

Hyperparathyroid bone disease in chronic renal failure

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SUMMARY

Much has been learnt over the past 80 years of the pathogenesis and management of hyperparathyroid bone disease in uraemia. Clinically it has changed from a rare disorder of childhood and adolescence to a common and difficult problem in patients maintained on dialysis programmes. Whereas effective treatments are now available for hyperparathyroid bone disease, these are not curative and there is clearly much more work to be done before a full understanding of its pathogenesis, and the best methods of treatment and prevention, can be reached.

INTRODUCTION

The skeletal abnormalities found in chronic renal failure are collectively termed renal osteodystrophy or renal bone disease. These include parathyroid bone disease, osteomalacia, osteoporosis, osteonecrosis, osteosclerosis and periosteal new bone formation. The pathogenesis of these disorders has been greatly clarified since the inception of regular dialysis programmes for treatment, with the result that treatment strategies have become defined more accurately and in some instances have proved more successful.¹⁻⁴ This article considers the bone disease related to increased secretion of parathyroid hormone which gives rise to parathyroid bone disease or osteitis fibrosa.

Abnormalities in parathyroid function have been known to occur in renal failure since the turn of the century,⁵ but, in the earlier reported cases, significant clinical problems were rare, except in children.^{6,7} It was only with the development of supportive treatments for renal failure, such as dialysis and transplantation, that patients survived long enough to develop symptomatic bone disease. This in turn provided a major stimulus to understand the disorder, even though hyperparathyroid bone disease is not exclusive to renal failure.

THE NATURE OF HYPERPARATHYROID BONE DISEASE

Bone is a self-repairing tissue and normally undergoes a sequence of cellular events to ensure that skeletal mass and architecture are maintained.⁸ In the adult skeleton, this process is termed 'remodelling' and comprises three phases which occur on the trabecular surfaces of bone. The first is the resorption of a packet of mineralised bone by the action of bone resorbing cells, the osteoclasts, and takes one or two weeks to be completed. Following the completion of a resorption cavity, osteoclasts leave the bone surface and are replaced by osteoblasts which lay down unmineralised bone matrix (osteoid) in an orderly lamellar array at the site of previous bone resorption. Some osteoblasts become trapped within the

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osteoid matrix to form osteocytes, and it is thought that these are responsible for the third phase of bone remodelling which is the mineralisation of this organic collagen matrix. The remodelling sequence is therefore a phenomenon occurring at bone surfaces and does not take place at the same rate in all parts of the skeleton. For example, bone turnover is more rapid in trabecular bone than in cortical bone where the surface-to-volume ratio is low.

Parathyroid hormone is an important activator of this remodelling sequence. In the presence of high secretion rates of parathyroid hormone, the frequency of activation of these remodelling packets is increased.⁸ The histological consequences are that an increased proportion of the bony surface is involved in both resorption and formation and less of the bone surface is resting. The rapid rates of bone resorption are associated with irregular excavations on the bone surface which can be detected histologically. Local imbalances in formation and resorption may result in patchy osteopenia, particularly of cortical bone. A further consequence of rapid rates of bone remodelling is that new bone formed is laid down in a haphazard fashion rather than in an orderly lamellar array (woven osteoid). This calcifies gradually to form woven bone occupying a relatively large volume, and the total bone volume may increase in hyperparathyroid bone disease so that osteosclerosis and osteoporosis co-exist in the same patient. These consequences of increased bone turnover impair both the structure and the mechanical properties of bone. An additional consequence of increased bone resorption is the deposition of fibrous tissue within the marrow cavity giving rise to the term 'osteitis fibrosa' for hyperparathyroid bone disease (Fig 1).

