Chronic kidney disease-mineral bone disorder

ABSTRACT

Chronic kidney disease-mineral bone disorder is typically seen in patients with advanced chronic kidney disease. It is managed primarily by renal physicians, but non-renal physicians are also likely to encounter patients undergoing treatment for this condition in both inpatient and outpatient settings so a basic understanding of the principles may be helpful. This article covers the fundamentals of the pathophysiology, diagnosis and treatment of chronic kidney disease-mineral bone disorder.

Chronic kidney disease-mineral bone disorder encompasses a collection of mineral bone pathologies that occur in people who have chronic kidney disease. While biochemical abnormalities start to be detected as the estimated glomerular filtration rate falls below 30 ml/min/1.73 m^2, and particularly when the estimated glomerular filtration rate is less than 20 ml/min/1.73 m^2, pathological changes can start as early as when the estimated glomerular filtration rate is between 60 and 89 ml/min/1.73 m^2 (chronic kidney disease stage 2).

The management of chronic kidney disease-mineral bone disorder is undertaken by nephrologists and renal dieticians in a specialist setting. Nevertheless, clinicians across many other specialties will care for patients who are receiving treatment for chronic kidney disease-mineral bone disorder. Thus, an understanding of the principles of this disorder will be helpful for the non-renal clinician.

Dr Thomas Cronin, Core Medical Trainee, Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne

Dr Mohammed Abdelmahamoud, Renal Specialty Registrar, Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne

Dr Derek Falls, Foundation Year 2 Doctor, Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne

Ms Katherine Punshon, Medical Student, Flinders University, Adelaide, Australia

Dr Jamie Willows, Renal Specialty Registrar, Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne

Dr Nony Mordi-Blair, Renal Specialty Registrar, Department of Renal Medicine, Freeman Hospital, Newcastle upon Tyne NE7 7DN

Correspondence to: Dr N Mordi-Blair (nonym@doctors.org.uk)

Chronic kidney disease-mineral bone disorder: pathophysiology

The drivers of chronic kidney disease-mineral bone disorder are increased levels of fibroblast growth factor 23 (FGF23), parathyroid hormone and phosphate, and decreased levels of active vitamin D and calcium (*Figure 1*). There is still debate on the chronology of changes, although it appears that the sequence of events that lead to chronic kidney disease-mineral bone disorder begins with increasing production of FGF23 (Quarles, 2008). It is unclear what stimulates its production in patients with chronic kidney disease, but it can be affected by levels of phosphate, calcium, parathyroid hormone and calcitriol (1,25(OH)2D, active vitamin D), and is found at significantly elevated levels in patients with chronic kidney disease.

FGF23 inhibits phosphate reabsorption within the renal tubule, initially overcoming the tendency to reduced renal phosphate excretion that results from reduced nephron numbers. This hormone also acts to suppress calcitriol production in the kidney. A lower calcitriol level and elevated FGF23 level both lead to increased parathyroid hormone secretion and reduced serum levels of calcium. The net effect of these changes is to reduce absorption of phosphate from the gut and increase phosphate excretion within the urine (Bergwitz and Jüppner, 2010), alongside increased calcium resorption from the bone. While this protects the body from the adverse effects of hyperphosphataemia, it comes at the expense of the damaging effects of hyperparathyroidism on bone (the 'trade-off' hypothesis – *Figure 2*) (Gutiérrez, 2010).

Broadly, two interchangeable states are identified in chronic kidney disease-mineral bone disorder: increased turnover bone disease and adynamic bone disease. High turnover bone disease, driven by secondary hyperparathyroidism, leads

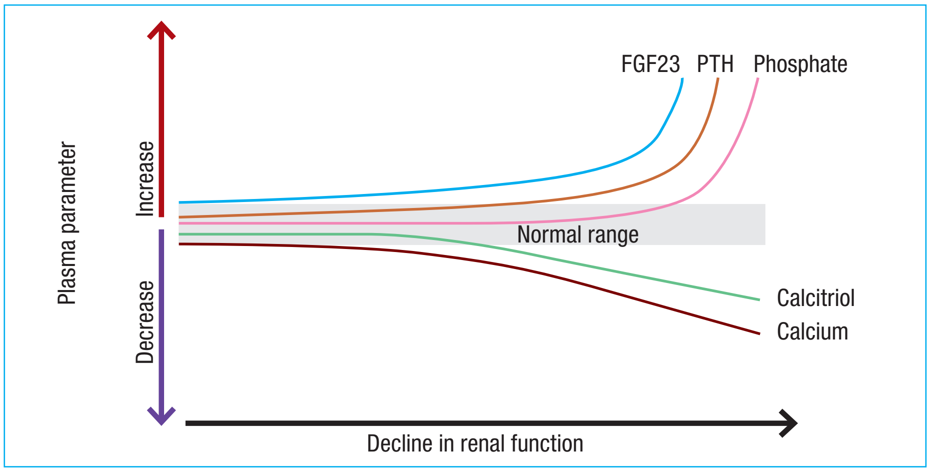

Figure 1. The sequence of events occurring in chronic kidney disease-mineral bone disorder. FGF23 = fibroblast growth factor 23; PTH = parathyroid hormone.

