Management of renal bone disease

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Summary

Renal bone disease occurs in patients with chronic kidney disease. There are changes in the concentrations of calcium, phosphate, vitamin D and parathyroid hormone. Systemic complications include renal osteodystrophy and soft tissue calcification, which contribute to morbidity and mortality. As the changes of renal bone disease are potentially modifiable, early referral to a nephrologist for monitoring and treatment is recommended. Early advice about diet and regular monitoring of calcium, phosphate and parathyroid hormone are necessary. Careful prescribing of drugs and dialysis to achieve specific biochemical targets can minimise the complications. Phosphate binders and vitamin D analogues are required by most patients with advanced renal failure.

Key words: kidney disease, parathyroid hormone, phosphate binders, vitamin D.

Introduction

Renal bone disease is a general term for the spectrum of complex changes to mineral metabolism and bone strength seen in patients with chronic kidney disease.[1] It is characterised by altered calcium, phosphate and vitamin D homeostasis and an altered physiological response to parathyroid hormone. The consequences of these changes include diminished bone strength and mineralisation (renal osteodystrophy)[2–4] as well as soft tissue and vascular calcification which occasionally results in the clinical syndrome of calcific uraemic arteriolopathy.[5] These systemic complications are collectively referred to as chronic kidney disease mineral and bone disorder.[1] This disorder impacts on cardiovascular disease progression, morbidity and mortality.[6,7]

Renal osteodystrophy encompasses a number of histologically different conditions. These include both low (adynamic bone disease) and high (osteitis fibrosa) bone turnover states, as well as conditions of altered mineralisation. These conditions all decrease bone strength and predispose the patient to pathological fractures.[2,6]

Calcium and phosphate physiology

Plasma concentrations of calcium and phosphate are normally tightly regulated. Calcium absorption from the gut is stimulated by calcitriol whereas phosphate absorption largely varies with dietary intake and has less regulation by calcitriol. Most of the absorbed calcium and phosphate is stored in the bones with very small amounts present in the circulation. Both calcium and phosphate are filtered at the glomerulus. Calcium reabsorption is regulated by a calcium sensing receptor and increased by parathyroid hormone. Phosphate reabsorption is decreased by parathyroid hormone and fibroblast growth factor-23 and increased by calcitriol (see Fig. 1 online).

Calcitriol and vitamin D

Vitamin D (calciferol) is synthesised *in vivo* by photoactivation of steroid precursors in the skin. Calciferol is hydroxylated in the liver to calcidiol (25-hydroxycalciferol) which is subsequently bioactivated to calcitriol (1,25-dihydroxycalciferol) by 1-α-hydroxylase. Most circulating calcitriol is produced by 1-α-hydroxylation in the proximal tubule. It is now known that hydroxylation can also occur in many extra-renal tissues, where calcitriol is presumed to have a paracrine effect.[8] Calcitriol is the most potent vitamin D analogue, but calcidiol may have a significant role in immunomodulation, cancer reduction, insulin secretion and other effects.[9–11] Vitamin D analogues increase the body stores of calcium.

Parathyroid hormone

Parathyroid hormone maintains the concentration of ionised calcium. It is synthesised and released into the circulation in response to hypocalcaemia and hyperphosphataemia. Its synthesis is inhibited by vitamin D analogues and hypercalcaemia. Parathyroid hormone has multiple systemic effects including increased bone turnover by stimulation of both osteoblasts and osteoclasts. In the kidney it decreases excretion of calcium, increases excretion of phosphate and induces 1-α-hydroxylation of calcidiol. In normal physiology, an increase in parathyroid hormone has the net effect of increasing the concentration of calcium and decreasing the concentration of phosphate.

