Today's Treatment

Diseases of the urinary system

Renal osteodystrophy

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As therapeutic advances improve the life expectancy of the patient with renal failure, so problems such as renal osteodystrophy, which restrict full rehabilitation, assume greater importance. Bone disease is usually a feature of slowly progressive renal failure. It often develops insidiously but causes symptoms only in a few patients. Although the management of advanced osteodystrophy may be difficult, the indications for early intervention are not always clear. The problem is compounded by the availability of powerful therapeutic agents, which, if used injudiciously, may result in hypercalcaemia or metastatic calcification. These complications are to be avoided because of the risk to blood vessels, which may be needed for shunts or transplantation. In the early stages of renal failure many patients will present to doctors working outside specialised centres catering for dialysis and transplantation. Since it is important to be aware of the principles of management at this time I will deal primarily with predialytic bone disease.

Pathophysiology

The bone disease that occurs in renal failure results from progressive hyperphosphataemia and altered vitamin D metabolism. As glomerular filtration rate (GFR) decreases the plasma phosphate concentration tends to rise and the calcium concentration tends to fall. This disturbance of homeostasis is counteracted by increased parathyroid hormone (PTH) secretion, which lowers plasma phosphate by decreasing tubular reabsorption.¹ An indication of the sensitivity of this mechanism is shown by increased serum immunoreactive PTH at GFR of 70-80 ml/min.² Depending on the level of PTH there may also be an element of calcium mobilisation from bone, although the ability of the gut to respond by an increased absorption probably becomes limited once renal function is more than slightly impaired. When GFR has fallen to about 25-30 ml/min the increased phosphate excretion per nephron produced by the high levels of PTH is insufficient to balance the phosphate absorbed from the diet, and hyperphosphataemia will become established. The serum calcium, however, may still be maintained by PTH-mediated bone resorption.

A second, and perhaps more important, cause of hypocalcaemia is change in vitamin D metabolism resulting from deteriorating renal function. Vitamin D absorbed from the intestine or synthesised in the skin must first be hydroxylated

in the liver to produce 25-hydroxycholecalciferol. This is the major circulating form but is without direct action at physiological concentrations. A second hydroxylation occurs in the kidney to produce 1,25-dihydroxycholecalciferol ($1,25(\text{OH})_2\text{D}_3$), which acts upon the target organs. Dependent on a complex inter-relationship with PTH, $1,25(\text{OH})_2\text{D}_3$ may act as either a calcium-mobilising or phosphate-transporting hormone.³ Hypocalcaemia, acting through PTH secretion, and hypophosphataemia acting independently of PTH, appear to be the main stimuli to $1,25(\text{OH})_2\text{D}_3$ production. Low serum concentrations of $1,25(\text{OH})_2\text{D}_3$ are found in chronic renal failure and are associated with calcium malabsorption, hypocalcaemia, and defective bone mineralisation.

Assessment of bone disease

There is no bone lesion that is specific to renal failure; osteomalacia, osteitis fibrosa, osteoporosis, and osteosclerosis occur singly or in combination. The commonest abnormality is that of hyperparathyroidism but the prevalence of the various types of bone disease shows considerable geographical variation. This is mainly because of differences in dietary intake of calcium, phosphorus, and vitamin D. Almost all patients with end-stage renal disease will show some evidence of osteodystrophy, but the prevalence in early renal failure is less certain.

Hyperparathyroid bone disease is often asymptomatic until well advanced, particularly in adults. Plasma calcium and alkaline phosphatase concentrations are often normal, although the latter rise as bone disease progresses. Plasma phosphate concentration is usually raised so that the calcium $\times$ phosphate product is increased, which predisposes to metastatic calcification. The earliest radiological change is a loss of cortical definition at the tip of the terminal phalanges of the fingers followed later by the classic lateral subperiosteal erosions. Bone radiographs may be normal despite clear histological evidence of bone disease.

Osteomalacia, often combined with hyperparathyroidism, is more likely to give rise to symptoms: these include diffuse bone pain, proximal muscle weakness, and loss of height due to vertebral collapse. Plasma calcium concentration is usually low, and, in contrast to the hypophosphataemia commonly seen in other types of osteomalacia, plasma phosphate concentration is either normal or raised. Serum alkaline phosphatase is often normal in the early stages but may rise to high concentrations as osteomalacia advances. The classic radiological feature of Looser's zones tends to occur late; radiolucency or unsuspected rib fractures may be an earlier development but bone radiographs are often normal.

