

What I tell my patients about renal bone disease

Chronic kidney disease (CKD) has been classified as having five stages. Stage 1 describes mild disease and stage 5 describes severe disease. As CKD progresses in severity, its effects on the rest of the body become apparent. The bones are an area that may be affected. Patients with CKD may develop a number of different types of bone problems. These are collectively known as renal bone disease (sometimes called renal osteodystrophy). Renal bone disease (RBD) is a complex problem. This article explains the different types of renal bone disease and their treatments.

The bones are a living part of the body and are constantly growing. Old bone is continuously being broken down (by cells called osteoclasts) while new bone is being produced (by cells called osteoblasts) to replace it. This process is called bone remodelling. Bones contain large amounts of minerals, such as phosphate and calcium. These minerals provide the bones' strength. Besides controlling the amount of fluid within the body, the kidneys also regulate the amounts of these minerals. Many of the bone problems occurring in patients with CKD result from an imbalance of these minerals. In theory, a sample of a patient's bone (a bone biopsy) is needed to clarify the extent to which each of the different forms of RBD may be present in a patient. In practice, however, doctors very rarely perform bone biopsies, and instead rely on blood tests (particularly the level of the parathyroid hormone [PTH], which increases the concentration of calcium in the blood) to provide this information.

Hyperparathyroid bone disease

Phosphate, calcium and PTH

Phosphate is taken into the body in food. As CKD progresses, the kidneys become less efficient at removing phosphate from the blood, which results in higher levels of phosphate in the blood. Calcium binds to this excess phosphate, and the levels of calcium in the blood therefore fall. The body responds to these reduced calcium levels by releasing greater amounts of PTH from the four parathyroid glands in the neck. Over time, this

Phosphate is taken into the body in food, such as hard cheeses like Parmesan



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increased production leads to enlargement of the glands – a condition called secondary hyperparathyroidism. PTH is a chemical messenger that acts to increase the level of calcium in the blood, in part through reclaiming calcium from the bones. Overall, therefore, secondary hyperparathyroidism removes calcium from the bones – leaving them weaker, brittle and more likely to fracture. This form of RBD is called hyperparathyroid bone disease. A simplified explanation is provided by the text boxes linked by the red arrows in Figure 1, overleaf. It is also sometimes called 'high turnover' bone disease, as the high levels of PTH stimulate increased activity of the osteoclast and osteoblast cells within the bones, leading to increased bone remodelling.

Vitamin D

As well as moving calcium from the bones into the bloodstream, PTH also raises the level of calcium in the blood by promoting the absorption of calcium from food. Adequate levels of the active (useful) form of vitamin D are essential for this process. Vitamin D is produced mainly in the skin (some is also obtained from food), but the

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kidneys are responsible for converting it to its active form. However, patients with CKD cannot convert vitamin D into the active form. Therefore, less calcium can be absorbed from food and the level of calcium in the blood falls, in turn leading to an increased production of PTH. A simplified explanation of this process is provided by the text boxes linked by the yellow arrows in Figure 1.

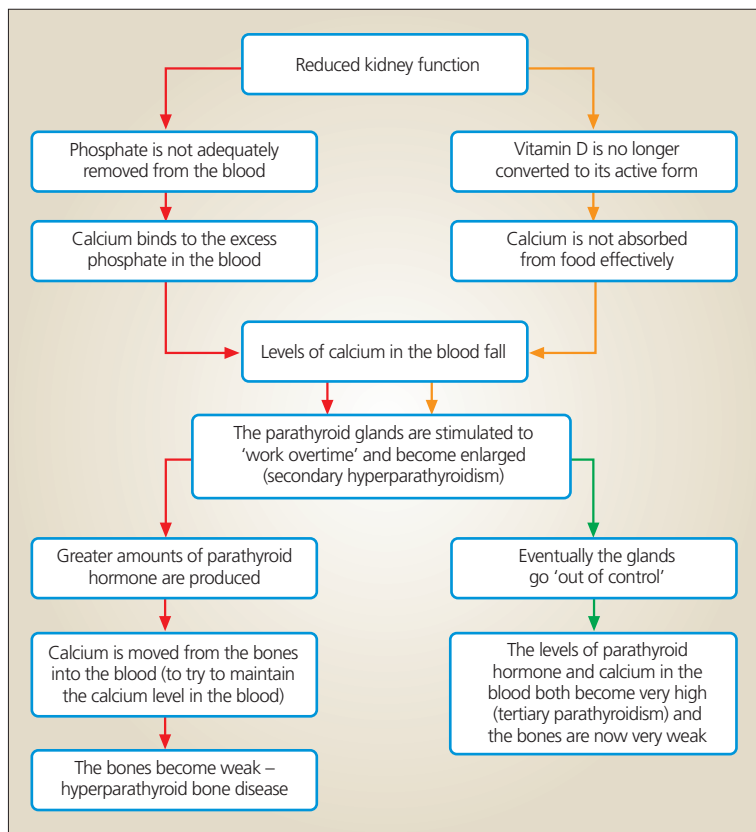
The symptoms of hyperparathyroid bone disease

RBD may develop as early as stage 3 CKD, when a patient's kidney function is approximately half of normal and before they have developed any of the symptoms of kidney failure. By the time patients have developed stage 5 CKD (for instance, those patients on dialysis), almost all will have some degree of RBD. Initially, hyperparathyroid bone disease may not cause any symptoms. As it progresses, itching, bone and joint pains, muscle weakness and fractures may develop.