Pathophysiology and progression of renal bone disease

Early changes in chronic kidney disease are hyperphosphataemia, due to impaired excretion, and

hypocalcaemia, due to decreased calcitriol production. Calcitriol deficiency impairs mineralisation of bone (osteomalacia) and increases the risk of fracture. Hyperphosphataemia, hypocalcaemia and calcitriol deficiency induce parathyroid hormone release (Fig. 2). This is called secondary hyperparathyroidism and is treated by correction of the imbalance of calcium, phosphate and vitamin D.[12] However, prolonged stimulation of parathyroid hormone secretion leads to hyperplasia of the parathyroid glands and insensitivity to changes in calcium, phosphate and vitamin D. Consequently there is autonomous secretion of parathyroid hormone which, when it results in hypercalcaemia, is sometimes referred to as tertiary hyperparathyroidism.

In patients with severe chronic kidney disease the biological activity of parathyroid hormone appears to be reduced, probably due to the presence of unmeasured parathyroid hormone metabolites which have a counter-regulatory effect on bone. Pathologically elevated parathyroid hormone has multiple deleterious effects including osteitis fibrosa, cardiac fibrosis with ventricular failure, marrow fibrosis with erythropoietin resistance, and proximal myopathy.

Fibroblast growth factor-23 appears to be produced by osteocytes in response to hyperphosphataemia. It is phosphaturic and inhibits the formation of calcitriol which may exacerbate chronic kidney disease mineral and bone disorder.

Other effects of renal failure include metabolic acidosis. This increases the dissolution of calcium from bone and possibly alters deposition, exacerbating renal bone disease.

Symptoms

Many pathological changes due to renal bone disease are asymptomatic. With marked hyperparathyroidism there may be arthralgias, bone pains and deformity, neuropathy and marrow fibrosis with anaemia despite sufficient erythropoietin.[12] These patients have an increased risk of fracture. In advanced disease, calcification of cutaneous blood vessels may rarely progress to thrombosis (calcific uraemic arteriolopathy or calciphylaxis), resulting in painful ulcerating nodules that are associated with a high mortality.[12,13]

Diagnosis and monitoring

All patients with chronic kidney disease, particularly if the glomerular filtration rate (GFR) is under 60 mL/min, should be screened for renal bone disease regularly. The concentrations of calcium, phosphate and parathyroid hormone are closely monitored to guide therapy. Guidelines are available to assist with treatment decisions, although many are based on expert opinion from observational studies and there are small regional variations.[14,15] Treatment targets for patients with chronic kidney disease are based on the Caring for Australasians with Renal Impairment guidelines.[16,17] These targets are:

- phosphate – within the reference range
- albumin-corrected calcium – within the reference range if the GFR is 15–30 mL/min, but at the lower end of the range if the GFR is lower. Ionised calcium may be a more accurate measurement.[18]
- calcium-phosphate product – less than 4 $mmol^2/L^2$
- parathyroid hormone – when the GFR is less than 15 mL/min the target is 15–22 pmol/L, as undertreatment may

Fig. 2

Pathophysiology of renal bone disease

Key
PTH   parathyroid hormone
Ca   calcium
PO_4 phosphate
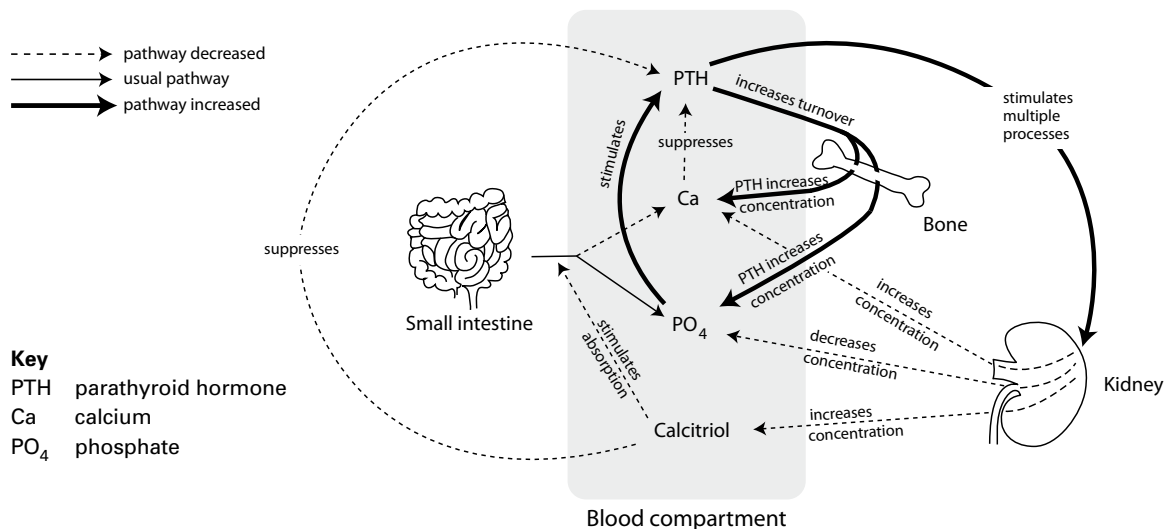
Impaired renal function leads to hyperphosphataemia, hypocalcaemia and hyperparathyroidism. This increases bone turnover which exacerbates hyperphosphataemia and hyperparathyroidism.