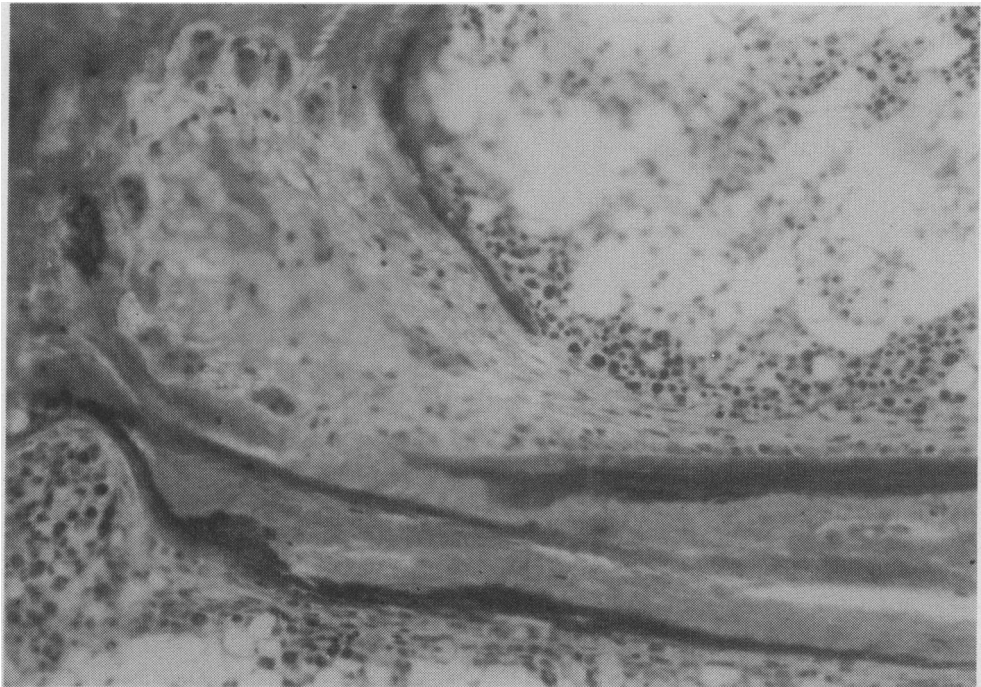


Fig. 1. Histological features of parathyroid bone disease in renal failure. Most of the unmineralised bone surface is occupied by multinucleated osteoclasts resorbing bone. The osteoid surface is increased due to an increase in the number of bone-forming cells. Marrow fibrosis occupies chiefly the resorption cavity but also extends over the formation surface.

Fig. 2.

Radiographic features of parathyroid bone disease in renal failure. Alternate bands of osteosclerosis give rise to the 'rugger jersey' appearance.

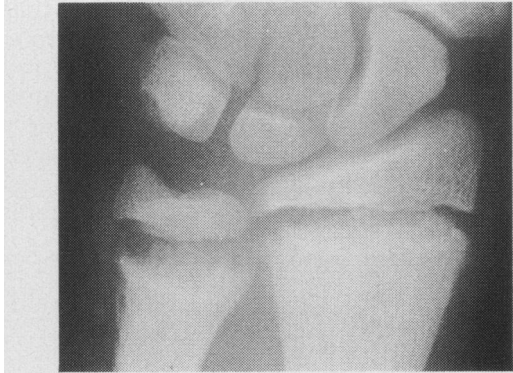
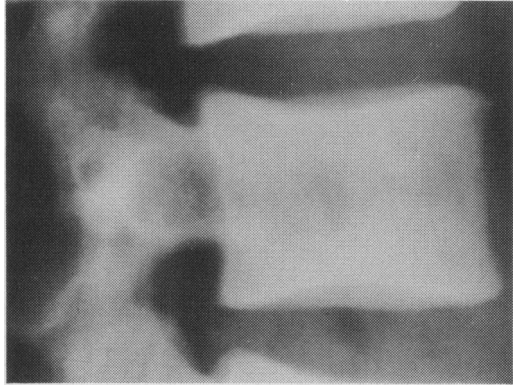
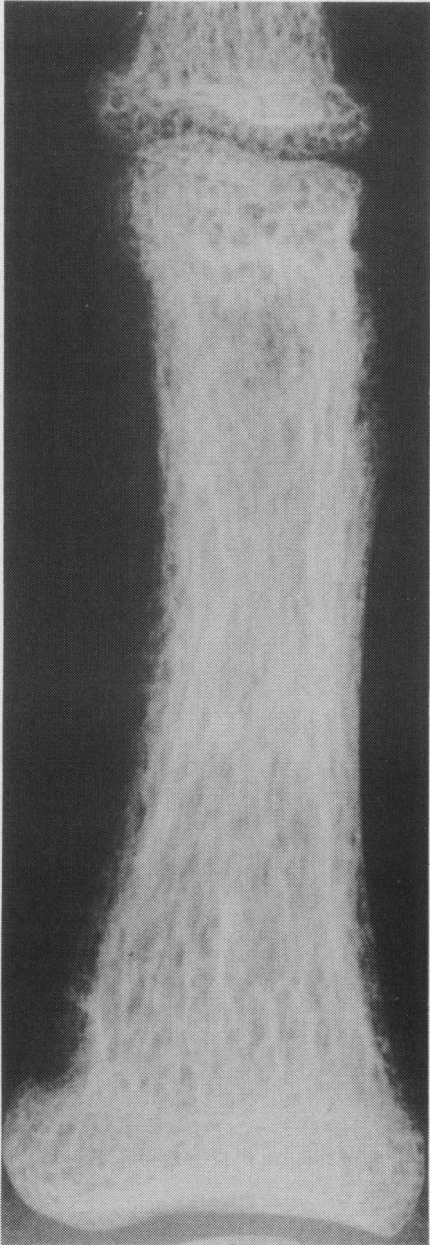