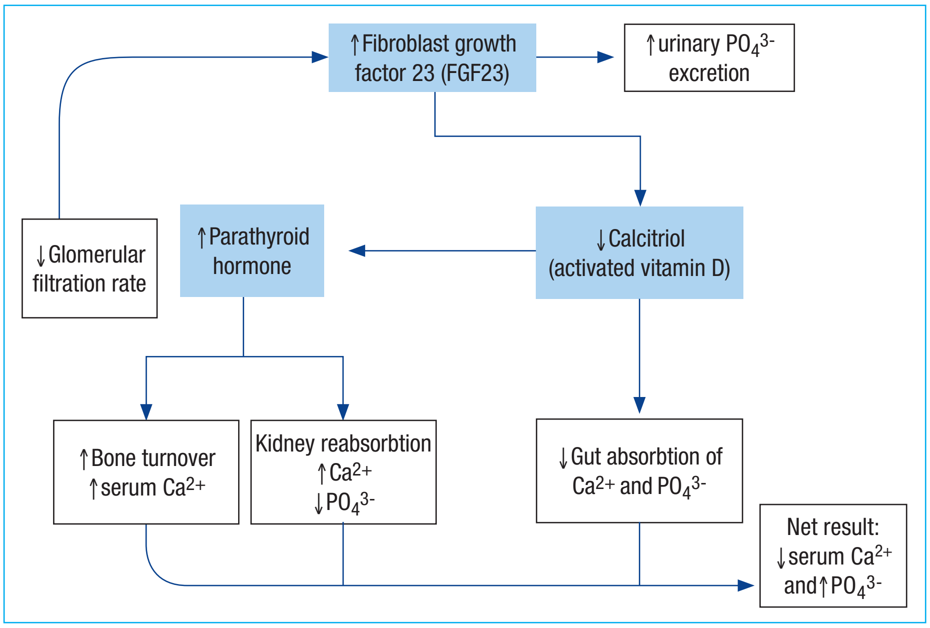

Figure 2. The pathophysiology of chronic kidney disease-mineral bone disorder.

CASE STUDY

A 36-year-old woman presented to the medical admissions unit with lethargy and shortness of breath. There was no past medical history available since she has just moved to the UK from sub-Saharan Africa and a translator had not yet been located. Physical examination demonstrated a right radiocephalic arteriovenous fistula. Her serum urea level was 16.0 mmol/litre and creatinine level was 748 µmol/litre. It was concluded that she was being treated with haemodialysis.

Blood tests (*Table 1*) demonstrated significantly elevated alkaline phosphatase and parathyroid hormone levels. She was hypocalcaemic and hyperphosphataemic – consistent with poorly controlled secondary hyperparathyroidism.

Radiographs of her pelvis and lumbar spine are shown in *Figures 3* and *4*. Her pelvis demonstrates a poorly healed left femoral neck fracture. Her lumbar spine shows an alternating sclerotic-lucent-sclerotic appearance (reflecting increased osteoclastic and synthetic activity); the so-called 'rugger-jersey' spine. A computed tomography scan of her mandible shows evidence of a Brown tumour on the right side (*Figure 5*).

This degree of renal bone disease is rarely seen in contemporary UK clinical practice, but demonstrates the consequences of unmanaged chronic kidney disease-mineral bone disorder.

Table 1. Biochemical profile

Bone profile	Measurements
Adjusted calcium	1.98 mmol/litre (2.20–2.60)
Phosphate	1.88 mmol/litre (0.80–1.50)
Albumin	34 g/litre (35–50)
Alkaline phosphatase	966 unit/litre (30–130)
Parathyroid hormone	287 pmol/litre (1.1–6.4)

Normal ranges in brackets

Figure 3. Pelvic radiograph showing a poorly healed left femoral neck fracture (arrow).

Figure 4. Lumbar spine radiograph showing alternating sclerotic-lucent-sclerotic appearance.