Osteoporosis is another cause of pain and fracture in chronic renal failure. Diagnosis rests on clinical, radiological, and histological criteria, there being no specific biochemical changes in serum. Osteosclerosis is a radiological or histological diagnosis

with no specific clinical or biochemical features. The classic radiological appearance is that of the "rugger jersey spine," best seen in the lumbar vertebrae.

In practical terms the assessment of patients with renal bone disease depends on regular measurement of plasma calcium, phosphate, and alkaline phosphatase concentrations. Total plasma calcium concentration may need to be corrected for low serum albumin concentrations ($+0.02$ mmol/l for every 1 g/l by which the serum albumin falls below 40 g/l) in those patients with appreciable proteinuria. Radiographs of hands including the lower end of the radius and ulna, posteroanterior chest and pelvis, lateral skull, and lumbar spine are the most useful for basic documentation. Iliac crest bone biopsy, despite the concern that it may be unrepresentative of the skeleton as a whole, remains the most sensitive guide to the presence and type of bone disease.

Treatment

Treatment should be aimed at relieving symptoms and preventing the development of deformity or fractures. Attempts should also be made to correct hypocalcaemia and hyperphosphataemia, thus minimising the stimulus to parathyroid hyperplasia. Largely encompassed by these aims is the control and prevention of defective bone mineralisation and metastatic calcification. Treatment is based on reducing dietary intake and absorption of phosphorus and giving vitamin D. Good results have been achieved from widely differing patterns of treatment but only at the cost of scrupulous attention to detail. Patients vary enormously in their individual needs and it is unrealistic to expect a standard regimen to be uniformly appropriate.

CONTROL OF HYPERPHOSPHATAEMIA

In early renal failure treatment is aimed at reducing the phosphate load that has to be excreted by the kidney, thus limiting the development of hyperphosphataemia and secondary hyperparathyroidism. The amount of phosphate absorbed from the gut may be decreased in two ways. Both clinical and experimental studies have shown that reducing dietary phosphate by the same proportion as the decrease in GFR may prevent the development of secondary hyperparathyroidism down to rates as low as 30 ml/minute.¹ Severe restriction of phosphate intake, however, results in a very unpalatable diet. It is rarely worth going beyond that obtained by moderate protein restriction—a 40 g protein diet containing about 25 mmol (600 mg) of phosphorus.

Phosphate absorption may be decreased, allowing a more liberal dietary intake, by using binding agents such as aluminium hydroxide. Phosphorus balance is generally unchanged since the decreased absorption is balanced by decreased urinary excretion resulting from a fall in PTH and a resetting of tubular reabsorption.⁵ Aluminium hydroxide should be given in large doses (10–50 ml four times daily) but as such may be unpalatable. An encapsulated preparation (Alu-Cap), given in a dose of 1–5 capsules four times daily (about 2–10 g dried aluminium hydroxide gel/day), may be more acceptable. It should not be forgotten that these doses of aluminium hydroxide diminish the absorption of antibiotics such as tetracycline. Particularly when they are combined with diet restriction, there is a real risk of phosphorus depletion, which itself may aggravate or produce osteomalacia.⁶ The dose of aluminium hydroxide must therefore be carefully regulated according to the serum phosphorus concentration. The aim should be to maintain the plasma phosphate concentration within the range 1.5–2.0 mmol/l (4.6–6.1 mg/100 ml). Overenthusiastic treatment is probably more harmful than none at all.

Phosphorus depletion may also be produced by dialysis and

lead to a poor response of established osteodystrophy to vitamin D treatment.⁷ Such patients often have a proximal myopathy, and relatively pure osteomalacia, with little evidence of secondary hyperparathyroidism; serum alkaline phosphatase concentration and PTH are often normal. Although calcium absorption increases with vitamin D, hypercalcaemia, rather than healing of osteomalacia, is the result.

Some of the aluminium given in antacids to control hyperphosphataemia is absorbed, and increased levels have been found in the serum, bone, and other tissues of patients with chronic renal failure. There is no evidence that these changes are harmful except in so far as excessive treatment may produce phosphorus depletion. Theoretical risks of aluminium toxicity are not an indication for using magnesium-containing antacids in chronic renal failure.⁸ Hypermagnasaemia so induced may lead to drowsiness, lethargy, hypotension, and coma.