cause osteitis fibrosa (for example when parathyroid hormone exceeds 50 pmol/L) while over-suppression may cause adynamic bone disease (for example when parathyroid hormone is under 10 pmol/L). According to American guidelines, if the GFR is 15–29 mL/min the target is less than 12 pmol/L and if the GFR is 30–60 mL/min the target is the reference range (1.6–7.2 pmol/L).[19]

Calcidiol, calcitriol and alkaline phosphatase may also be monitored, but the extent to which this influences clinical decisions is less defined. For example, calcidiol less than 75 nmol/L is probably suboptimal, but the target concentration is uncertain. The role of fibroblast growth factor-23 and biomarkers of bone turnover used in osteoporosis have not been sufficiently evaluated in renal bone disease.

In stable disease, calcium and phosphate concentrations are checked every 1–3 months and parathyroid hormone is checked every 3–6 months. Calcidiol concentrations should usually be checked before starting treatment with calcitriol, but there is no recommendation regarding the frequency of ongoing testing.

Measuring bone mineral density to predict fracture risk in patients with chronic renal failure is controversial. The measurements do not differentiate between high, low and normal bone turnover states nor do they reliably detect abnormal mineralisation.[20–22] Consequently, they are unhelpful in guiding management.

Patient education to limit the progression of renal bone disease

The management of chronic renal failure is multidisciplinary. In particular, dietary education regarding a low phosphate diet may limit progression of chronic kidney disease mineral and bone disorder. Education regarding medication adherence, dialysis attendance and regular medical review is also important. Early referral to a specialist is recommended.

Treatment

Preventing renal bone disease is a priority because advanced disease responds poorly to treatment. Observational studies show that many patients do not achieve their desired treatment targets, although over the last decade some improvement has been observed.[7,14] There is an opportunity for both clinicians and patients to improve management to optimise clinical outcomes (see Fig. 3 online).

Phosphate reduction

Controlling phosphate concentrations helps to control the secretion of parathyroid hormone.

Dietary restriction

Dietary review and information regarding avoidance of foods high in phosphate, such as dairy products, cola soft drinks and nuts, may be needed in less severe renal disease. This is particularly important for patients with hyperphosphataemia and secondary hyperparathyroidism.[19] It is usually necessary once the patient reaches the end stage. The need for dietary restriction needs to be balanced against the risk of malnourishment.

Phosphate binders

Various compounds are available and all are taken with meals to adsorb dietary phosphate in the gut. Calcium salts are most commonly administered because they are cheap and help to maintain serum calcium. They tend to be unpalatable and constipating and may have the unwanted effect of causing hypercalcaemia.[23]

Sevelamer and lanthanum are newer drugs for patients intolerant of calcium salts. Sevelamer is a non-metal polymer-based binder that is not absorbed from the gut, while lanthanum is a rare earth metal which is minimally absorbed. These drugs are generally prescribed for hyperphosphataemia not controlled by calcium or when the calcium-phosphate product is greater than 4 mmol^2/L^2. Both drugs decrease phosphate absorption, but long-term data confirming health benefits are currently only available for sevelamer.[23,24]

Aluminium salts are effective phosphate binders, but are not recommended because aluminium accumulates in renal impairment. This can cause anaemia and neurological complications.