Diagnosing hyperparathyroid bone disease

Doctors usually diagnose hyperparathyroid bone disease through blood tests that measure the levels of phosphate, calcium and PTH. The phosphate level is likely to be high or normal. The calcium level may be high, low or normal. The PTH level is high. A bone biopsy is rarely required. If it is considered necessary, it is usually done under local

Figure 1. How phosphate, calcium, parathyroid hormone and vitamin D are related



anaesthetic. A small sample of bone is taken from the hip and examined under a microscope. X-rays of the hands, feet or spine may show changes indicating hyperparathyroid bone disease but are rarely required to make the diagnosis.

Treating hyperparathyroid bone disease

Once damage to the bones begins to occur, it cannot be fully reversed. Therefore, rather than waiting for symptoms to develop, the treatment of hyperparathyroid bone disease should begin when it first becomes apparent from the blood results. The aims of treatment are to:

- Prevent the level of phosphate in the blood becoming too high
- Keep the level of calcium in the blood normal
- Prevent the parathyroid glands enlarging dramatically, and therefore keeping the level of PTH normal or only slightly raised.

A variety of treatments are available to achieve these goals. These are outlined below.

Dietary measures to reduce phosphate levels

The amount of phosphate reaching the bloodstream can be reduced by avoiding excessive amounts of the foods that are rich in phosphate (see Table 1, opposite). Dietitians can help patients to identify and avoid these foods.

Medications to reduce phosphate levels

It is difficult to restrict dietary phosphate sufficiently while maintaining an adequate intake of protein. Doctors may therefore also prescribe tablets to reduce the phosphate levels. Phosphate binders are tablets that soak up the phosphate released from food while it is still in the stomach. This prevents it reaching the bloodstream and the phosphate is excreted in the stool instead. Phosphate binders should be taken 15 minutes before a meal; patients may need to take multiple tablets. As different meals contain different levels of phosphate, dietitians can help patients to spread their daily tablets out appropriately across their meals. Patients may also need to take these tablets with certain snacks.

Phosphate binders should not be taken simultaneously with certain antibiotics, as both tablets will be less effective. Furthermore, phosphate binders should not be taken at the same time as iron supplements.

A number of phosphate binders are available and suit different patients. Phosex® (Vitaline, UK) (calcium acetate), Calcichew® (Shire, UK), and Adcal® (ProStrakan, UK) (all calcium carbonate) are calcium-based medicines that may taste



'chalky'. Phosex[®] should be swallowed whole while Calcichew[®], Adcal[®] and Titalac[®] should all be chewed. They reduce blood phosphate levels and may increase blood calcium levels. Unlike these tablets, Renagel[®] (Genzyme, UK) (sevelamer) and Fosrenol[®] (Shire, UK) (lanthanum carbonate) do not contain calcium. They are useful in patients in whom the level of calcium in the blood is already too high. Alu-cap[®] (3M, UK) (aluminium hydroxide) is an alternative phosphate binder. It is used less commonly these days as it can lead to memory problems through aluminium accumulation if taken for a long time. The capsules should be swallowed whole.

Vitamin D supplements

The active form of vitamin D may be prescribed as a once-daily tablet. This is helpful, as patients with CKD cannot convert vitamin D to its active form. These tablets are called Rocaltrol[®] (Roche, UK) (calcitriol) or One-Alpha[®] (LEO, UK) (alfacalcidol) and help to raise the level of calcium and lower the level of PTH in the blood.

Dialysis

Patients requiring dialysis have little or no remaining kidney function and cannot remove phosphate from their blood themselves. Dialysis will help to remove phosphate from the blood of these patients. However, even good-quality dialysis only removes a small amount of phosphate, so the other treatments outlined above are usually also required in these patients.

Surgery (parathyroidectomy)

Persistently low calcium levels drive the parathyroid glands to produce high levels of PTH. All four glands become enlarged (each to the size of a pea) and may eventually go out of control, despite the use of the medications mentioned above. When this happens, the secondary hyperparathyroidism has become tertiary hyperparathyroidism. The high levels of PTH lead to high levels of calcium. A simplified explanation is provided by the boxes linked by the green and yellow arrows in Figure 1, opposite.

Although the glands become enlarged, they are not cancerous. The treatment for tertiary hyperparathyroidism is an operation to remove the glands, called a parathyroidectomy.