CORRECTION AND CALCIUM MALABSORPTION

Calcium malabsorption leading to hypocalcaemia is an important component of the disordered mineral metabolism of renal failure. It may be corrected by massive calcium supplements or by pharmacological doses of vitamin D.

The increased calcium absorption that can be achieved with large oral doses of calcium carbonate (up to 20 g/day)⁹ presumably depends on passive diffusion along concentration gradients rather than on the normal process of vitamin D-mediated active absorption. Calcium carbonate also binds intestinal phosphorus, decreasing its absorption. Calcium balance becomes positive, and raised concentrations of PTH are reduced. Phosphorus excretion decreases as a result of the fall in PTH, but the serum phosphorus concentration may also return towards normal because of a decreased input from intestine and bone. Since the concentration of serum calcium depends on a high dietary intake, hypercalcaemia can be rapidly reversed. There is a real risk of metastatic calcification, however, particularly in the presence of hyperphosphataemia. Plasma phosphate concentration falls with treatment, but this is slower than with aluminium hydroxide and should not be relied on to prevent metastatic calcification. Although the positive calcium balance is associated with remineralisation of osteoid, this is patchy and, unlike the response to vitamin D, the calcification front is not restored.¹⁰ Patients with chronic renal failure may have a poor dietary calcium intake because of anorexia or the use of protein-restricted diets. In these cases calcium supplementation to give an intake of about 1 g/day (25 mmol) is necessary to maintain balance.

Correction of malabsorption is best achieved with vitamin D. This also results in restoration of the calcification front, remineralisation of osteoid, and regression of the clinical features of osteomalacia. Large doses of vitamin D are needed but the effects on serum calcium and alkaline phosphatase are slow, and dosage should not be increased more than monthly. In the early stages of treatment the absorbed calcium may be deposited in osteoid so that osteomalacia may heal without much of an improvement in hypocalcaemia.⁸ This is not an indication for increased doses of vitamin D since the serum calcium concentration will rise once the bones are healed.

Serum calcium and phosphate concentrations should be measured frequently during treatment; fasting concentrations are preferable but may be difficult to arrange on an outpatient basis. Blood should be taken weekly at first so that the initial response to treatment may be assessed. Monthly determinations are sufficient when the serum concentrations have stabilised, but measurements should be made more often as the alkaline phosphatase approaches normal levels. Hypercalcaemia may first appear at this time, and it is a wise precaution to reduce the dose of vitamin D before the bones are completely healed. Treatment should be adjusted to maintain the decline in alkaline phosphatase but with a serum calcium concentration in the lower part of the normal range.

Several preparations of vitamin D are, or soon will be, available. The starting dose of cholecalciferol should be 1.25 mg (50 000 IU) daily, increments depending on response. Dihydro-tachysterol (AT 10) appears to be more effective than cholecalciferol in renal failure. This may be due to absence of product inhibition of the hepatic 25-hydroxylase and because the parent compound is already hydroxylated at a site equivalent to the carbon⁻¹ of cholecalciferol and thus may be regarded as an analogue of 1,25(OH)₂D₃. Treatment should begin with doses of about 0.25 mg (1.0 ml) daily; as with other preparations dose increments must be made slowly.

Although 1,25(OH)₂D₃ improves renal osteodystrophy, technical difficulties in synthesis have restricted its general availability. An analogue, 1- α -hydroxycholecalciferol will shortly become generally available. It is more rapidly acting than the other vitamin D preparations and has a much shorter half life so that hypercalcaemia regresses more quickly when treatment is withdrawn. Treatment should begin with 1-2 μ g daily, reducing by half once the serum calcium and alkaline phosphatase approach normal concentrations.

SUBTOTAL PARATHYROIDECTOMY

The management of painful osteitis fibrosa without evidence of defective mineralisation is particularly difficult.¹¹ Such patients are usually in preterminal renal failure with substantial hyperphosphataemia. Although vitamin D treatment will produce a clinical remission, there is a real risk of metastatic calcification. In some patients the problems are eased by starting dialysis, which controls the hyperphosphataemia. In the patient who is not considered suitable for dialysis, subtotal parathyroidectomy followed by vitamin D treatment may be justified if the patient's prognosis is good enough.

