Renal osteodystrophy: from aching bones to breaking hearts

By Dr Mark Thomas,
Renal Physician RPH

The management of renal osteodystrophy associated with dialysis has shifted focus from relief of overt musculoskeletal symptoms, to avoidance of aluminium toxicity or excessive PTH suppression, and now to prevention of vascular and valvular calcification. Exciting new therapies such as non-calcium phosphate binders or calcimimetics are awaiting longterm outcome data to prove their cost-effectiveness. **Patients with GFR <30mls/min should maintain a serum PO4 in the normal range, through avoidance of dietary phosphate excess plus use of calcium carbonate with main meals.**

Pathophysiology

The two fundamental abnormalities in kidney failure causing hyperparathyroidism (HPTHism) are:

1. phosphate retention, and
2. reduced capacity to synthesise calcitriol (1,25-Vitamin D, the most active form of Vitamin D).

The relative balance between these two can accelerate or slow the normal sequence of bone formation (marked by serum alkaline phosphatase, ALP) and bone resorption (marked by urinary N-telopeptide excretion). This produces *high turnover bone diseases* (high ALP, e.g. HPTHism) or *low turnover bone diseases* (low ALP, e.g. osteomalacia, adynamic bone disease) or a mixture of both. See Table 1.

The compensatory rise in PTH (*secondary HPTHism*) partially corrects low calcium levels, through increased resorption from the gut, kidney and bone, as well increasing urinary PO4 excretion. Sustained stimulation of PTH glands can produce autonomously secreting PTH cells, generating high blood calcium levels (*tertiary HPTHism*). HPTHism and osteomalacia may co-exist.

Rarely, after many years of kidney failure (and usually a decade of dialysis), serum ß2-microglobulin can slowly proteolyse into amyloid fibril sheets, depositing in synovium and bone with resultant carpal tunnel syndrome, shoulder pain, and fractures through bone cysts.

Treatments

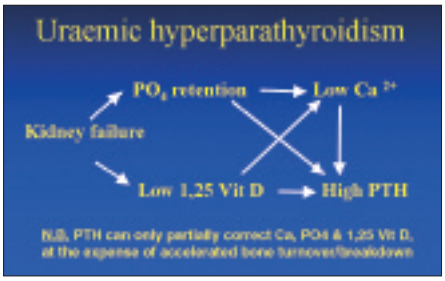
Dietary PO4 restriction is a constant challenge (main sources = dairy foods, bread and Cola); excessive restriction risks malnutrition. Skin itch is most closely linked to serum PO4 elevations, and the most immediate benefit of avoiding dietary excess.

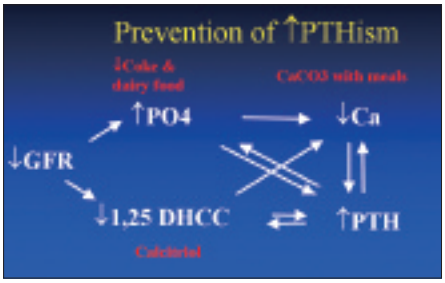
Optimising renal function applies both before and after end-stage kidney disease. Inadequate dialysis delivery can markedly exacerbate renal bone disease; use of more biocompatible dialysis membranes may reduce the incidence of ß2-amyloid.

PO4-binders taken with main meals minimise intake and maintain a serum PO4 <2.0 mmol/L, ideally in the normal range. *Aluminium hydroxide* was the main PO4-binder until its long term cumulative toxicity in renal failure was recognised. *Calcium carbonate* replaced Al in the late '80s but exacerbated the risk of hypercalcaemia. *Magnesium* is a weak PO4-binder, with the risk of diarrhoea if accumulating in renal failure. *Sevelamer* is a non-PBS ($6000/yr/patient) non-calcium resin that concurrently reduces cholesterol and bile acid.

Calcitriol increases gut absorption of both Calcium and PO4 and is prime therapy for osteomalacia, where Ca and PO4 levels are usually in the low-normal range. Although it acts directly on the PTH gland to suppress secretion, the concurrent rise in PO4 can undo any benefit, so its use needs careful Ca and PO4 monitoring. It is favoured over cheaper Vitamin D in kidney disease, as its shorter half life means hypercalcaemic episodes can resolve within days rather than weeks, but its expense requires PBS authorisation.

Calcimimetics such as *cinacalcet* are recently developed agents that mimick the action of calcium on the parathyroid gland cell surface calcium-sensing receptor. Expense has limited introduction to Australia, but daily dosing can achieve 30-70% suppression of moderate PTH levels (i.e. 3-10 x normal range).





Parathyroidectomy is necessary in up to 50% of patients after a decade of dialysis, usually requiring an experienced surgeon to find ectopic glands in the thymus, whilst avoiding local vessel or nerve trauma. Patients with high ALP levels, large glands (>1g vs 30mg normally) or bone erosions are at risk of post-operative "hungry bone syndrome" and hypocalcaemia, requiring prolonged high-dose calcium and calcitriol until bone stores are replete again.

Renal transplantation, if successful, reverses the root cause of renal osteodystrophy (i.e. kidney impairment), but hypertrophied PTH glands may involute only slowly over years or never, producing low serum PO4 levels and persistent hypercalcaemia. Osteoporosis can develop rapidly from steroid usage, and is improved in the short-term by bisphosphonates.

Cardiovascular disease and osteodystrophy

Kidney failure of all degrees accelerates vascular disease and mortality. Extensive arterial calcification involving the media layer (not the intima seen in the general population) is characteristic, as is progressive cardiac valve calcification. This is strongly correlated with high levels of PO4 and calcium-PO4 product, which can be a result of either renal disease *per se* or the side-effects of PO4 binder or calcitriol therapy.

Rarely, calciphylaxis, a rapidly progressive illness with subcutaneous small vessel calcification and thrombosis, can produce widespread necrosis of fat and skin, with a high mortality from secondary infection. Predisposing factors include conventional vascular risk factors, plus obesity, recent steroid or warfarin use, and high phosphate levels. Infusions of sodium thiosulphate can have dramatic benefit in some cases.

Table 1. Manifestations and therapy of the major forms of renal osteodystrophy.

Bone disease	Symptoms	Biochemistry	X Rays	Treatment
2° HPTH (v. common, early)	Pruritus, Ca deposits	↑PO4→↓Ca →↑PTH→↑ALP	Late, phalangeal erosions, rugger-jersey spine, pepperpot skull	Low PO4-diet, PO4-binders, calcitriol, calcimimetics, PTHx
3° HPTH (late)	Ditto plus heel pain, red eyes	Ditto but ↑↑Ca	Ditto	Ditto, but no CaCO3 or calcitriol
Osteomalacia +/- Al^{3+} toxicity (uncommon)	Bone pain, prox myopathy	↓1,25D→↓ALP & ↓Ca/↓PO4→ ↓↑PTH	Pseudofractures (esp. pubic rami & ribs), fractures	Calcitriol
Adynamic bone disease (common)	Esp. diabetics, elderly	Ditto but ↑Ca	Nil	Avoid calcitriol or CaCO3
B2M-amyloid (rare, late)	Carpal tunnel, synovitis	Nil	Carpal bone cysts	Steroids for symptoms. Renal transplant for prevention

Abbreviations: ALP = serum alkaline phosphatase; Ca = serum calcium; CaCO3 = calcium carbonate; HPTH = hyperparathyroidism; PO4 = serum phosphate; PTH = parathyroid hormone; 1,25D = 1,25 Vitamin D or calcitriol. PTHx-Parathyroidectomy

This clinical update is supported by an independent educational grant to *Medical Forum* by Amgen Australia Pty Ltd.