Renal bone disease

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Abstract

Sustained loss of kidney function leads to the evolution of progressive secondary hyperparathyroidism associated with a characteristic high-turnover form of metabolic bone disease. The drivers to hyperparathyroidism include the failure of renal bioactivation of vitamin D, phosphate retention and, in some cases, hypocalcaemia. As renal impairment becomes more severe, some patients, particularly under the influence of treatment, and particularly if they have diabetes, evolve in a different direction with the development of low-turnover adynamic bone disease associated with relative suppression of the parathyroid glands. Uraemic patients also develop an internal milieu that favours soft tissue calcification involving peri-articular tissue, skin, and the vasculature. Arterial calcification is associated closely with arterial stiffening, left ventricular disease, and increased cardiovascular morbidity and mortality. Current therapies aim to minimize disturbances to skeletal integrity by maintaining calcium, phosphate, vitamin D and parathyroid hormone within defined target ranges. It is hoped, but not yet established, that these measures will also result in a reduction of cardiovascular events in this vulnerable population.

Keywords Calcimimetics; chronic kidney disease; hyperparathyroidism; vascular calcification; vitamin D

What's new?

- The phosphaturic FGF-23 and its role in CKD
- Novel therapies for managing osteoporosis in CKD
- Iron-based phosphate binders
- Latest clinical trial evidence

The onset of a significant and sustained reduction in renal function is invariably associated with the development of metabolic bone disease, disturbances to the metabolism of calcium and phosphorus, and with abnormalities of the principal calcium-regulating hormones, calcitriol, parathyroid hormone (PTH) and the phosphatonin, fibroblast growth factor 23 (FGF-23).[1,2] In addition, there are important links between these disturbances of mineral metabolism and adverse cardiovascular outcomes in patients with chronic kidney disease,[3–5] collectively termed the chronic kidney disease-mineral and bone disorder (CKD-MBD).

Hyperparathyroidism and high-turnover bone disease

Reduction of renal cell mass and glomerular filtration rate (GFR) leads to progressive phosphate retention and failure of renal bioactivation of vitamin D. These abnormalities powerfully stimulate the parathyroid glands to synthesize and release increased amounts of PTH, and to increase proliferative activity (Figure 1). Failure of vitamin D bioactivation leads to a lower extracellular fluid (ECF) calcium concentration, providing further stimulus to the parathyroid glands. Calcitriol has a direct inhibitory effect on PTH gene transcription, mediating its effects via a nuclear vitamin D receptor (VDR) that is present in parathyroid glands, osteoblasts and intestinal epithelial cells, as well as in many other tissues. The parathyroid glands also express the calcium-sensing receptor (CaR), a G-protein coupled receptor that mediates rapid minute-to-minute responses to changes in extracellular calcium concentration.

At the level of bone, PTH at physiological or just supra-physiological concentration is anabolic. In contrast, sustained elevation of PTH is catabolic, increasing the activity of both osteoblasts and osteoclasts, accelerating bone turnover and leading ultimately to significant resorptive damage.[6]

Phosphate

There has been much interest in FGF-23 (a potent phosphaturic hormone secreted by osteocytes), as a potential biomarker of early bone mineral disorder in CKD. Elevated FGF-23 is associated with both progression of kidney disease and mortality,[7] and rises early in CKD, preceding rises in serum phosphate and PTH.

Elevation of PTH and FGF-23 are adaptive mechanisms, but are under different feedback control. PTH is upregulated in response to decreases in serum calcium and calcitriol concentrations, and increases in serum phosphate concentration, all of which are partially or completely normalized by the PTH increment. In contrast, FGF-23 release is upregulated by increases in serum phosphate. It augments, and may even dominate, the PTH-driven phosphaturic response to decreasing GFR.[8]

Low-turnover bone disease

In some patients, particularly those subjected to treatment with pharmacological doses of active vitamin D metabolites and high exposure to calcium derived from the diet or dialysate fluids, there is relative suppression of PTH with the result that the skeleton lacks stimulatory anabolic input. Abnormally low bone turnover develops, with low cellular activity. This is associated with increased skeletal morbidity and an associated increase in the tendency to develop vascular calcification, with increased cardiovascular morbidity and mortality. The risk of low-turnover bone disease increases progressively with the severity of CKD, and in some studies has been the dominant bone lesion identified in CKD 5D patients.[9] For this reason, most guidelines have recommended supraphysiological target ranges for PTH in dialysis patients.

