Renal Bone Disease

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Current interest in the aetiology and treatment of azotaemic osteodystrophy has been stimulated only since recent advances in therapy have extended the life expectancy of patients with chronic renal failure and shown that bone disease is an important factor in limiting their full rehabilitation (Ogg, 1973). This review will describe advances in understanding renal osteodystrophy and discuss both its prevention and treatment.

The association of chronic renal failure and bone disease was first suggested by Virchow in 1855, although a patient with renal bone disease may have been described by Howship in 1826. However, not until Fletcher (1920) described a boy with 'infantilism and polyuria' was interest in azotaemic osteodystrophy aroused. Within a few years many similar cases, all children with retarded physical development, were described (Parsons, 1911; Naish, 1912; Miller, 1911; Sutherland, 1912; Cameron, 1918a,b). The children became known as 'renal dwarfs' (Barber, 1920) and the bone disease as 'renal rickets' (Shipley et al., 1922) because of the clinical, radiological and histological similarities to nutritional rickets (Paterson, 1920, 1921; Barber, 1921). Nevertheless, it was soon appreciated that conventional cod liver oil therapy, of proven value in nutritional rickets, was ineffective in renal rickets (Parsons, 1927).

By 1930 it was observed that many adults with chronic renal failure demonstrated not the typical radiological features of rickets or osteomalacia but more indistinct X-ray changes similar to those observed in hyperparathyroidism. For the next 20 years much of the earlier work was to be forgotten as attention focused on the importance of the parathyroid glands and parathyroid hormone in the aetiology of renal bone disease.

However, in 1943, Follis and Jackson reported that the predominant histological abnormality observed in bone samples from patients who had died of renal failure was not osteitis fibrosa cystica but osteomalacia. Only when Stanbury (1957) and Dent et al. (1961) demonstrated that renal bone disease, although not influenced by physiological amounts of vitamin D, could be healed by pharmacological doses, did the balance of opinion again shift to favour 'an acquired insensitivity to the action of vitamin D' (Stanbury, 1957) as the principal cause of azotaemic osteodystrophy (Ball, 1960; Garner and Ball, 1966). Developments in the understanding of vitamin D metabolism and calcium absorption have provided further information on the pathogenesis of this disease process.
VITAMIN D METABOLISM

More than twenty years ago, it was suggested that vitamin D might be metabolised in vivo to an active form (Cruickshank and Kodicek, 1953; Cruickshank et al., 1954). This theory was advanced to explain the observation that vitamin D does not act immediately to facilitate either calcium absorption or mobilisation; a delay of 10 to 12 hours has generally been noted (DeLuca, 1967). When labelled vitamin D with high specific activity was prepared (Neville and DeLuca, 1966) and the dosage of vitamin D administered experimentally to animals could be reduced to physiologic levels, the existence of potent, biologically-active metabolites was demonstrated (Lund and DeLuca, 1966). In 1968 the first polar metabolite isolated in a pure form was identified as 25-hydroxycholecalciferol (Blunt et al., 1968).

This compound acts more rapidly than the parent vitamin; calcium absorption is stimulated after a lag period of only three to four hours (Blunt et al., 1968). The hydroxylation of cholecalciferol to 25-hydroxycholecalciferol occurs in the liver (Ponchon et al., 1969) and is feedback regulated; the quantity of 25-hydroxycholecalciferol in the liver determines the rate of hydroxylation.

Further studies, however, from several laboratories demonstrated that 25-hydroxycholecalciferol is not the final, active metabolite of vitamin D (Haussler et al., 1968; Lawson et al., 1969; Cousins et al., 1970). In 1971, from the intestines of 1500 vitamin D-deficient chicks, Holick et al. isolated 2 μg of a pure metabolite identified as 1,25-dihydroxycholecalciferol. This compound acts even more rapidly in promoting calcium absorption and mobilisation; it may be one hundred times more potent than 25-hydroxycholecalciferol (Trummel et al., 1971).

In 1970, Fraser and Kodicek had demonstrated that the kidney is the principal site of synthesis of the compound subsequently identified as 1,25-dihydroxycholecalciferol; this was rapidly confirmed in several other centres (Gray et al., 1971; Norman et al., 1971). 1,25-dihydroxycholecalciferol cannot be detected in animals subjected to bilateral nephrectomy (DeLuca, 1973); calcium absorption in these animals is stimulated by 1,25-dihydroxycholecalciferol but not by 25-hydroxycholecalciferol (Boyle et al., 1972b). Thus, in 1973 DeLuca could state that 1,25-dihydroxycholecalciferol 'is most probably a metabolically active form of the vitamin in both the intestine and bone. Since it is synthesised in the kidney it must be regarded as a hormone derived from vitamin D' (DeLuca, 1973a).