Renal replacement therapy

Dialysis removes phosphate and this is enhanced if the duration and frequency of dialysis are increased.

Vitamin D analogues

Multiple vitamin D analogues are available, but their relative advantages are debated.[25,26] Colecalciferol (vitamin D$_3$), and less commonly ergocalciferol (vitamin D$_2$) are oral formulations used in Australia by patients who do not require dialysis. In patients having dialysis, preliminary studies suggest colecalciferol partially corrects chronic kidney disease mineral and bone disorder.[27,28] However, routine supplementation is controversial and not currently recommended in every guideline. American guidelines recommend supplementation to a plasma concentration of calcidiol of more than 75 nmol/L.[19]

Calcitriol is listed on the Pharmaceutical Benefits Scheme for hypocalcaemia due to renal failure, but in clinical practice it is mainly prescribed to suppress elevated parathyroid hormone concentrations. Calcitriol is a potent vitamin D analogue so careful monitoring for hypercalcaemia is necessary.

Alfacalcidol (1-α-calciferol) and other dihydroxyvitamin D analogues such as paricalcitol (intravenous) and doxercalciferol are used less commonly in Australia.

All vitamin D analogues can cause hypercalcaemia and hyperphosphataemia. Appropriate monitoring and dose adjustment of phosphate binders is therefore required.

Other treatments

Cinacalcet

Cinacalcet is a calcium receptor sensitiser (calcimimetic) that inhibits parathyroid hormone release. It is usually used for patients receiving dialysis when parathyroid hormone exceeds 50 pmol/L, or is 15–50 pmol/L with hypercalcaemia, despite conventional treatment. Doses are titrated from 30 mg to 180 mg daily. Cinacalcet has the advantage of lowering parathyroid hormone, serum calcium and phosphate[29] (see Fig. 4 online).

Calcium salts

In addition to phosphate binding properties, calcium salts are often administered with vitamin D to suppress parathyroid hormone and to normalise body stores and ionised calcium for normal cell function. High doses should be avoided because they are associated with vascular calcification.[30]

Sodium bicarbonate

Correction of metabolic acidosis may be useful because studies of alkali therapy in patients who are not in renal failure suggest an improvement in bone parameters.[31–33] Sodium bicarbonate is poorly tolerated in higher doses due to flatulence, and imposes a sodium load which can exacerbate problems with fluid retention.

Bisphosphonates

Routine use of bisphosphonates is not currently recommended due to limited data on their efficacy and safety in patients having dialysis. Concerns include exacerbation of chronic kidney disease mineral and bone disorder (including adynamic bone disease and secondary hyperparathyroidism) and toxicity due to impaired clearance. However, they may reduce vascular calcification[34] and limit hypercalcaemia when there is high bone turnover.

Surgical parathyroidectomy

This is indicated for severe secondary or tertiary hyperparathyroidism that fails to respond to optimum medical treatment, particularly if the patient is symptomatic or if there is coexistent hyperphosphataemia, hypercalcaemia or evidence of high turnover bone disease. Surgical parathyroidectomy is potentially avoidable with careful treatment of the mineral and hormonal disturbances in chronic kidney disease.[7]

Conclusion

Renal bone disease is an important consequence of chronic kidney disease. Frequent monitoring of the plasma concentration of calcium, phosphate and parathyroid hormone is essential to minimise complications. Treatment includes dietary advice and titrated doses of oral phosphate binders such as calcium salts, vitamin D analogues, sodium bicarbonate and cinacalcet. Dialysis is beneficial for patients with end-stage renal failure. Early referral to a nephrologist to guide monitoring and treatment is recommended.

Note: Figures 1, 3 and 4 are available online at www.australianprescriber.com with this article in Vol 33 No 2.

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The full list of references is available online at www.australianprescriber.com with this article in Vol 33 No 2.

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