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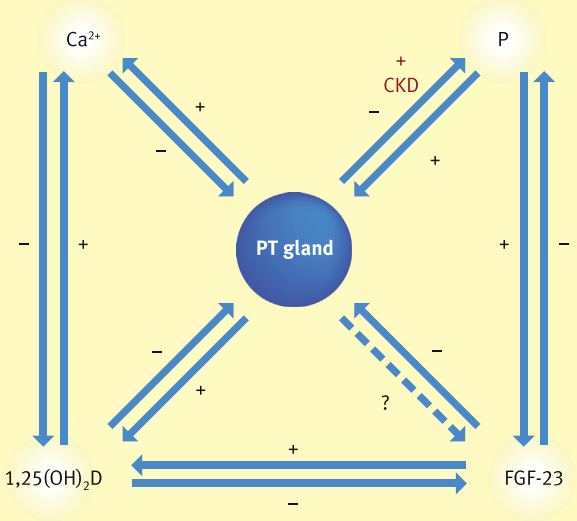
Positive and negative feedback loops in mineral homeostasis



Under normal conditions, an increase in serum phosphate will exert negative feedback on serum phosphate via the parathyroid gland. However, in chronic kidney disease (CKD), the kidney cannot mount a phosphaturic response to parathyroid hormone (PTH) with the result that rising PTH, by promoting mineral ion efflux from bone, elevates phosphorus. FGF-23, fibroblast growth factor-23.

Redrawn from Ben-Dov, Silver et al., 2007[19]

Figure 1

Another contributor to low turnover is the use of anti-resorptive agents such as bisphosphonates for the treatment of osteoporosis. These agents reduce osteoclastic activity, but bone metabolism remains coupled and so new bone formation is also reduced. Bisphosphonates are excreted by the kidney, and accumulate in patients with CKD. These drugs should generally be avoided when the GFR is below 30 ml/min/m^2.

Extra-skeletal calcification

Soft tissue calcification, especially that involving large arteries is a frequent complication in patients with CKD.[9] This calcification occurs in the vascular media and is distinct from the intimal calcification seen in patients with atheromatous disease. Medial calcification in uraemia is closely associated with loss of vascular compliance, arterial stiffening and increased pulse wave velocity, abnormalities that increase ventricular afterload and which may be important in the genesis of uraemic cardiac disease and the high cardiovascular mortality seen in these patients.

Assessment of osteodystrophy — bone pathology associated with CKD

The typical derangement seen in a biochemical snapshot of the *untreated* patient with advanced CKD shows high phosphate and low calcium with resulting secondary hyperparathyroidism. If measured, calcitriol is invariably low and FGF-23 very high. Skeletal X-rays are frequently normal, except in cases of severe hyperparathyroidism in which subperiosteal erosion and cortical tunnelling may be seen (Figure 2). The diagnosis of osteoporosis and osteodystrophy in patients with advanced CKD can be difficult

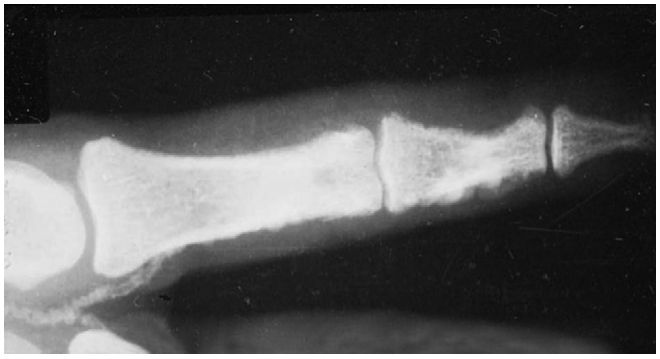


Figure 2 Severe hyperparathyroid bone disease in phalanges. Note tuft erosion, subperiosteal resorption and vascular calcification.

because traditional measurement of bone mineral density by dual X-ray absorptiometry (DXA) is not predictive of fractures in these patients. Quantitative computerized tomography (QCT) may be a more useful tool. Additionally, sclerostin (a marker of bone formation) and tartrate-resistant acid phosphatase-5b (TRAP-5b; a marker of bone resorption produced by osteoclasts) are both raised in CKD patients with bone fractures compared to those without,[10] and therefore may be useful biomarkers.

Management

The pathogenesis described above implies that management should include measures to increase serum calcium, decrease phosphate and replace deficiency of both substrate 25-hydroxyvitamin D and activated calcitriol. Available therapies are illustrated in Table 1.

Hyperphosphataemia is managed using a combination of dietary phosphate restriction and oral phosphate binders, which bind dietary phosphate in the intestinal lumen, preventing its absorption. Several agents are used, including calcium carbonate, calcium acetate and aluminium hydroxide (now rarely used on account of unpredictable neurotoxicity and skeletal toxicity). Sevelamer, an exchange resin, and lanthanum are alternatives.[11] All these agents have limited efficacy, suffering from relatively low potency and the need to take large doses timed to coincide with meals. Patient compliance is frequently poor. New iron-based phosphate binders, such as ferric citrate and sucroferric oxyhydroxide are undergoing clinical trials to establish relative

Therapeutic levers in CKD

	Calcium	Phosphate	Parathyroid hormone
Calcium binder	↑↑	↓↓	↓↓
Calcium-free binder	↔	↓↓	↓
Native vitamin D	↔	↔	↔[a]
Active vitamin D	↑	↑	↓↓↓
Calcimimetic	↓	↓	↓↓↓
Lowered dialysate Ca^{2+}	↓	↔	↑

The arrows depict the expected response(s) of serum biochemical parameters.
[a] May lower PTH in early CKD.

Table 1