The rate of synthesis of 1,25-dihydroxycholecalciferol is regulated by the plasma calcium concentration (Boyle et al., 1972a) but only indirectly. DeLuca (1973b) has summarised the position:

'when serum calcium falls below 10 mg per 100 ml this sequence of events takes place: the parathyroid glands are stimulated to secrete parathyroid
hormone; parathyroid hormone proceeds directly to bone where it mobilises calcium provided there is a form of vitamin D present, and also to the kidney where it stimulates the synthesis of 1,25-dihydroxycholecalciferol; this renal hormone then proceeds to both bone and intestine where it stimulates mobilisation of calcium; this calcium then restores the serum calcium to normal shutting off parathyroid reactions and completing the feedback loop.

Two further facts are worthy of mention. The first is that animals maintained on low phosphorus diets continue to produce 1,25-dihydroxycholecalciferol in spite of a continuing hypercalcaemia and even after thyroparathyroidectomy. Thus, parathyroid hormone may not be an essential factor in the synthesis of 1,25-dihydroxycholecalciferol when hypophosphataemia is present (Tanaka and DeLuca, 1973) and, in the absence of parathyroid glands, the concentration of plasma phosphorus has an important role in the control of 1,25-dihydroxycholecalciferol formation.

The second factor is that the rate of production of 1,25-dihydroxycholecalciferol varies inversely with the concentration of inorganic phosphate in the renal cortex. Hypophosphataemia, probably causing a reduction in the concentration of cellular inorganic phosphate in the tubular cells of the renal cortex, stimulates synthesis of 1,25-dihydroxycholecalciferol (Tanaka and DeLuca, 1973). Thus, hyperphosphataemia should be controlled in uraemic patients in an attempt to prevent the inhibition of 1,25-dihydroxycholecalciferol production.

**CALCIUM METABOLISM**

A healthy adult on an average diet ingests approximately one gram of calcium each day (Spencer et al., 1969). As only 25 to 40 per cent of ingested calcium is absorbed, the factors regulating the absorption of calcium are of great importance in maintaining calcium balance (Coburn et al., 1973). The uptake of calcium from the gut involves the transfer of calcium from the lumen of the intestine into the mucosal cell, transport across the cell and, finally, extrusion of calcium from the cell into the interstitial fluid (Coburn et al., 1973). Movement of calcium into the cell depends upon facilitated diffusion (Martin and DeLuca, 1969), active transport (Schachter and Rosen, 1959) and, when the concentration of calcium in the gut is high, simple diffusion (Krawitt and Schedl, 1968). A specific calcium-binding protein, localised on the surface of the mucosal cells, is increased in quantity by the administration of vitamin D (Taylor and Wasserman, 1967).

Little is known about the movement of calcium within the cell but the extrusion of calcium from the serosal surface of the cell may also be increased by vitamin D (Schachter et al., 1966).

1,25-dihydroxycholecalciferol rapidly stimulates calcium absorption from the gut (DeLuca, 1973a,b; Coburn and Norman, 1973; Kodicek, 1974). The mode of action has been outlined: 1,25-dihydroxycholecalciferol attaches to a receptor site
in the nucleus of the mucosal cell; messenger RNA synthesised in the nucleus stimulates the ribosomes to synthesise calcium-binding protein (Kodicek, 1974) which, in turn, promotes calcium absorption from the gastrointestinal tract.

From this review it may be seen that many of the factors known to regulate normal calcium metabolism — parathyroid hormone, phosphate retention and 1,25-dihydroxycholecalciferol — may be implicated in the pathogenesis of bone disease in patients with azotaemic osteodystrophy.

FACTORS CONTRIBUTING TO THE DEVELOPMENT OF AZOTAEMIC OSTEODYSTROPHY

Vitamin D Metabolism
The only important abnormality of vitamin D metabolism noted in patients with chronic renal failure is impairment in the production of 1,25-dihydroxycholecalciferol. This metabolite cannot be detected in rats (Fraser and Kodicek, 1970) or in man (Mawer et al., 1971) after bilateral nephrectomy, and is absent in patients with renal failure (Mawer et al., 1973). On the other hand, 1,25-dihydroxycholecalciferol administered to patients with renal disease increases the intestinal absorption of calcium (Brickman et al., 1972; Henderson et al., 1974) and results in an improvement in both the radiological manifestations of osteodystrophy and the associated myopathy (Henderson et al., 1974). Thus, a reduction in the quantity of 1,25-dihydroxycholecalciferol produced by the kidney is probably a major factor in the pathogenesis of renal bone disease.