Before the operation, the surgeon may ask an ear, nose and throat specialist to check the patient's vocal cords, as there is a small risk of damaging them during the operation. High doses of calcium and vitamin D tablets are usually given

Table 1. Foods containing high levels of phosphate

Beverages	Beers, cocoa, colas
Dairy products	Milk, cheese, cream soups, ice cream
Protein meals	Beef liver, chicken liver, oysters, sardines, crayfish, carp
Vegetables	Dried beans and peas (baked beans, kidney beans, chick peas, soy beans, lentils, black beans)
Others	Cereals, seeds, nuts, peanut butter

in the days preceding the operation. The operation is performed under a general anaesthetic by a specialist surgeon. Although enlarged, the glands may be difficult to find (they may vary in number and location). Sometimes scans are undertaken before the operation to identify the glands. The operation takes about two hours and the surgeon will usually try to remove all of the glands. Patients are usually in hospital for about five days. During this time, the calcium levels are monitored closely.

Some patients may not be well enough to undergo this operation. An alternative treatment for these patients is a medicine called a calcimimetic. An example is cinacalcet (Mimpara[®], Amgen, UK). These medications trick the body into thinking the levels of calcium in the blood are higher than they really are. The parathyroid glands, therefore, produce less PTH, which helps to reduce the high levels of calcium and phosphate in the blood. These medications remain very expensive and can only be prescribed by kidney specialists.

Adynamic bone disease

Unlike hyperparathyroid bone disease (where high levels of PTH stimulate the osteoclast and osteoblast cells to become overactive), adynamic bone disease results from underactivity of these cells. Old bone is not removed and new bone is not produced. Adynamic bone disease is, therefore, also called 'low turnover' bone disease. Adynamic bone disease is the other end of the spectrum of RBD from hyperparathyroid bone disease. However, the end result is similar. The bones become weaker and patients with adynamic bone disease are also at an increased risk of breaking bones. Adynamic bone disease is usually diagnosed through blood tests.

The most common cause of adynamic bone disease is low levels of PTH, which is usually the result of the medications used to treat hyperparathyroid bone disease. Doctors must,



therefore, find a balance between treating hyperparathyroid bone disease and preventing adynamic bone disease in each patient.

Osteomalacia

This form of RBD is the result of the failure of the kidneys to convert vitamin D into its active form. There is reduced activity of the osteoclast and osteoblast bone cells in osteomalacia, and it is considered a 'low turnover' bone disease like adynamic bone disease. However, in osteomalacia there is also a significant loss of minerals from the bone and treatment involves replacing vitamin D.

Osteoporosis

As in osteomalacia, the bones become less dense in patients with osteoporosis. However, whereas in osteomalacia this loss of bone density is the result of low levels of the minerals calcium and phosphate, the levels of calcium and phosphate are normal in osteoporosis. Instead, the loss of bone density is the result of thinning of the bony spicules (the structural supports within the bone). The bones of patients with osteoporosis are, therefore, weaker and prone to breakage.

Although osteoporosis may occur in otherwise healthy people, it is more common in patients with CKD. Those patients with CKD who receive a kidney transplant will lose bone mass after their transplant, especially in the first few months after the operation. This is partly due to the medicines that they are given.

Doctors may use bone density scans (also called DEXA scans) to assess osteoporosis, although these are less reliable in patients with CKD. Medicines called bisphosphonates (such as alendronate [Fosamax[®], MSD, UK] or risedronate [Actonel[®],

Procter & Gamble, UK]) are often used to treat osteoporosis. However, the role of these medicines in patients with severe CKD is unknown. In any case, the main concern for these patients is usually the treatment of hyperparathyroid bone disease or adynamic bone disease.

Gout

Gout may occur in otherwise healthy people. However, patients with CKD suffer gout more commonly because they often have high levels of uric acid (or urate) in their blood. This is mainly because their kidneys are less effective at removing uric acid from their blood. Patients with CKD may also take medicines (such as water tablets or diuretics) or have other medical conditions (such as high blood pressure) that lead to higher levels of uric acid. The uric acid forms crystals within the patient's joints. These crystals lead to inflammation and the affected joint becomes hot, red and swollen. Gout can be extremely painful. Any joint may be affected but the big toe is the most common site.

Treatment of sudden attacks of gout

Although non-steroidal anti-inflammatory drugs, such as ibuprofen (Brufen[®], Abbott, UK) or diclofenac (Voltarol[®], Novartis, UK) are the most common treatment for gout in patients without kidney disease, they should be avoided in patients with CKD. A tablet called colchicine is often used instead. This is a very effective treatment for gout, but some patients find that it causes diarrhoea, in which case it should be stopped. If possible, colchicine tablets should be taken at the very beginning of an attack. A short course of steroids (such as prednisolone tablets) may also be used.

Prevention of further attacks of gout

Dietitians can help patients reduce the amount of uric acid they ingest in their food. Patients with gout should reduce their consumption of beer, wine, yeasts (for example, Marmite[®]), red meats (especially liver) and certain fish (particularly anchovies, herring and mackerel). The drugs used to treat acute attacks of gout will not help to prevent further episodes. If the attacks become frequent, medications to lower the levels of uric acid in the blood might be considered; the most common of which is called allopurinol ■

Key points

- Patients with chronic kidney disease are at risk of developing various problems with their bones. These are collectively known as renal bone disease.
- Renal bone disease may develop before the symptoms of kidney failure.
- The effects of renal bone disease can be limited by treatments, which are usually prescribed before symptoms begin to develop.



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