Bone: a novel endocrine organ at the heart of CKD-MBD

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For decades the association between chronic kidney disease and bone disease has been acknowledged and ascribed to secondary hyperparathyroidism and vitamin D deficiency. However, data derived from CKD cohorts suggested that the skeleton in CKD can have a more active role contributing to cardiovascular disease. It acts as a “buffer” allowing excess calcium and phosphate to be stored, preventing its otherwise likely deposition as soft tissue calcifications affecting in particular cardiovascular structures. In addition it was recognised that diseased bone tissue could act as a source of excess calcium and phosphate, leached out by excessive circulating PTH for example, leading to further ectopic calcification.

Yet, novel insights announce another paradigm shift in the perception of the role of bone. The recent discovery of bone-derived humoral factors which are likely to be intimately involved in distant regulation of metabolic systems has given rise to a new understanding of the extreme susceptibility of CKD patients to CVD. Currently foremost amongst these is fibroblast growth factor 23 (FGF-23). This hormone, mainly secreted by osteocytes, regulates phosphorus homeostasis, vitamin D metabolism and parathyroid function. Inappropriately high serum concentrations of FGF-23 in turn might induce left ventricular hypertrophy(1). CKD-related research led to the recent discovery of additional important bone-derived humoral factors - like sclerostin and Dickkopf 1 (DKK-1), which tonically inhibit Wnt signalling(2). These may also promote vascular calcification and impair arterial wall functional properties, as their levels are significantly increased in renal failure. Since these Wnt pathways are thought to be involved in cardiovascular disease in the general population it is conceivable that the role of bone is currently underappreciated in the pathogenesis of CVD more widely(3). In addition, osteocalcin, produced by osteoblasts or released from mineralised bone by physiological, insulin-dependent bone resorption, has emerged as a
crucial factor in insulin secretion and sensitivity, and its deranged metabolic fate in CKD will likely be contributing to the marked insulin resistance which is frequently observed in CKD and as such contribute to cardiovascular disease.

A more mature understanding of these novel concepts is important as this may ultimately lead to novel therapeutic approaches to thus far unmet needs for the virtually insoluble problem of cardiovascular disease in CKD.

Figure 1: Schematic link between CKD Bone disease and biochemical abnormalities and clinical events. Dysparathyroidism represents both hyper- and hypoparathyroidism; FGF-23: Fibroblast Growth Factor 23; DKK-1: Dick-Kopf 1; LVH: Left ventricular hypertrophy
Calcium and phosphate balance in early and late CKD
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Calcium and phosphorus are essential to many vital physiological processes. Phosphorus is vital to intracellular signaling, as a component of membrane lipids and to build the backbone of DNA, while muscle contraction, blood clotting, and neuronal excitation all require calcium. Last but not least, calcium and phosphorus give strength to bone. Thus, not surprisingly, the maintenance of phosphorus and calcium homeostasis is essential to health. This, overall, requires a neutral balance. Balance essentially is input minus output in a steady state[1]. Given the paramount importance of urinary disposal, balances may be suggested to be disturbed in CKD. In addition, patients are often exposed to high doses of calcium, either as supplement or calcium containing phosphate binder. Studies investigating mineral balances in CKD and the impact of therapeutic interventions on these balances are scarce. This is mainly related to the fact that the formal balance studies are complex and demanding both for participants and investigators. It should be emphasized that serum levels of calcium and phosphorus are a very bad proxy of balances. Very, recently two elegant balance studies have been reported in CKD patients not yet on dialysis which substantially improved our understanding[2;3]. The current state of the art with regard to mineral balances in early and late CKD is as follows:

Phosphorus balance:
- Habitual dietary phosphorus intake in CKD patients is well above the recommended daily allowances
- Phosphorus balance in CKD patients not yet on dialysis is neutral and not affected by phosphate binder therapy
- Dietary phosphate restriction and phosphate binder therapy is required to maintain a neutral phosphorus balance in patients with CKD 5 treated with conventional HD or PD.
- Dialytic phosphorus mass removal differs importantly between modalities: Nocturnal HD >> HDF > HD > PD

Calcium balance:
- Habitual dietary calcium intake is in CKD patients is well below the recommended daily allowances
- Calcium balance in CKD patients not yet on dialysis is tight
- Calcium balance in CKD patients treated with calcium supplements turns positive.

Targeting a neutral mineral balance is like walking a tightrope[4;5]. Recent data may call for a revision of guidelines with regard to optimal calcium and phosphorus intake in CKD. This may not restrain us from performing additional studies (a) to define the fate of retained calcium and (b) to investigate what happens during prolonged high dietary calcium exposure. Finally, as always, therapy
(binder, dialysate) should be individualized. Guidelines are for the population, clinicians are for the patients.

Reference List


Comment:

Sclerostin is a soluble Wnt-signalling inhibitor, which modulates beta-catenin activity and degrades beta-catenin into the cytoplasm. It is produced by osteocytes, which are osteoblasts that have differentiated into a more mature state.

Sclerostin interacts with the Wnt signalling pathway, which is important in bone metabolism. When sclerostin binds to the Wnt signalling pathway, it inhibits the activity of beta-catenin, a protein that promotes bone formation.

In CKD-MBD, sclerostin plays a role in regulating bone metabolism. Its production is increased in response to PTH (parathyroid hormone), which is a hormone that is produced in the parathyroid glands and stimulates bone resorption. This leads to a decrease in bone density, which can result in bone fragility and fractures.

Dr. Vincent Brandenburg
Basic principles of the canonical Wnt-signalling

Vervloet M. et al
CKD-MBD WG; 2014

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