concept of CKD-MBD that was developed in 2005, followed by the CKD-MBD guidelines in 2009,[1] is that the kidneys, bone and vasculature do not act separately, but as an interactive coregulatory system mediating mineral homeostasis; and that with advancing kidney disease, abnormalities of this integrated system compromise cardiovascular and musculoskeletal health.

The past decade has seen progress in understanding the complex pathogenesis of CKD-MBD, including previously unrecognized interactions with the brain, autonomic nervous system, the microbiome and many metabolic pathways. While the updated KDIGO guidelines will reflect advances in this understanding, the guidelines rely on evidence; and the availability of an adequate evidence base for treatments of CKD-MBD remains an unmet need. There is currently a dearth of well designed and executed randomized, double blind, placebo-controlled trials, demonstrating the effectiveness of interventions to influence morbidity and mortality or to improve quality of life of patients with CKD-MBD. This is a formidable challenge and reflects the difficulty of designing studies for patients with heterogeneous kidney diseases and accompanying bone disease. Compounding this difficulty, many investigations used in the diagnosis and management of CKD lack sensitivity and/or specificity, or only detect late disease. This lack of high level evidence imposed a conservative approach to management in the 2009 KDIGO CKD-MBD guidelines, and the revised guidelines will necessarily have similar short comings that will frustrate the expectations of some clinicians.

With these limitations in mind, a 'CKD-MBD Controversies and Directions' workshop was convened in September 2015, involving renal physicians, endocrinologists, skeletal physiologists and imaging specialists from the Australian and New Zealand Society of Nephrology (ANZSN) and Australian and New Zealand Bone and Mineral Society (ANZBMS) to bring the challenges we face into sharper focus. Areas for discussion included current and emerging treatment targets for CKD-MBD, an assessment of current and proposed laboratory investigations and imaging modalities, and an exploration of ways to improve management and direct research. This supplement contains the proceedings of that meeting, updated by authors to the end of 2016, and is intended to identify unmet needs in the field of bone and mineral metabolism. Some comments are provided in the succeeding text.

FOR WHOM THE BELL TOLLS – TOO LATE

Some of the earliest CKD studies that associated abnormal mineral metabolism to increased risks for mortality, implicated elevated serum phosphate as a potentially causative agent.[2,3] Serum phosphate is modifiable using aluminium, calcium and more recently non calcium-based phosphate binders, making it an attractive target for clinicians, guideline developers and the pharmaceutical industry. Of course, defining serum phosphate target ranges for CKD stages 3–5D presumes that evidence exists for the efficacy of interventions that attain those goals. However, phosphate disturbances occur late in CKD, and signal a failure of compensatory, homeostatic increases in the phosphaturic hormones fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH), along with early, likely homeostatic suppression of the phosphataemic hormone 1,25-dihydroxyvitamin D ($1,25(OH)_2D$).

Because hyperphosphataemia, hypocalcemia and hyperparathyroidism are late manifestation of CKD, managements that focus on these laboratory measures are unlikely to substantially change the course of CKD-MBD.[4,5] On the other hand, an elevated FGF23 measured in CKD stages 2 to 3, might reveal an opportunity to modify dietary inorganic phosphate, before FGF23 and PTH levels rise to potentially harmful values. CKD stages 2–3 may also be an appropriate time to measure Fetuin A or serum calcification propensity,[6] because those investigations may assist in directing the prescription of dietary phosphate restriction and non calcium-based phosphate binders, or combinations of drugs that reduce phosphate absorption. The use of low dose calcitriol early in CKD is also tempting, but possibly counterproductive. Calcitriol might increase serum phosphate levels and FGF23 values; although balancing this, renal klotho expression and soluble serum klotho might be increased.[7,8] Drs Steve Holt and Nigel Toussaint discuss whether serum phosphate is a useful target

in CKD and dissect the evidence for modification of dietary phosphate. Drs Jean Tan and Michael Cai discuss FGF23, α Klotho, sclerostin and serum calcification propensity testing and their current clinical relevance.

TO BIND OR NOT TO BIND?

For some years, calcium-based phosphate binders have been first line management to reduce phosphate absorption and hyperphosphataemia. Nevertheless, "the demise of calcium-based phosphate binders" in favour of these non calcium-based drugs was announced in 2013.[9,10] More recently, a meta analysis of sevelamer versus calcium-based binders indicated a 46% survival benefit for sevelamer,[11] another supported a reduced risk of coronary artery calcification,[12] and it has been argued that the use of calcium-based binders may be unethical.[13] These views are supported by the finding of positive calcium balance in patients with CKD 3–4 treated with modest dose calcium supplementation.[14] While the evidence for non calcium-based binders remains contested, it is clear that calcium has no *advantages* over the newer non calcium-based phosphate binders. Whether *any* binder should be used before patients progress to dialysis, remains uncertain,[15] and may be addressed by the IMPROVE-CKD study.[16] But for patients on dialysis, with an exaggerated risk for vascular calcification, it is reasonable to question the current Australian Pharmaceutical Benefits Scheme criterion that non calcium-based drugs only be used for patients on dialysis after a trial of calcium. Dr Jacqueline Center and I discuss phosphate binder use, and Drs Rathika Krishnasamy and Eugenie Pedagogos discuss the assessment of vascular calcification.