Fig. 4.

X-rays of the wrist to show marked metaphyseal erosion due to hyperparathyroidism in an adolescent (above).

The X-ray below shows the response to treatment with 1α -OHD₃.

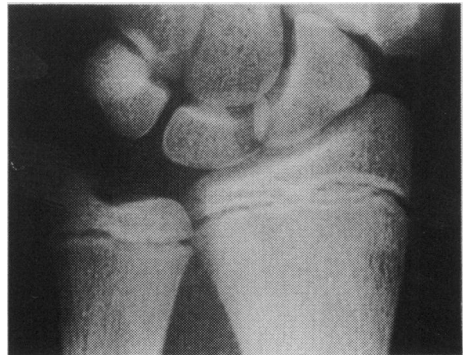


Fig. 3.

Marked sub-periosteal erosions of bone in hyperparathyroidism. Erosions are more marked on the radial aspect of the phalanx (left).

FEATURES OF HYPERPARATHYROID BONE DISEASE

Osteosclerosis is frequently noted in skeletal radiographs, particularly in the spine (Fig 2), but the characteristic radiographic feature of hyperparathyroid bone disease is subperiosteal erosion of bone. Erosions are found most frequently in the radial borders of the phalanges, the distal ends of the clavicles and the terminal phalanges (Fig 3). Gross erosion of the terminal phalanges (acro-osteolysis) may result in the collapse of soft tissue, normally supported by bone, giving rise to the appearance of pseudo-clubbing. In children, erosions are commonly found in the metaphyseal region of long bones where the rate of bone remodelling is high (Fig 4). Periosteal new bone formation is a less common feature in renal hyperparathyroidism (Fig 5).

Plasma or serum alkaline phosphatase activity is a useful biochemical marker of bone remodelling, since the bone-derived fraction reflects the numbers of active osteoblasts. Plasma hydroxyproline, reflecting in part bone collagen destruction by osteoclasts, may also be used as a biochemical marker, but in renal hyperparathyroidism resorption and formation are both increased to a similar extent, and there is little advantage in measuring both, except for the investigation of treatment régimes.⁹

Clinically, hyperparathyroid bone disease may give rise to bone pain, tenderness and to muscle weakness. Children and adolescents are affected more frequently and more severely than adults. Metaphyseal erosions in the growing skeleton seen on x-rays may bear some resemblance to rickets (Fig 6), but may give rise to marked skeletal deformities (Fig 7). It is for these reasons that almost all the early descriptions of renal bone disease related to children and adolescents.^{6, 7}



Fig. 5. Sub-periosteal new bone formation in hyperparathyroid bone disease. Note the periosteal elevation along the shafts of the metatarsals.