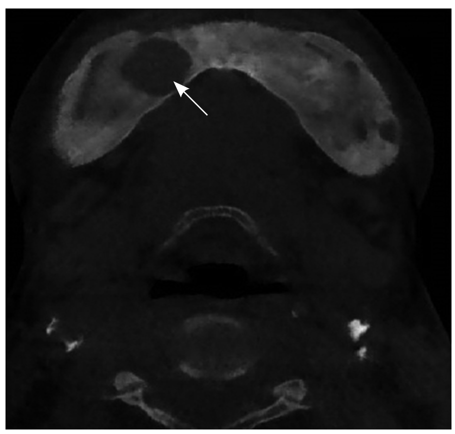

Figure 5. Cone beam computed tomography of the mandible showing a Brown tumour on the right side (arrow).

to the changes seen in the *Case study* of Brown tumours and 'rugger-jersey' spine.

Adynamic bone disease is characterized by markedly low bone turnover. A poorly understood process, treatments which lower parathyroid hormone levels may contribute to this state, hence reducing parathyroid hormone levels to normal ranges is not recommended in patients with chronic

Figure 6. Calciphylaxis affecting the lower limbs.

kidney disease-mineral bone disorder. Both high turnover and adynamic bone disease predispose to fractures – the incidence of hip fractures is fourfold higher in dialysis patients than the general population (Alem et al, 2000).

Risk of cardiovascular disease in patients with chronic kidney disease-mineral bone disorder

The purpose of managing chronic kidney disease-mineral bone disorder is two-fold: to protect the bones and to limit the adverse effects of bone mineral disturbances on the cardiovascular system. Elevated FGF23, parathyroid hormone and phosphate levels, and decreased calcitriol levels have all been linked to increased risk of cardiovascular disease (Palmer et al, 2011; Ärnlöv et al, 2013). In patients with advanced chronic kidney disease, vascular smooth muscle cells can undergo transition to an osteoblastic phenotype, resulting in vascular medial calcification, stiffening of arteries, increased systolic blood pressure, left ventricular hypertrophy and reduced coronary filling (London, 2002). Hyperphosphataemia is considered a driver of this process and in animal models of chronic kidney disease lowering phosphate levels attenuates this pathology (Shobeiri et al, 2010). While there is limited trial evidence that phosphate control leads to improved outcomes in cardiovascular disease (Navaneethan et al, 2009), observational data are highly supportive of this (Eddington et al, 2010).

Calciphylaxis (*Figure 6*) is a consequence of vascular calcification occurring at the level of the arterioles. Extensive calcification impairs microvascular blood flow, causing ischaemia and skin necrosis. It is an extremely painful condition and is frequently complicated by infection. The presence of calciphylaxis carries a poor prognosis (Mazhar et al, 2001). Warfarin is a risk factor for its development because it reduces the activity of the vitamin K-dependent calcification inhibitor matrix Gla protein (Nigwekar et al, 2015). This is one reason for caution when prescribing warfarin for patients with end-stage renal disease.

Diagnosing chronic kidney disease-mineral bone disorder

Although interventions are required mainly at an estimated glomerular filtration rate below 20 ml/min/1.73 m^2, it is recommended that testing for chronic kidney disease-mineral bone disorder begins when estimated glomerular filtration rate falls below 60 ml/min/1.73 m^2 (the cut off for chronic kidney disease stage 3a) (Ketteler et al, 2017).

Assessment of chronic kidney disease-mineral bone disorder is based on identifying abnormalities of serum calcium, phosphate, 25(OH) vitamin D, and parathyroid hormone (*Figure 1*). FGF23 is not currently routinely measured in clinical practice.

Bone mineral density testing is not typically used in the investigation of patients with chronic kidney disease-mineral bone disorder. Bone biopsy is the gold standard for defining the nature of renal bone disease (particularly to distinguish increased bone turnover and adynamic bone disease), but because of its invasive nature is rarely performed in clinical practice.

Treating chronic kidney disease-mineral bone disorder

Treatment aims to limit biochemical disturbances in calcium, phosphate and parathyroid hormone without necessarily returning parameters to their normal healthy ranges. Treatment should be based on the serial measurement of these parameters to determine the trend of the results rather than on one single reading.

In non-dialysis patients with chronic kidney disease stage 3–5, the aim should be to maintain serum phosphate levels within the normal range. In dialysis patients, the treatment goal for limiting hyperphosphataemia is a pre-dialysis serum phosphate level between 1.1 and 1.7 mmol/litre.