Calcium Metabolism
Malabsorption of calcium is a feature of chronic renal failure (Liu and Chu, 1943; Dent et al., 1961). However, the quantity of calcium absorbed by uraemic patients may be increased when large amounts (2 to 8 g daily) of elemental calcium are administered orally. This therapy by itself may cause both improvement in the radiological features of hyperparathyroidism and reduction in plasma alkaline phosphatase concentrations (Clarkson et al., 1971; Curtis et al., 1970) but has occasionally produced hypercalcaemia (Ginsburg et al., 1973).

Possibly because of anorexia, together with the imposition of a low protein diet, patients with renal failure generally ingest smaller quantities of calcium per day than do healthy subjects (Clarkson et al., 1973; Coburn et al., 1973); this provides an additional reason for supplying calcium supplements to these patients.

Secondary Hyperparathyroidism
It has been appreciated for more than a half century that secondary hyperparathyroidism is involved in the pathogenesis of renal osteodystrophy (Bergstrand, 1921). The importance of parathyroid hormone has been emphasised both by the work of Albright and his colleagues (Albright and Reifenstein, 1948) and
by the ability to measure plasma parathyroid hormone concentrations by a radioimmunoassay technique. This latter method, despite its two disadvantages of employing heterologous antigens and measuring immunoreactive fragments of the hormone normally excreted in the urine, has repeatedly demonstrated increased levels of parathyroid hormone in the plasma of patients with renal failure (Berson and Yalow, 1966) and has been widely used to monitor the effect of different forms of therapy. The importance of parathyroid hormone in causing bone disease in a proportion of uraemic patients is shown by the beneficial effects of surgical parathyroidectomy (Dreskin and Fox, 1950). Although after surgery the bone lesions respond to treatment with vitamin D without hypercalcaemia (Stanbury et al., 1960), the prevailing state of vitamin D resistance is unaltered (Stanbury, 1971b).

**Phosphate Metabolism**

Of the one gram elemental phosphorus ingested daily by healthy subjects, 70 per cent is excreted by the kidneys (Slatopolsky and Bricker, 1973). Phosphate retention usually accompanies renal insufficiency (Marriott and Howland, 1916); Stanbury (1968) stated that 'the physico-chemical relationship between the bone crystals and the extra-cellular fluid makes it inevitable that an increase in plasma phosphate will tend to depress plasma calcium'. This mechanism may produce the hypocalcaemia of acute renal failure.

A mechanism has been proposed to explain the occurrence of hyperparathyroidism in chronic renal failure. In early renal failure the phosphaturia produced by hyperparathyroidism limits the rise in serum phosphate associated with a reduction in glomerular filtration rate (Slatopolsky et al., 1966). It was proposed that a reduction in glomerular filtration rate produces an increase in plasma phosphate and a corresponding reduction in plasma calcium; normal plasma concentrations of both calcium and phosphate are sustained by an increased secretion of parathyroid hormone until the phosphaturic effect of the hormone is inadequate to compensate for the progressive fall in glomerular filtration (Bricker, 1969). Thus, in mild renal failure it was suggested that the increased urinary excretion of phosphorus is sufficient for the phosphate, reabsorbed from bone along with calcium by the action of parathyroid hormone, not to cause a rise in plasma phosphorus. As glomerular filtration falls, however, and no further increase in the urinary excretion of phosphorus is possible, more bone resorption is promoted by the increased secretion of parathyroid hormone; plasma phosphorus rises further, hypercalcaemia sometimes develops and a vicious circle is established (Bricker, 1972).

This hypothesis has received support from many centres; treatment with aluminium hydroxide has been shown to produce a significant reduction in the plasma concentrations of both phosphorus and parathyroid hormone (Clarkson et al., 1972) and it is claimed that the prevalence of azotaemic osteodystrophy is
lower in Israel, where the average diet contains more calcium and less phosphorus, than in the U.K. Moreover, Slatopolsky et al. (1972) were able to prevent the development of bone disease in uraemic dogs by feeding them a low phosphate diet.

Nevertheless, this elegant theory does not offer a complete explanation of the aetiology of renal bone disease; when a patient with renal failure is noted to have hypocalcaemia associated with a low or normal plasma phosphorus concentration, a factor other than secondary hyperparathyroidism must be present (Stanbury, 1971a). Reduction in the production of 1,25-dihydroxycholecalciferol with consequent changes in calcium metabolism may be that additional factor.

