

Osteomalacia and chronic renal failure

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Dialysis and transplantation have revolutionised the management of chronic renal failure. Many patients with end-stage chronic renal failure are surviving for a long time, but there are some penalties attached to this survival, namely the complications associated with prolonged renal failure as well as the side effects of the treatments (drugs, dialysis and transplantation). Major factors which influence the morbidity and mortality of this population include anaemia, accelerated cardiovascular disease, disturbances in gonadal function, hypertension and abnormalities in lipid and skeletal metabolism.

Significant progress has been made in the past few years concerning the pathophysiology and treatment of renal bone disease. This has been due to advances in our understanding of hormone metabolism, particularly that of vitamin D, and of skeletal physiology. In addition, large populations of dialysis-or transplant-treated patients have now been studied for more than a decade with the result that the natural history of this bone disease is more clearly understood.

Renal bone disease is a constellation of skeletal abnormalities (Table 1), none of which is specific for chronic renal failure. These disorders are frequently, though not invariably, found in combination, and consideration of one of these in isolation has obvious limitations. Nevertheless, the emphasis of this review is on the aetiology and management of osteomalacia, but several more thorough and integrated approaches have appeared recently as reviews or proceedings of symposia.¹⁻⁵

HISTOLOGICAL DEFINITIONS OF OSTEOMALACIA

Osteomalacia can have a variety of meanings. The clinician may apply the term to the syndrome associated with vitamin D deficiency, whereas to the bone histologist it implies defective mineralisation of bone. There is, however, a need for precision, even in histological definitions since, for example, a histological characteristic of vitamin D deficiency in man is an increase in the amount of unmineralised bone matrix; but increased amounts of osteoid are also associated with many other disorders with normal or augmented rates of mineralisation. These include

Table 1 *Features of renal bone disease and some clinical manifestations of disturbed calcium and phosphate metabolism in chronic renal failure*

<i>Feature</i>	<i>Clinical consequence</i>
1 Hyperparathyroidism and osteitis fibrosa	Skeletal deformity, bone pain, pruritis? anaemia, impotence, neuropathy etc
2 Osteomalacia and decreased availability of vitamin D, calcium, and phosphate	Skeletal deformity, bone pain and tenderness, pathological fracture, proximal myopathy, haemolytic anaemia
3 Osteoporosis	Pathological fracture, skeletal deformity
4 Osteonecrosis	Joint pain
5 Osteosclerosis and periosteal new bone formation	None known
6 Extraskeletal calcification	Depends on site—skin ulcers, vascular disease, cardiac failure etc

Paget's disease, hyperparathyroidism, fracture repair and hyperthyroidism, indicating that an increase in osteoid volume alone (hyperosteoidosis) is an inadequate criterion for osteomalacia.^{6,7}

The amount of osteoid present in bone depends upon several factors including the rate of apposition of osteoid by osteoblasts, upon the rate of its calcification, and upon the area of the bone surface involved. When considering osteomalacia it is therefore important to distinguish hyperosteoidosis due to an increase in the proportion of bone surfaces on which osteoid is being deposited, as seen in hyperparathyroidism, from that due to a delay or absence of mineralisation—particularly in chronic renal failure where osteomalacia and hyperparathyroidism often coexist. Much confusion and apparently conflicting reports exist in the published reports concerning the pathophysiology of osteomalacia and its response to various treatments. A notable factor contributing to this confusion has been the lack of precision in defining osteomalacia, particularly in appreciating the significance of

hyperosteoidosis in hyperparathyroid bone disease (Table 2).