The optimal parathyroid hormone target in non-dialysis patients with chronic kidney disease stage 3–5 is not known. However, it is suggested that patients with levels of parathyroid hormone which are progressively rising or persistently elevated be evaluated for modifiable factors including high phosphate intake and vitamin D deficiency. For dialysis patients it is recommended that the parathyroid hormone level be maintained between two and nine times the upper limit of normal (Ketteler et al, 2017), because it is believed that lowering parathyroid hormone values to the normal range can increase the incidence of adynamic bone disease.

Hyperphosphataemia is addressed through dietary phosphate restriction and

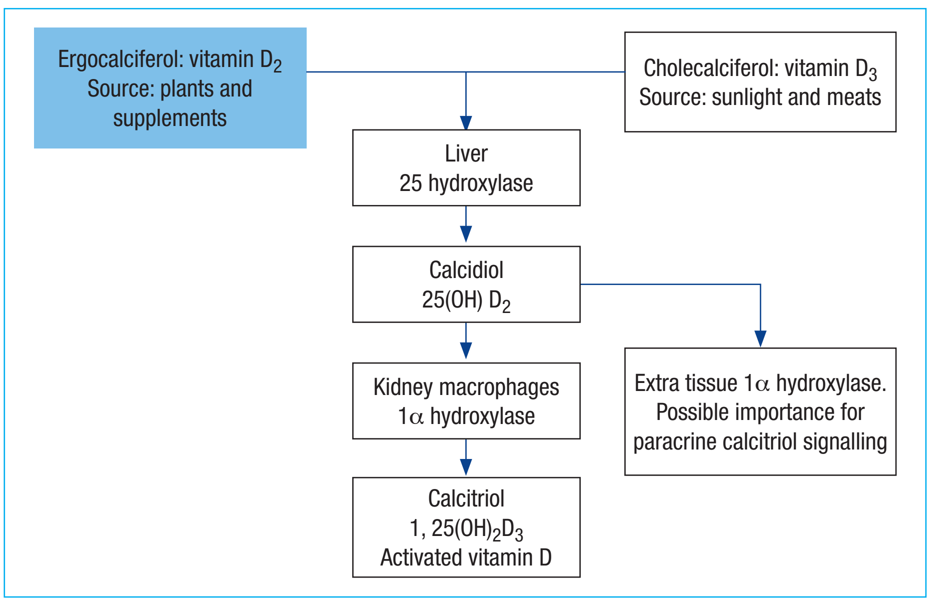

Figure 7. The process of vitamin D activation.

CURRICULUM CHECKLIST

This article addresses the following requirements from the general internal medicine training curriculum

- Managing patients in an outpatient clinic, ambulatory or community setting (including management of long term conditions)
- Managing medical problems in patients in other specialties and special cases.

phosphate binders. Phosphate binders are given with food to reduce gut phosphate absorption. These may be calcium-based (calcium acetate and calcium carbonate) or non-calcium-based (sevelamer, lanthanum, iron-based, magnesium preparations, or aluminium hydroxide).

To control hyperparathyroidism, alfacalcidol may be used. This is 1-alpha hydroxylated vitamin D (i.e. bypassing the need for 1-alpha hydroxylation in the kidney) that is activated to calcitriol in the liver (*Figure 7*). Calcitriol suppresses parathyroid hormone production, but also increases the intestinal absorption of calcium and phosphate. Thus hypercalcaemia and hyperphosphataemia may limit its use. In these circumstances, cinacalcet (a calcimimetic) may be used or, should medical treatment fail, parathyroidectomy may be needed.

Although the process of converting 25(OH) vitamin D to active vitamin D is inhibited by FGF23 in people with chronic kidney disease, normalizing 25(OH) vitamin D levels is still recommended. This is because 1-alpha hydroxylation may take place in tissues outside the kidney and calcitriol may have important local tissue actions. Therefore vitamin D deficiency and insufficiency should be corrected using treatment strategies as for the general population (Ketteler et al, 2017).

Managing osteoporosis in chronic kidney disease

In patients with chronic kidney disease who have an estimated glomerular filtration rate above 30 ml/min/1.73 m^2 and osteoporosis, treatment is typically instigated as for the general population (Ketteler et al, 2017).

Below an estimated glomerular filtration rate of 30 ml/min/1.73 m^2, bisphosphonates are contraindicated. This is because bisphosphonates work by suppressing bone turnover (inhibiting osteoclastic activity) and in patients with chronic kidney disease-mineral bone disorder this can lead to a state of adynamic bone disease (Toussaint et al, 2009).

Denosumab, a monoclonal antibody, may be a preferred option in treating osteoporosis in patients with chronic kidney disease, although it is associated with hypocalcaemia and is used for short periods of time only (Ketteler et al, 2017).