Fig. 6. Radiographic features of rickets. Note the widened epiphyseal plate and splayed metaphysis which contrasts with the metaphyseal erosion of hyperparathyroidism (Fig 4).

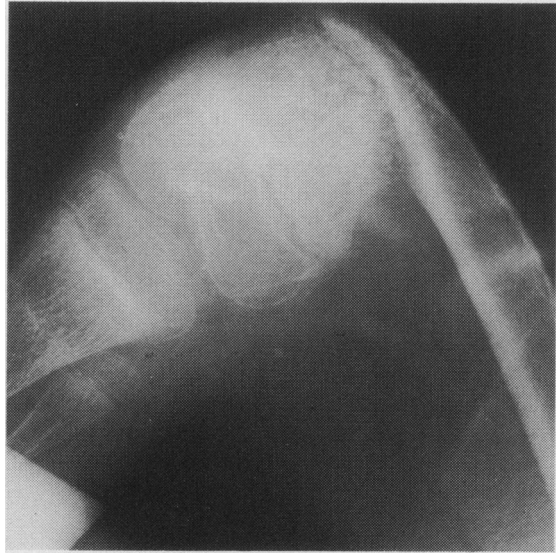


Fig. 7. Severe metaphyseal bone resorption in the femur of an adolescent uraemic.

Symptomatic bone disease occurring before end-stage chronic renal failure is relatively uncommon in adults¹⁰ and suggests the presence of additional disorders interfering with skeletal metabolism, such as nutritional deficiency of vitamin D. The prevalence of hyperparathyroid bone disease in patients reaching end-stage chronic renal failure depends on the criteria used for diagnosis. The bones of most patients show some changes of hyperparathyroidism when examined microscopically as judged by increased numbers of bone-forming and bone-resorbing cells, but only 30-40% have significant degrees of osteitis fibrosa. Less have radiographic changes and a small minority have symptoms. In patients maintained on haemodialysis treatment the incidence rises, but symptoms are still confined to a minority in most dialysis centres (10-15%).¹⁰

PATHOGENESIS OF HYPERPARATHYROID BONE DISEASE

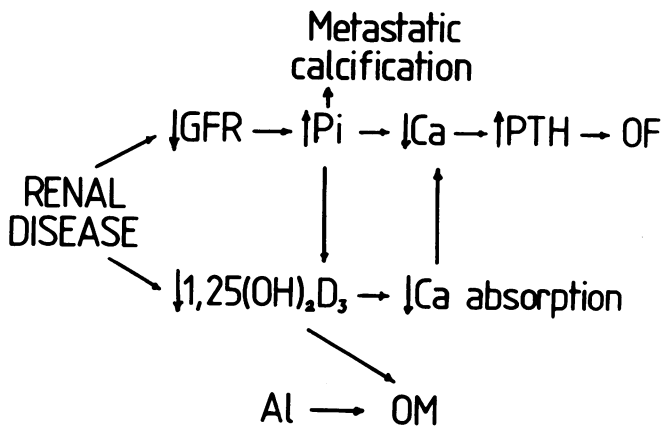
There is little doubt that hyperparathyroid bone disease is due to an increased secretion of parathyroid hormone (PTH) by the parathyroid gland. Eighty years have now passed since the first description of parathyroid gland enlargement in uraemia,⁵ and it has been known for 50 years that this was a common finding.¹² However, it is only recently that the causes of increased parathyroid secretion in uraemia have become clarified.