DeLuca (1973a) has suggested that these two aetiological factors may be linked; as renal function declines, the filtered phosphate load is increased to the remaining nephrons: the inorganic phosphate in the remaining renal cells rises to abnormally high levels and prevents synthesis of 1,25-dihydroxycholecalciferol. This may occur before an appreciable quantity of renal substance is lost. Clinically, it is thus important that plasma phosphorus concentrations are maintained as close to normal values as possible to prevent secondary hyperparathyroidism, inhibition of 1,25-dihydroxycholecalciferol production or even hypophosphataemic osteomalacia should phosphate depletion occur.

**Metabolic Acidosis**

The effect of metabolic acidosis associated with renal failure on calcium metabolism has been investigated by Goodman et al. (1965); correction of the acidosis restored a small negative calcium balance to normal (Litzow et al., 1967). However, as healing of bone disease has been well documented with vitamin D therapy in the presence of a continuing acidosis (Stanbury, 1957; Dent et al., 1961), it seems likely that metabolic acidosis plays at most a secondary role in the pathogenesis of azotaemic bone disease.

**Haemodialysis Therapy and Bone Disease**

Stanbury (1971a) has emphasised that 'dialytic bone disease should be examined objectively without the assumption that it is necessarily the same as azotaemic osteodystrophy'. He suggested that haemodialysis could, by prolonging life, permit the further evolution of renal osteodystrophy to an extent not encountered in the undialysed patients or could contribute new factors to which undialysed patients are not exposed.

At the time of starting haemodialysis most patients have bone disease; although this may not have been noted clinically or radiographically it has been demonstrated by bone biopsy studies (Kim et al., 1970; Kaye, 1969). The fact that features of osteomalacia have been reported less frequently from patients in the U.S.A. than from British patients has been attributed to 'the American national habit of vitamin consumption' (Stanbury et al., 1971a).
Although dialytic bone disease is symptomatic in a greater proportion of patients than is azotaemic osteodystrophy and although there are marked international and regional differences in prevalence (Stanbury, 1971a), the same factors seem to influence the development of the two diseases. Radiologically and histologically the majority of patients present a complex picture of both osteomalacia and hyperparathyroidism. Examination of excised parathyroid glands reveals hyperplasia; adenomata are very rarely found.

There is no information to suggest that the anomalies of vitamin D metabolism associated with renal failure are altered by haemodialysis. Calcium metabolism is changed only to the extent that dialysis offers the opportunity of an additional route by which additional calcium may be given to, or removed from, the patients. Several studies have shown improvement in the bony lesions when supplementary calcium, supplied either orally or by an increase in the calcium content of the dialysis fluid, was combined with aluminium hydroxide therapy to maintain plasma phosphate concentrations within normal limits (Goldsmith et al., 1971; Bone et al., 1972). This form of supplementary calcium treatment also produces a reduction in the plasma concentrations of parathyroid hormone (Goldsmith et al., 1971).

Elevation of the plasma magnesium concentration above normal suppresses the secretion of parathyroid hormone (Care et al., 1966; Pletka et al., 1971). Heierli and Hill (1972) demonstrated that an increase in the magnesium concentration of the dialysate produced an elevation in predialysis plasma magnesium concentrations in patients on haemodialysis and suggested that an increased magnesium concentration in the dialysis fluid might, by suppressing parathyroid activity, limit progressive dialytic bone disease. The optimum concentration of magnesium in the dialysate may thus be decided principally by the effect of changes in the concentration of dialysate magnesium on the disease; supplementary magnesium is unlikely, however, to prove an important form of treatment (Catto and MacLeod, 1976).

There is at present no evidence to suggest that fluoride, aluminium, heparin or any toxic factor in the water supply are of major significance in the pathogenesis of bone disease.

TREATMENT OF RENAL BONE DISEASE
The value of vitamin D in the treatment of azotaemic osteodystrophy has been a controversial issue for almost a hundred years. Lucas (1883) claimed that the rickets in three of five adolescents with proteinuria improved on therapy with cod liver oil; unfortunately, no description of the bone lesions was provided either before or after treatment. Parsons (1927) concluded that cod liver oil in doses known to cure nutritional rickets was not effective in the treatment of renal rickets.

