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 of 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 of skeletal integrity by maintaining calcium, phosphate, vitamin D and parathyroid hormone concentrations 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; CKD-MBD; hyperparathyroidism; vascular calcification; vitamin D

Key points

- Hyperparathyroidism develops early in chronic kidney disease (CKD), so should be treated early — if parathyroid hormone (PTH) concentration is elevated and rising, check the calcium, phosphate and 25-hydroxyvitamin D and treat accordingly
- Fibroblast growth factor-23 (FGF-23) rises as an early adaptive mechanism to hyperphosphatemia in CKD
- There are important links between metabolic bone disease and cardiovascular disease in CKD patients, so when treating the bone, keep an eye on cardiovascular issues too
- Uraemic bone disease is heterogeneous; high-turnover hyperparathyroid bone disease and low-turnover adynamic bone disease dominate the two ends of the spectrum
- PTH measurement is a reasonable surrogate for the severity and type of bone disease but may in future be superseded by novel biomarkers such as FGF-23

Introduction

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

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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 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 that is present in parathyroid glands, osteoblasts and intestinal epithelial cells, as well as many other tissues. The parathyroid glands also express the calcium-sensing receptor, a G-protein-coupled receptor that mediates rapid minute-to-minute responses to changes in extracellular calcium ion 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 ultimately leading to significant resorptive damage.

Phosphate

There has been much interest in FGF-23 as a potential biomarker of early bone mineral disorder in CKD. Elevated FGF-23 is associated with both progression of kidney disease and mortality, and rises early in CKD, preceding rises in serum phosphate and PTH.[1]

Elevation of PTH and FGF-23 are adaptive mechanisms but are under different feedback controls. PTH is upregulated in response to decreases in serum calcium and calcitriol

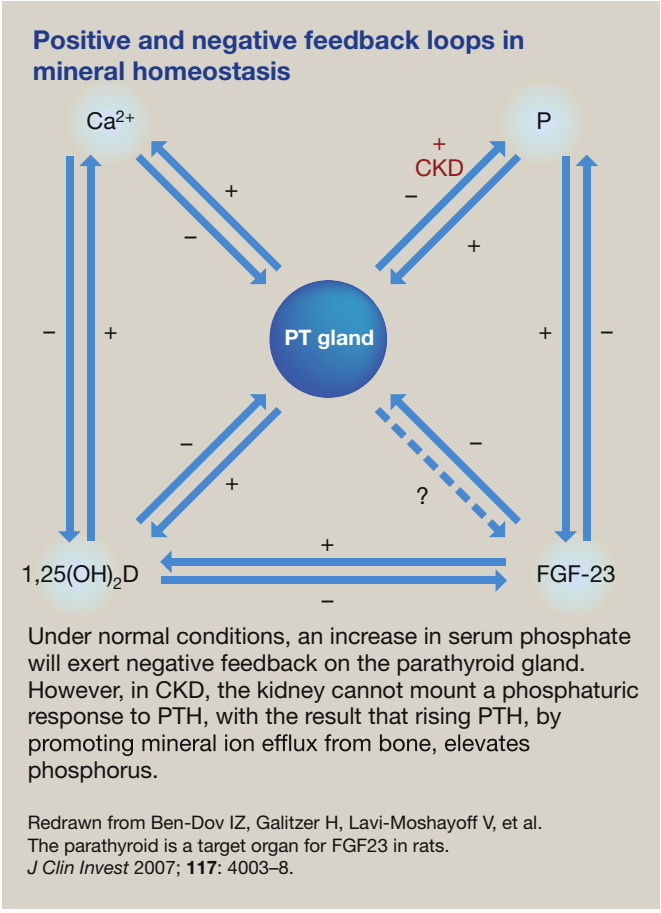

Figure 1

concentrations, and increases in serum phosphate concentration, all of which are partially or completely corrected by the PTH increment. In contrast, FGF-23 release is upregulated by increases in serum phosphate, so augments, and may even dominate, the hormone-driven phosphaturic response to decreasing GFR. Finally, FGF-23 powerfully downregulates the renal production of calcitriol, thereby opposing the action of PTH on the vitamin D endocrine system.

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 stage 5 patients on dialysis. For this reason, most guidelines have recommended supraphysiological target ranges for PTH in dialysis patients.