Abnormalities in phosphate transport appear to be of great importance. The kidney is a major route for the excretion of phosphate, and when renal function fails the serum phosphate rises. Albright in the 1930s was the first to speculate on the importance of phosphate retention in causing hyperparathyroidism in renal failure by suggesting that hyperphosphataemia might lower serum calcium values, which would in turn stimulate the parathyroid gland.¹³ This theory was later refined by elegant experimental evidence from Slatopolsky and Bricker and

their colleagues,¹⁴ who were able to delay the development of hyperparathyroidism in dogs with progressive renal failure by decremental reductions in dietary phosphate. In contrast, dogs who were allowed unrestricted dietary phosphate developed hyperphosphataemia and hyperparathyroidism as their renal function declined.

The discovery that the kidney was the major site of conversion of vitamin D to its biologically active form, 1,25-dihydroxyvitamin D₃ (calcitriol),¹⁵ provided another important clue in understanding the pathogenesis of hyperparathyroid bone disease. Progressive loss of renal tissue and the associated hyperphosphataemia impair the enzyme responsible for the production of this hormonal form of vitamin D, in turn responsible for calcium absorption from the gut. Diminished intestinal absorption of calcium may therefore aggravate hypocalcaemia and, in turn, increase the secretion of parathyroid hormone and the size of the parathyroid gland.

These hypotheses (Fig 8) have been partially tested in man, but there are still some gaps in our knowledge. Although these mechanisms are an oversimplification, they nevertheless provide a useful background on which to investigate affected patients and to design and test various treatment strategies. Not all uraemic patients have bone disease, nor will all develop bone disease, despite the ubiquity of phosphate retention and impaired synthesis of calcitriol. It becomes relevant, therefore, to pose the question as to why some patients do not develop bone disease and others are at particular risk. Several factors appear to predispose to renal bone disease at the time of starting dialysis treatment. Not surprisingly, these include young age and a long duration of renal disease. Tubulo-interstitial forms of renal disease more commonly give rise to



renal bone disease than glomerular forms: probably this is related to the destruction of the tubular cells responsible for the metabolism of vitamin D. Women have recently been identified as being at particular risk from renal bone disease, and impaired ovarian steroid production may therefore be an important determinant of the susceptibility to hyperparathyroidism.¹⁰

Fig. 8. The role of vitamin D and parathyroid hormone in the pathogenesis of renal bone disease. Progressive renal disease induces decrements in glomerular filtration rate (GFR) and synthetic capacity for calcitriol (1,25(OH)₂D₃) giving rise to osteomalacia (OM). An increase in plasma phosphate (Pi) due to the fall in GFR stimulates the secretion of parathyroid hormone (PTH) indirectly by decreasing plasma calcium levels (Ca). Malabsorption of calcium may contribute to secondary hyperparathyroidism. During progressive renal failure plasma calcium and phosphate tend to remain normal (because of the renal and skeletal effects of PTH) at the expense of an increasing secretion rate of PTH and its skeletal consequence, osteitis fibrosa (OF). When the compensatory abilities of the kidney are compromised by renal failure, hyperphosphataemia and hypocalcaemia prevail. Retention of aluminium may also cause osteomalacia.

THERAPEUTIC APPROACHES

Haemodialysis and chronic peritoneal dialysis provide the opportunity for manipulating the biochemical environment, which can modify bone disease. In many instances hyperparathyroid bone disease may regress, but sometimes at the expense of other forms of bone disease. With respect to skeletal metabolism, the institution of dialysis results in an increase in serum calcium and a decrease in serum phosphate towards normal values. Adequate control of serum phosphate may not be achievable by dialysis alone and often requires the use of antacids such as aluminium hydroxide which bind phosphate in the gut and render it unavailable for absorption. Despite these dramatic biochemical improvements, hyperparathyroid bone disease increases both in severity and frequency with increased duration of dialysis (Fig 9) in most renal units (except those in which aluminium toxicity is endemic). The normalisation of serum calcium might be expected to suppress PTH secretion, and in the short term it appears to do so. Thus, after patients have begun regular haemodialysis, plasma values of alkaline phosphatase decrease towards normal, and sub-periosteal erosions may heal. These improvements are, however, transient, and bone disease tends to recur despite the maintenance of normocalcaemia. A similar approach has been to increase serum calcium values above normal by the use of high concentrations of calcium in the dialysis fluid.¹⁶ Once again, any improvements which occur in hyperparathyroid bone disease are transient and are offset by the increased risk of extraskelatal calcification. In a recent study of long-term survivors on maintenance haemodialysis, two-thirds of patients dialysed for 10 or more years required parathyroidectomy.¹⁷