Conclusions

The management of renal bone disease is complex, requiring multidisciplinary efforts including renal physicians and dieticians. Regular monitoring in a specialist setting is required for the expert management of such patients. **BJHM**

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Alem AM, Sherrard DJ, Gillen DL et al. Increased risk of hip fracture among patients with end-stage renal disease. Kidney Int. 2000 Jul;58(1):396–399. https://doi.org/10.1046/j.1523-1755.2000.00178.x

Ärnlöv J, Carlsson AC, Sundström J, Ingelsson E, Larsson A, Lind L, Larsson TE. Serum FGF23 and risk of cardiovascular events in relation to mineral metabolism and cardiovascular pathology. Clin J Am Soc Nephrol. 2013 May 07;8(5):781–786. https://doi.org/10.2215/CJN.09570912

Bergwitz C, Jüppner H. Regulation of phosphate homeostasis by PTH, vitamin D, and FGF23. Annu Rev Med. 2010 Feb;61(1):91–104. https://doi.org/10.1146/annurev.med.051308.111339

Eddington H, Hoefield R, Sinha S et al. Serum phosphate and mortality in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010 Dec;5(12):2251–2257. https://doi.org/10.2215/CJN.00810110

Gutiérrez OM. Fibroblast growth factor 23 and disordered vitamin D metabolism in chronic kidney disease: updating the "trade-off" hypothesis. Clin J Am Soc Nephrol. 2010 Sep;5(9):1710–1716. https://doi.org/10.2215/CJN.02640310

Ketteler M, Block GA, Evenepoel P et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int. 2017 Jul;92(1):26-36. https://doi.org/10.1016/j.kint.2017.04.006

London GM. Left ventricular alterations and end-stage renal disease. Nephrol Dial Transplant. 2002 Jan 1;17(suppl_1):29-36. https://doi.org/10.1093/ndt/17.suppl_1.29

Mazhar AR, Johnson RJ, Gillen D, Stivelman JC, Ryan MJ, Davis CL, Stehman-Breen CO. Risk factors and mortality associated with calciphylaxis in end-stage renal disease. Kidney Int. 2001 Jul;60(1):324–332. https://doi.org/10.1046/j.1523-1755.2001.00803.x

Navaneethan SD, Palmer SC, Craig JC, Elder GJ, Strippoli GFM. Benefits and harms of phosphate binders in CKD: a systematic review of randomized controlled trials. Am J Kidney Dis. 2009 Oct;54(4):619–637. https://doi.org/10.1053/j.ajkd.2009.06.004

Nigwekar SU, Kroshinsky D, Nazarian RM et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015 Jul;66(1):133–146. https://doi.org/10.1053/j.ajkd.2015.01.034

Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, Strippoli GF. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. JAMA. 2011 Mar 16;305(11):1119–1127. https://doi.org/10.1001/jama.2011.308

Quarles LD. Endocrine functions of bone in mineral metabolism regulation. J Clin Invest. 2008 Dec 1;118(12):3820–3828. https://doi.org/10.1172/JCI36479

Shobeiri N, Adams MA, Holden RM. Vascular calcification in animal models of CKD: A review. Am J Nephrol. 2010;31(6):471–481. https://doi.org/10.1159/000299794

Toussaint ND, Elder GJ, Kerr PG. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. Clin J Am Soc Nephrol. 2009 Jan;4(1):221–233.https://doi.org/10.2215/CJN.02550508

KEY POINTS

- The pathophysiology of chronic kidney disease-mineral bone disorder begins with elevated levels of fibroblast growth factor 23 which suppresses vitamin D activation and promotes hyperparathyroidism, maintaining phosphate excretion.
- Uncontrolled hyperparathyroidism causes lytic bone lesions, but low turnover bone disease can also occur.
- The assessment of chronic kidney disease-mineral bone disorder is based on serial measurements of calcium, phosphate, 25(OH) vitamin D and parathyroid hormone.
- Goals of treatment are to preserve bone strength and limit vascular calcification.
- Interventions include dietary phosphate restriction, phosphate binders, normalisation of 25(OH) vitamin D if deficient, 1-alpha hydroxylated vitamin D to suppress hyperparathyroidism, and cinacalcet or parathyroidectomy if parathyroid hormone levels cannot be adequately controlled without causing hypercalcaemia.
- Owing to concerns regarding adynamic bone disease, bisphosphonates are considered contraindicated at an estimated glomerular filtration rate <30 ml/min/1.73 m^2.