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 so new bone formation is also reduced. Bisphosphonates are excreted by the kidney and therefore accumulate in patients with CKD. These drugs should viewed with caution when GFR is <30 ml/minutes/1.73 m^2.

Extraskeletal calcification

Soft tissue calcification, especially involving large arteries, is a frequent complication in patients with CKD. 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. These abnormalities increase ventricular afterload and 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 *untreated* patients with advanced CKD shows high phosphate and low calcium concentrations 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 (Figure 2), in which subperiosteal erosion and cortical tunnelling may be seen.

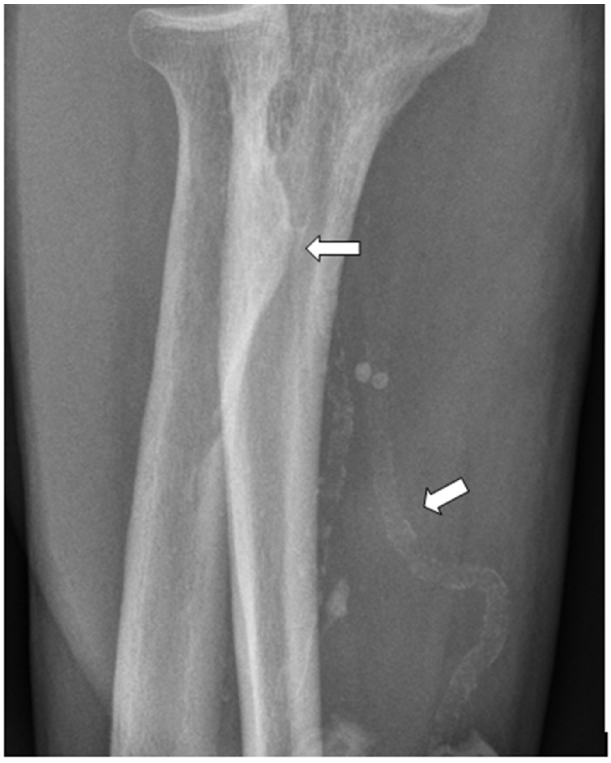

Figure 2 Plain X-ray of the right elbow in a patient on long-standing dialysis, showing osteodystrophy and vascular calcification.

The diagnosis of osteoporosis and osteodystrophy in patients with advanced CKD can be difficult because traditional measurement of bone mineral density by dual-energy X-ray absorptiometry (DEXA) is not predictive of fractures in these patients. Quantitative computed tomography 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 with those without,[2] and can therefore be useful biomarkers.

Bone disease after renal transplantation

Despite transplantation, these patients still have a higher fracture risk than the general population. Part of this results from glucocorticoid use after transplantation, and part is undoubtedly caused by pre-existing MBD as well as other factors. These contribute to osteodystrophy and osteoporosis, which in turn increases fracture risk and mortality in these patients.

Phosphate is often low in the post-transplant period, driven by persistent elevation of FGF-23 and PTH — the latter remains high in nearly 45% of transplant recipients and represents a significant risk factor for fracture. Vitamin D is also low in some recipients, and its replacement is currently recommended in the absence of hypercalcaemia as it can also play a role in acute cellular rejection. Cinacalcet has been shown to be effective in reducing PTH in transplant recipients in the absence of adverse effects on the transplanted kidney. Osteoporosis can be treated with bisphosphonates or denosumab; although these agents can induce low bone turnover, fracture risk reduction is demonstrable in patients with CKD stages 2–4. DEXA scanning is widely used to assess bone mineral density (BMD, although it is still less predictive than in the normal population.[3]

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 (the latter now rarely because of its unpredictable neurotoxicity and skeletal toxicity). Sevelamer, an exchange resin, and lanthanum are alternatives. 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, have undergone clinical trials to establish relative efficacy and dosage. Ferric citrate has been shown to decrease the need for erythropoiesis-stimulating agents and intravenous iron in dialysis patients; both iron-based agents exhibit effects on phosphate and PTH similar to conventional phosphate-binding drugs.