VITAMIN D, CINACALCET, HYPERPARATHYROIDISM AND CALCIPHYLAXIS

Cholecalciferol and ergocalciferol (calciferol) supplementation is widely used to improve deficient or insufficient levels of 25-hydroxyvitamin D, and low 25-hydroxyvitamin D values predispose to rickets and osteomalacia. Treatment with calciferol may also blunt rising levels of PTH till CKD stage 4, and ameliorate albuminuria in adults with CKD stages 3 and 4.[17,18] However, in CKD stages 5 and 5D, evidence is lacking for a positive effect of short-term calciferol supplementation, although as in other patients groups, lower 25-hydroxyvitamin D values may be a surrogate for poorer health and a heightened risk of mortality.[19] Drs Wai Lim and Emma Duncan discuss data for and against the use of vitamin D supplementation in CKD.

Calcitriol and its analogues are widely used in CKD stages 3–5D to suppress rising PTH values. However, target ranges for PTH have remained controversial since the 2009 KDIGO CKD-MBD guidelines. PTH is a key hormone regulating calcium, phosphate, 1,25-dihydroxyvitamin D metabolism and sclerostin expression, and because of its homeostatic role, a PTH target in the normal range, as suggested by the 2009 KDIGO guidelines, seems inappropriate for patients transitioning from CKD stage 3–5. As renal function deteriorates, values of PTH increase because of skeletal resistance and due to artefact from retention of long C-terminal fragments of PTH that are measured by the intact-PTH assay; all of which informed the KDIGO PTH target in CKD stage 5D of 2–9-times the upper normal range of the PTH assay. Drs Nigel Toussaint and Matthew Damasiewicz discuss the role of vitamin D receptor agonists, following trials that provide little support for their cardiovascular benefits, and the controversial role of cinacalcet.[20] Drs Carmel Hawley and Steve Holt discuss redefining PTH targets and the management of severe hyperparathyroidism.

EVALUATING RENAL OSTEODYSTROPHY AND FRACTURE RISK

Bone biopsy is a generally painless procedure that remains the sole means to accurately define the spectrum of renal osteodystrophy. However, it is rarely performed, processing is time consuming, and patients are reluctant. On the other hand, physicians are constrained from treating patients sustaining fractures with antiresorptive medications, because the 2009 KDIGO guidelines suggested these drugs be avoided unless high bone turnover is confirmed by histomorphometry.[1] Fracture efficacy for antiresorptive drugs *is* lacking beyond CKD stages 3–4, and expert opinion supports the importance of avoiding low bone turnover,[21] which is a final stage of skeletal adaptation to a surfeit of calcium.[22] Nevertheless, there is a possibility that we may be overestimating risks for low bone turnover and 'adynamic bone disease'.

The bone biopsy studies upon which some of these concerns are based, included up to 41% of patients dialysed against a dialysate ionized calcium of 1.75 mmol/L.[18] Patients may also have received intravenous calcitriol or analogues, aiming for lower Kidney Disease Outcomes Quality Initiative PTH targets.[23] The prevalence of adynamic bone may also be overestimated if defective mineralisation is present, because osteoclasts do not initiate resorption where osteoid covers the bone surface.[24] Dr Terry Diamond and I comment on the current status and future prospects for bone biopsy and Drs Ashish Sharma and Nigel Toussaint discuss virtual bone biopsy using high resolution peripheral quantitative computerized tomography and micro magnetic resonance imaging. Dr Nicholas Pocock comments on the role of bone densitometry by dual-energy X-ray absorptiometry, quantitative computerized tomography and the advantages and limitation of these modalities when used diagnostically, or as a means to assess fracture risk and guide therapy.

REMODELLING MARKERS REVISITED

Reliable biochemical markers of bone remodelling may improve the non invasive diagnosis of renal osteodystrophy and our ability to monitor therapy. However, standard markers,

such as procollagen type 1 N-terminal propeptide and the C-terminal telopeptide of type 1 collagen are uninterpretable in patients on dialysis, being 2–5-fold higher than when remeasured in those same patients immediately after transplantation (unpublished data). Dr Cherie Chiang comments on the role of PTH and biochemical markers of bone turnover and whether combinations of available markers provide useful information to inform treatment.

TURNOVER, MINERALISATION, VOLUME – CORTEX?