The two mainstays of treatment of parathyroid bone disease have been the use of vitamin D derivatives and parathyroidectomy. The choice of treatment has changed somewhat over the years. Problems with the unpredictable content and formulation of vitamin D, vitamin D toxicity and dangers of increasing extra-skeletal calcification made the use of high doses of vitamin D unpopular. As a result, in the early 1970s, the more radical approach of parathyroidectomy was favoured.¹⁸ The discovery of the renal 1α -hydroxylase system¹⁵ and the subsequent availability of calcitriol and its synthetic analogues, 1α -hydroxyvitamin D and dihydrotachysterol has re-focused attention on the use of preparations of vitamin D.^{2, 3}

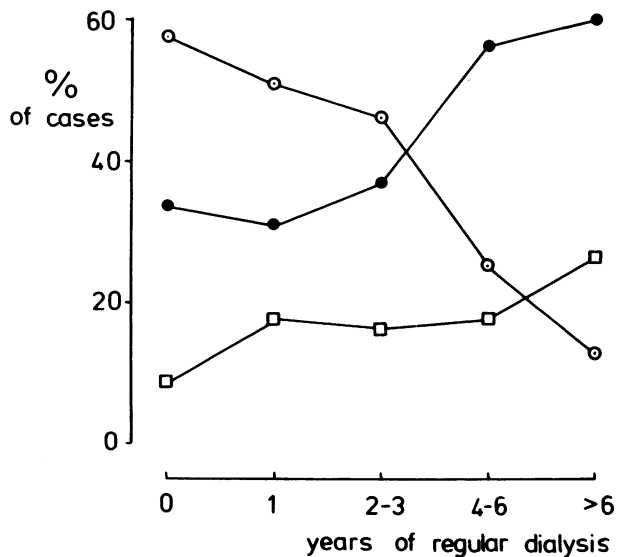


Fig. 9. Natural history of renal bone disease in 207 patients receiving dialysis treatment at the Oxford Renal Unit. The prevalence of osteitis fibrosa (with or without osteomalacia) (●) and osteomalacia alone (□) both increased with time, though changes in the former are more marked. In the 78 patients dialysed for 6 years or more, only 13% had no evidence of marked disease (○).

Vitamin D may act simply by increasing intestinal absorption of calcium and thereby raising the serum calcium, but some recent research has suggested that it may also act directly on parathyroid tissue to suppress its secretion. The evidence that this contributes to a therapeutic response is not clear. Even less clear is the question whether or not vitamin D may have a direct action on the skeleton. Thus, the use of metabolites of vitamin D may improve hyperparathyroid bone disease by mechanisms in addition to raising serum calcium, but this requires more investigation.

The short-term responses of many manifestations of hyperparathyroid bone disease are now well documented in response to treatment with vitamin D derivatives. Bone pain improves, subperiosteal and metaphyseal erosions heal, serum alkaline phosphatase and hydroxyproline values fall, and growth in children may accelerate.¹⁹⁻²² In dialysis-treated patients, the long-term results are not so reassuring. The histological changes in bone are not as striking as the clinical, biochemical and radiographic improvements,²³ and dialysis-treated patients appear to respond less favourably than less uraemic patients.^{24, 25} Moreover, following long-term treatment, hyperparathyroidism tends to recur despite continued treatment and the maintenance of normal or high plasma calcium levels (Fig 10).²⁶ Although the newer vitamin D compounds are much easier to control,²⁷ the outcome of therapy with them is comparable to those observed with high doses of 25-hydroxyvitamin D or vitamin D₂.^{28, 29} Nevertheless, the improvement in hyperparathyroid bone disease may persist for many years and thus vitamin D remains a valuable adjunct to management.