Deficient calcitriol is replaced either by giving calcitriol as an oral or injectable formulation, or in many cases by giving a calcitriol pro-drug, alfacalcidol. This agent is then subjected to 25-hydroxylation in the liver, yielding calcitriol. Deficiency of the parent compound 25-hydroxyvitamin D should also be addressed. This can be replaced using oral colecalciferol (D_3) or ergocalciferol (D_2), which can be given in both oral and intramuscular forms. Doses of at least 1000–3000 U/day are required to raise 25-hydroxyvitamin D to sufficient levels (>75 nmol/litre).

These treatments are generally very effective in the control of secondary hyperparathyroidism, but are prone to cause hypercalcaemia and possibly vascular calcification. This has led to a search for alternative and more selective ways of treating hyperparathyroidism.

First, there has been a substantial move away from calcium-based phosphate binders to calcium-free resins and salts. These agents are much less prone to causing hypercalcaemia, and there is some evidence that they have a lesser tendency to cause vascular calcification and adynamic bone disease. Sevelamer and lanthanum are the two most commonly prescribed non-calcaemic phosphate binders, but use is limited by gastrointestinal adverse effects with sevelamer and concerns (probably ill-founded) about chronic absorption and toxicity with the heavy metal lanthanum.

Second, new active vitamin D compounds have been developed, some of which exhibit the potential for more selective action on the parathyroid glands, with less tendency to raise serum calcium via actions on intestine and bone. Experimental work using these agents has sometimes shown very impressive evidence of target organ selectivity, but in clinical practice little significant difference has emerged. Vitamin D compounds in this category include 22-oxacalcitriol (maxacalcitol), widely used in Japan, and paricalcitol, which is widely used in the USA and to a lesser extent in some European countries.

The third approach is to use calcimimetic agents to modulate the action of the calcium-sensing receptor on parathyroid cells. These compounds bind to the transmembrane domain of the receptor, resulting in an allosteric modification that increases its sensitivity to calcium. As a result, the parathyroid cell perceives extracellular calcium concentration as being higher than it really is. Predictably, this leads to simultaneous reduction of PTH and calcium (and additionally in patients with CKD stage 5, elevation of phosphate). Oral cinacalcet, has proved an extremely effective means of moving PTH, calcium and phosphate into the desired

Therapeutic levers in CKD

	Calcium	Phosphate	PTH
Calcium binder	↑↑	↓↓	↓↓
Calcium-free binder	↔	↓↓	↓
Iron-based 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

target ranges when given to patients with hyperparathyroidism and CKD. However, its use has been limited by gastrointestinal adverse effects and compliance issues. The approval of etelcalcetide by the National Institute for Health and Care Excellence for dialysis patients who cannot tolerate or are non-compliant with cinecalcet medication provides an alternative calcimimetic in clinical practice. Intravenous administration can help to reduce gastrointestinal exposure and upset, avoid compliance issues and provide more reliable and effective dosing.

The other challenge in CKD is the management of osteoporosis. Bisphosphonates, as described above, can contribute to low bone turnover, especially in dialysis patients, and should therefore generally be avoided in advanced CKD. The anti-osteoclast monoclonal antibody denosumab is not excreted by the kidneys so has been reported to be safe in patients with CKD stages 3 and 4. However, there have been reports of severe hypocalcaemia in dialysis patients. Teriparatide, a PTH analogue, is an anabolic agent that promotes new bone growth; however, its utility is limited by the need for administration as daily subcutaneous injections. Another promising anabolic agent is romosozumab (unlicensed in UK), a monoclonal antibody against sclerostin, an inhibitor of osteoblast function. This agent is highly promising in that it causes a sustained reduction in bone resorption markers, with stabilization of bone formation markers.

Biochemical targets in patients with CKD

Observational studies have led to the development of several sets of guidelines and biochemical targets relating to bone and mineral metabolism in CKD, in the hope of improved clinical outcomes.

Calcium, phosphate and 25-hydroxyvitamin D should be maintained within normal ranges. PTH should be maintained in or just above the normal range in patients with CKD stages 1–5 not on dialysis. In CKD stage 5 patients on dialysis, the most recent guidelines recommend supraphysiological (2–9 times the upper limit of normal) concentrations of PTH.[4] The aim is to set PTH in a range most likely to be associated with normal or near-normal bone turnover, and to avoid the extremes of adynamic bone disease or hyperparathyroid bone disease. Although it has to be accepted that the use of PTH as a surrogate marker of bone turnover is quite imprecise, it remains the best compromise of utility and feasibility in clinical practice.