An initiative of KDIGO has been to support the use of a turnover, mineralisation, volume (TMV) classification when reporting bone biopsy samples from patients with renal osteodystrophy. Given the limited number of available bone biopsy studies, this has improved the potential to compare histomorphometry and to evaluate treatment efficacy. However, the TMV focus on bone remodelling, the degree of tissue mineralisation and bone volume, generally excludes an assessment of cortical data (Fig. 1). Using microCT, bone biopsy samples from patients on dialysis often show severely thinned and porous cortices, which have been fragmented and cavitated by intracortical remodelling. This 'trabecularisation' and reduction in cortical thickness has recently been highlighted,[25] and in patients with a biopsy diagnosis of low bone turnover, changes in treatments that increase PTH values have in fact been associated with a worsening of cortical parameters.[26] Loss of cortical integrity is likely to be a major contributor to bone fragility and fracture risk. Dr Ego Seeman provides an overview of bone microstructure, fragility and its treatment in CKD.

TRANSPLANTATION MANAGEMENT AND RESEARCH GOALS

When patients are identified to have values for bone mineral density in the osteopenic or osteoporotic range after kidney or simultaneous pancreas kidney transplantation, questions of management remain unresolved. Some management algorithms have been published,[27] but there is a prevailing reluctance to prescribe anti-resorptive therapy. Drs Peter Ebeling and Matthew Damasiewicz discuss post transplant management. Finally, Dr Emma Duncan concludes with suggestions for future directions and collaboration between our societies.

The CKD-MBD paradigm is becoming more complex as interactions of bone, muscle, brain, the gastrointestinal tract, fat cells and blood vessels are investigated. A useful modulation of the CKD-MBD paradigm may be to refocus on early homeostatic adaptations that prevent critical biochemical changes, but if left unchecked can be damaging to end organs and increase mortality (Fig. 2). The workgroup hope these contributions highlight what we do not know, question what we think we do and provide insights to evaluate areas for research.

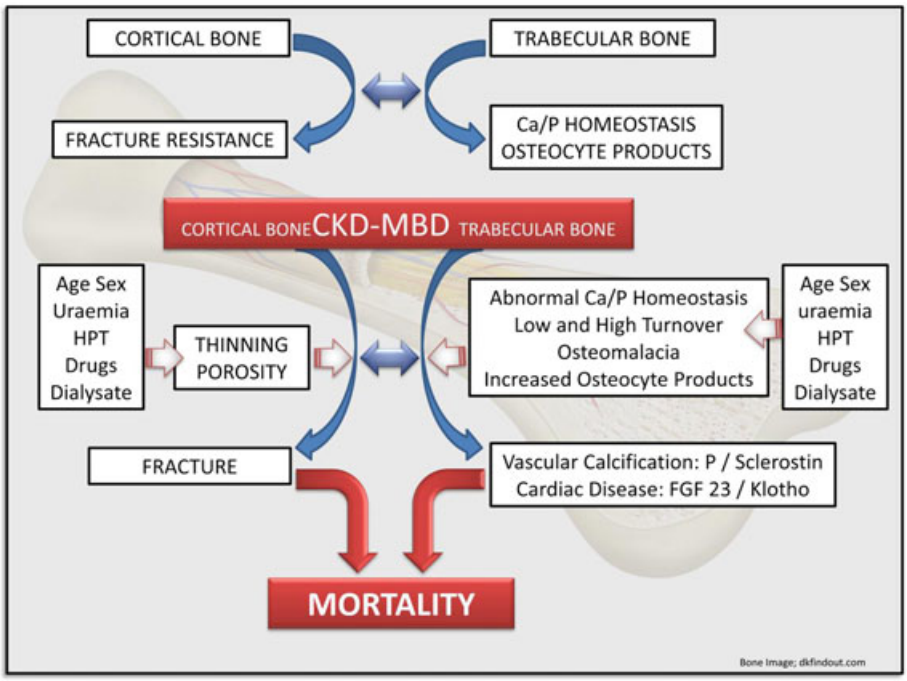

Fig. 1 Including the cortex in renal osteodystrophy and its consequences. HPT: hyperparathyroidism.

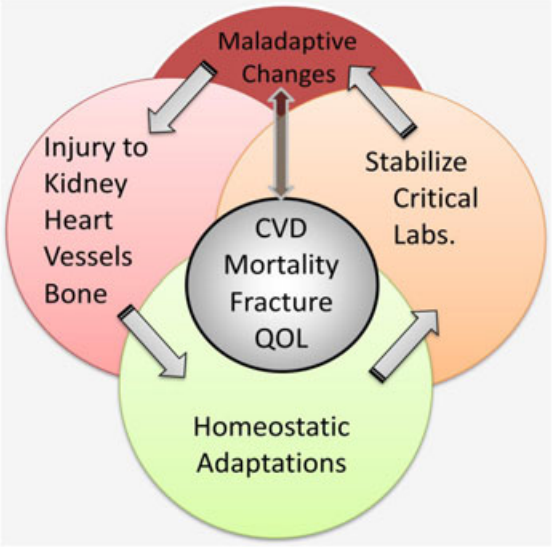

Fig. 2 A new way to conceive CKD-MBD. CVD: cardiovascular disease, QOL: quality of life.

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