Hypercalcaemia in chronic renal failure is usually due to injudicious use of vitamin D or calcium supplements but occasionally may be a spontaneous occurrence. This is usually a phenomenon of end-stage renal failure and is possibly due

to massive hyperplasia of the parathyroid glands, which fail to involute in the face of altered calcium fluxes from bone.⁸ In the absence of dialysis or transplantation these patients usually have a short life expectancy, but if this is not so then subtotal parathyroidectomy followed by vitamin D treatment may restore normocalcaemia.

The general availability of analogues of 1,25(OH)₂D₃ that have rapid biological effects confers a greater degree of safety and flexibility of management than was previously possible with more conventional preparations. This may make prophylactic treatment a more realistic proposition but at present there is little experience in this sphere. It does seem important to ensure that dietary intakes of calcium and vitamin D are adequate during the early stages of renal failure, and barbiturate hypnotics must be avoided because of their adverse effects upon vitamin D metabolism. Anticonvulsant drugs should be given in the smallest effective dose for similar reasons. Disordered mineral metabolism should be considered at an early stage in managing the patient with renal failure since it may be easier to limit the progression of bone disease than to treat the established condition.

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What are the indications for surgery in a middle-aged man with a hiatus hernia?

The diagnosis of hiatus hernia covers two distinct anatomical defects. Rolling hiatus hernia comprises only about 10% of the cases of hiatus hernia, and possibly even a good deal less, since the incidence of sliding hernia is so uncertain. Rolling hernia consists of a prolapse of the stomach through the oesophageal hiatus with the oesophago-gastric and gastroduodenal junction remaining within the abdomen. Because the arterial supply enters and the venous drainage leaves the hernia there is continuing danger of a strangulation. Minor increases in venous pressure are probably common, and venous engorgement of the mucous membrane of the herniated stomach accounts for the frequent finding of positive occult blood in the stools and an associated iron deficiency anaemia. These patients may present with iron deficiency anaemia or the haemorrhage may be enough to produce a melaena. Much less common is the development of a gastric ulcer in the pouch, and the patients sometimes get symptoms from gaseous distension of the part. Because this is an entirely mechanical problem no conservative treatment helps, and the constant threat of anaemia, haemorrhage, and strangulation necessitates surgical repair.

Far more common is the sliding hiatus hernia, when the oesophago-gastric junction displaces into the chest accompanied by a pouch of the upper end of the stomach. Its exact incidence is indeterminate since diagnosis by barium-meal examination, manometry, or oesophago-gastroscopy depends on the skill of the operator and the general physical condition of the patient. The herniae show up more when the patient is tired. In itself, a sliding hiatus hernia causes no symptoms, but it is the association with incompetence of the oesophagogastric sphincter mechanism that makes it a condition of importance. It is more important to describe the patient as suffering from a reflux

oesophagitis than a hiatus hernia. The characteristic symptoms are regurgitation of gastric contents on bending or lying down, burning behind the sternum, and dysphagia due to a stricture. Occasionally, there is real ulceration of the oesophagus, and penetrating ulcers of the oesophagus may, of course, penetrate the aorta. Occasionally, also, there may be a peptic ulcer in the thoracic portion of stomach. Vague symptoms of dyspepsia associated with a hiatus hernia discovered on barium-meal examination should not be assumed to be a cause and effect relationship. Control of the symptoms of reflux oesophagitis will be medical at first. The antacid of choice is dried aluminium hydroxide gel (Gaviscon), which is slightly sticky, to coat the inside of the oesophagus. The value of cimetidine is being assessed. Of most importance is weight reduction. Even a fairly slim patient should be encouraged to lose a few kilograms because there is often a trigger weight below which the symptoms of reflux disappear. Attention to general health may help, as may a holiday.

The presence of a penetrating ulcer in the oesophagus is alarming and, if medical measures fail, surgery is indicated shortly after starting treatment. Otherwise continuing reflux oesophagitis will lead to a benign stricture. Direct observation is the only accurate method of assessing the reflux oesophagitis, and this procedure is much safer with a flexible oesophagoscope than with the rigid instrument. Generally reflux oesophagitis cannot be allowed to continue indefinitely because of the development of a stricture, and oesophagoscopy or radiological evidence of the development of a stricture indicates surgery to control the reflux. These strictures are often reversible as soon as the reflux stops, and dilatation is rarely necessary. In summary, if the patient is at all fit, rolling hiatus hernia is an absolute indication for surgical repair. Sliding hiatus hernia is repaired after failure of medical treatment to control reflux oesophagitis. Malignancy does not need repair: it requires excision.