After 1930 attention centred on parathyroid hyperplasia and osteitis fibrosa
cystica as the principal factors involved in renal bone disease. Perhaps for this reason the work of Graham and Oakley (1938) caused little interest. These authors administered alkalis and moderate doses of vitamins A and D to two patients with renal rickets: bone lesions healed although the patients died from progressive renal failure less than two years later.

Liu and Chu (1943) concluded that dihydrotachysterol did, while vitamin D did not, heal the bone disease. Stanbury (1957), however, reported that vitamin D was of value but only when large doses were administered. This confusing situation was clarified by Dent et al. (1961) who treated fourteen patients with vitamin D in large doses; marked improvement in the bone lesions was produced despite progression of the renal insufficiency. Dent et al. (1961) also noted that Liu and Chu (1943) had used very much larger doses of dihydrotachysterol than vitamin D and suggested that, given in similar quantities, vitamin D would have been equally effective in healing the bone lesions. Kaye and Sager (1972), however, confirmed that in high doses dihydrotachysterol was more effective than vitamin D. As the production of 25-hydroxydihydrotachysterol is not subject to the same feedback control by the liver as 25-hydroxycholecalciferol, higher plasma concentrations of the dihydrotachysterol metabolite may be achieved; this may account for the fact that dihydrotachysterol is clinically more effective at high doses than equivalent doses of vitamin D (DeLuca, 1973a).

The problems of controlling vitamin D therapy have limited its widespread acceptance; the hypercalcaemia produced by overdosage of vitamin D is commonly severe and persistent. 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol are more polar, less lipid soluble, and more potent than the parent vitamin. When these drugs are administered to patients with evidence of vitamin D deficiency, the lower doses required and the reduced tissue stores may limit toxic effects in situations of inadvertent overdose (Brickman and Norman, 1972). This may be the most important clinical advantage of the new vitamin D metabolites.

Although improvement in the osteodystrophy has been demonstrated following therapy with 1,25-dihydroxycholecalciferol (Henderson et al., 1974), this treatment may not become readily available in the near future because of technical difficulties associated with the biosynthesis of the drug (DeLuca, 1973a). An analogue of vitamin D that may bypass the renal hydroxylating mechanism has been synthesised with a hydroxyl group at carbon-1 in alpha position. This substance, 1-alpha-hydroxycholecalciferol has been shown to increase both calcium absorption from the gut and the calcium content of bone (Catto et al., 1975); DeLuca (1973b) has commented that 'it is likely to be the drug of choice in the treatment of patients who may lack sufficient 1-hydroxylating activity in their kidneys'.

1-alpha-hydroxycholecalciferol in starting doses of 1 to 2 μg daily for several weeks and thereafter in maintenance doses of 0.5 to 1 μg daily appears to be successful in healing the bone lesions of azotaemic osteodystrophy. Administra-
tion of higher dosages may result in bone resorption and subsequent hypercalcaemia; however, elevated plasma calcium levels caused by overdosage of 1-alpha-hydroxycholecalciferol will return to normal values within one week of stopping treatment. The response to therapy may be assessed within one month of starting treatment by improvement in the histological features of bone biopsy specimens, although the radiological features of azotaemic bone disease may take several months to resolve. As the bone lesions heal adequately with normal plasma calcium concentrations, hypercalcaemia should not be induced.

Until these potentially less toxic metabolites of vitamin D are readily available, lesions of renal bone disease will generally respond to treatment with vitamin D or preferably dihydrotachysterol, administered in doses of 0.25 mg daily (which may be increased cautiously only after several months and provided that the concentrations of plasma phosphate are maintained within normal limits – by aluminium hydroxide therapy when necessary). A calcium intake of at least 2 g elemental calcium daily is required; for dialysis patients, the calcium content of the dialysate should be not less than 1.5 mmol/litre.

Although therapy with 1-alpha-hydroxycholecalciferol will heal both the osteomalacia and the osteitis fibrosa cystica associated with renal failure, such treatment is potentially hazardous in those patients with pre-existing hypercalcaemia. Parathyroidectomy to control the elevated plasma calcium concentrations may be required prior to therapy with a vitamin D analogue; this is now possibly the principal indication for the operation.

These measures should prevent the development, or cause resolution, of bone lesions. For the future, it would seem advisable that replacement therapy with either 1,25-dihydroxycholecalciferol or 1-alpha-hydroxycholecalciferol in doses of 0.25 to 0.5 µg daily be started when the glomerular filtration rate has fallen to approximately 50 ml per minute. Present clinical impressions suggest that it may prove easier to prevent renal bone disease than to heal established lesions.

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