Parathyroidectomy remains an important component of the management of patients with hyperparathyroid bone disease. Though still a matter for debate,

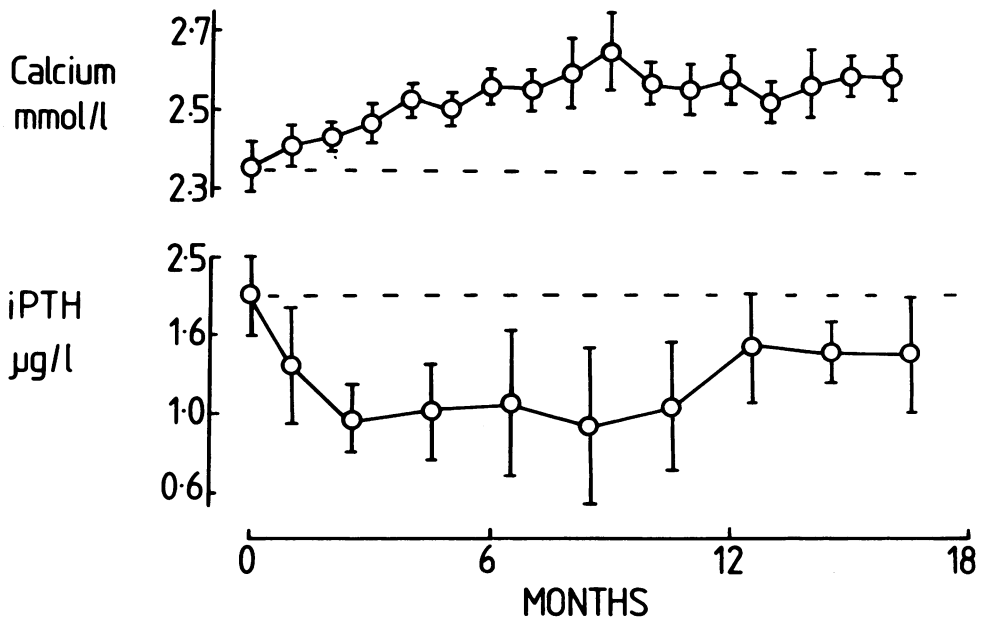


Fig. 10. Sequential changes in plasma calcium (mean \pm SEM), and serum immunoreactive parathyroid hormone (iPTH) in 13 patients treated continuously with 1,25-OH₂D₃. Note the sustained increase in plasma calcium but ill-sustained suppression of iPTH.

partial parathyroidectomy may be preferable to removal of all parathyroid tissue. However, the long-term follow-up of patients following partial parathyroidectomy indicates that this treatment, like many others for hyperparathyroid bone disease, has transient effects, and bone disease tends to recur despite the concurrent use of vitamin D and the maintenance of normocalcaemia.³⁰ The remission period is probably longer than that observed in patients treated with vitamin D preparations alone. One of the reasons for avoiding total parathyroidectomy is that this may precipitate a refractory form of vitamin D-resistant osteomalacia,³¹ similar to that observed in patients with aluminium retention.

A partial or transient suppression of hyperparathyroidism in dialysis-treated patients therefore seems possible to achieve in a number of ways. These include phosphate restriction, the infusion of calcium via the dialysate, the use of vitamin D derivatives or parathyroidectomy. Despite the efficacy of these methods, bone disease tends to recur, and it is clear that in dialysis patients there remains a potent stimulus to the growth of parathyroid tissue in addition to low values of serum calcium. The vigour with which parathyroid tissue continues to grow has been demonstrated in studies of auto-transplanted parathyroid tissue removed from patients with hyperplastic glands and embedded in sternomastoid or forearm muscles. Such transplanted tissue may become disseminated and histologically demonstrate paramalignant behaviour by locally invading blood vessels and muscle tissue.^{32, 33} The nature of this stimulus to parathyroid growth is not known. Research of this aspect of parathyroid function is in its infancy and provides one of the challenges for the future.

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