Clinical outcomes

Very large cohort studies have looked at the influence of vitamin D therapies on survival and other outcomes. Somewhat surprisingly, quite good evidence has emerged that treatment with active vitamin D compounds is associated with a significant increase in life expectancy among dialysis patients. However, new data testing vitamin D receptor activators in dialysis patients without raised PTH concentrations has shown no overall benefit in all-cause mortality or cardiovascular events; there is also a potential trend towards increased harm in patients treated with vitamin D receptor activators.[5] There is somewhat less convincing evidence that some vitamin D metabolites are better than others in this respect.

In the case of calcimimetics, analysis of data from a series of comparative studies has shown a 10-fold reduction in parathyroidectomy rate and 50% reduction in fracture rate among patients treated with cinacalcet, compared with those treated conventionally. The A Randomized Study to Evaluate the Effects of Cinacalcet plus Low-Dose Vitamin D on Vascular Calcification in Subjects with Chronic Kidney Disease Receiving Haemodialysis (ADVANCE) study demonstrated a modest reduction in cardiac calcification scores in patients treated with a combination of cinacalcet and low-dose vitamin D. A large prospective study, Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE), demonstrated a significant reduction in PTH, but this was not matched by a significant reduction in death or cardiovascular events.

In relation to phosphate binders, the only prospective outcome study (Dialysis Clinical Outcomes Revisited (DCOR)) of sevelamer versus calcium phosphate binders in dialysis patients showed no mortality benefit, except in selected subgroups. In osteoporosis, the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial demonstrated that denosumab given subcutaneously twice-yearly for 36 months was associated with a reduction in the risk of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis. A study of romosozumab in postmenopausal women with low bone density demonstrated significant improvements in bone density at the lumbar spine. However, patients with advanced CKD were excluded from these studies, and therefore efficacy and safety in this patient group remains unclear.

Summary

It is now clear that there is substantial overlap between the pathogeneses that lead to bone disease and those that are associated with accelerated vascular disease in patients with CKD; this is reflected in current terminology in which the phenotypes are collectively termed CKD–MBD. This is a major therapeutic target in the overall management of these patients, but the perceived advances in the therapeutic tools available have not yet led to demonstrably enhanced clinical outcomes. Advances in knowledge of the broader roles of activated vitamin D and FGF-23 may provide new therapeutic opportunities, and novel biomarkers might facilitate earlier diagnosis and management. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 40-year-old man patient presented for review. He had recently been found to have chronic kidney disease stage 4, with an estimated glomerular filtration rate of 24 ml/minute/1.73 m^2.

Investigations

- Corrected serum calcium 1.99 mmol/litre (2.2–2.6)
- Serum phosphate level 1.89 mmol/litre (0.8–1.5)
- Serum parathyroid hormone 60 pmol/litre (1.6–6.9)

What is the most appropriate treatment for these results??

A Cinacalcet and calcium carbonate
B Cinacalcet
C Alfacalcidol
D Alfacalcidol and colecalciferol
E Colecalciferol

Question 2

A 74-year-old woman presented with pain in her left distal femur. There had been no trauma. She had diabetes and chronic kidney disease treated with dialysis. She was taking alendronic acid, alfacalcidol and colecalciferol.

Investigations

- Corrected serum calcium 2.85 mmol/litre (2.2–2.6)
- Serum parathyroid hormone 10 pmol/litre (1.6–6.9)
- X-ray of the femur showed an insufficiency fracture at the site of the pain

What is the likely cause of her fracture?

A Secondary hyperparathyroidism
B Low-turnover/adynamic bone disease
C Myeloma
D Calciphylaxis
E Tertiary hyperparathyroidism

Question 3

A 25-year-old man presented for review 2 months after transplantation for chronic kidney disease. He was clinically well.

Investigations

- Corrected serum calcium 3.0 mmol/litre (2.2–2.6)
- Serum parathyroid hormone 75 pmol/litre (1.6–6.9) and a stable baseline creatinine of 90 (53–97).

What is the best management for these results?

A Colecalciferol and cinacalcet
B Alfacalcidol and colecalciferol
C Alendronic acid and colecalciferol
D Colecalciferol
E Cinacalcet