Table 2 *Some of the quantitative measurements made on bone biopsies which have been used (often erroneously) in the assessment of osteomalacia*

1 Surface osteoid	proportion of trabecular surfaces covered by osteoid (depends on resolving power of microscope)
2 Osteoid volume	proportion of bone matrix (or sectional area) occupied by non-mineralised bone matrix
3 Osteoid index	mean osteoid seam width: may be derived indirectly from osteoid volume and surface osteoid
4 Maximum number of osteoid lamellae	semiquantitative
5 Calcification front	the proportion of the trabecular surface (or osteoid surface) undergoing calcification as judged by stains in vitro—for example, toluidine blue or in vivo—for example, tetracycline
6 Appositional rate	mean thickness between two tetracycline markers laid down per unit time
7 Bone formation rate	derived from 5 and 6

The definition of osteomalacia as impairment of mineralisation indicates that evidence for osteomalacia should be obtained by indices of mineralisation rather than by the amount of osteoid present. The extent of the bone surface undergoing calcification can be measured by suitable staining techniques such as toluidine blue in vitro or tetracycline labelling in vivo. A decrease in the calcification front is commonly thought to reflect a decreased rate of mineralisation and hence osteomalacia. There are several objections to this view. Thus, the calcification front does not measure the rate of mineralisation but only its extent. Also the calcification front correlates well with the proportion of bone surface covered by active-looking osteoblasts in patients with chronic renal failure, and is therefore a better index of the number of functional osteoblasts than of the adequacy of bone mineralisation.⁸ Moreover, calcification fronts are commonly expressed as a proportion of the non-mineralised (osteoid) bone surface, clearly an inadequate baseline in renal osteodystrophy, where surface osteoid may be increased because of augmented bone turnover due to hyperparathyroidism. Indeed, reports that osteomalacia has improved in response to treatment such as vitamin D may be misleading where the "improvement"—that is, reduction in the calcification front, is due to a decrease in the amount of the bone trabecular surface occupied by osteoid.

The double labelling of bone with tetracyclines provides a direct method for measuring mineralisation in man,^{7,9} although the technique is time consuming to perform. Nevertheless, care must be taken in the interpretation of findings when hyperparathyroidism is present. Thus, woven osteoid,* which may take up tetracycline more easily than lamellar bone,¹⁰ is laid down in hyperparathyroidism so that normal mineralisation measured in woven bone may coexist with metabolic abnormalities which might impair mineralisation in more normal bone.

An alternative and simpler method of assessing mineralisation is to measure the maximum number of osteoid lamellae visible under polarised light.¹¹ In hyperparathyroidism the "hyperosteoidosis" is mainly due to an increase in osteoid surfaces (and sometimes an increase in lamellar thickness), rather than to an increase in the number of osteoid lamellae.⁶ Another simple method is to measure the thickness of the osteoid seams themselves or to derive this indirectly from the measurement of osteoid area and the bone surface covered by osteoid—the osteoid index (osteoid area divided by surface osteoid × 100).⁶

The prevalence of "osteomalacia" according to some of these histological criteria is shown in Fig. 1. It is important to recognise that all these indices of osteomalacia have their limitations, particularly in the presence of hyperparathyroidism. However, without a clear understanding of what is meant by osteomalacia and the problems of its definition, judgements about its pathophysiology and treatment can be misleading.

CLINICAL, BIOCHEMICAL AND RADIOGRAPHIC FEATURES OF OSTEOMALACIA

The diagnosis of osteomalacia in chronic renal failure depends mainly on the histological examination of bone, since most patients have no characteristic clinical, biochemical, or radiographic features. The frequency with which osteomalacia causes symptoms is very variable and in the Oxford Renal Unit, symptoms are confined to 10-20% of affected patients whereas in the Newcastle Renal Unit, where the incidence of osteomalacia is greater¹² (see Fig. 2), symptoms appear also to be more frequent. Symptoms of osteomalacia include bone pain and tenderness, and proximal muscle weakness. Pains in the lower limbs, pelvis and back are particularly common and may be worse on exercise. It is our experience¹³ that bone pain occurs with equal frequency in osteomalacia and osteitis fibrosa and is therefore not a diagnostic feature. Fractures,

*Osteoid is normally laid down in tight lamellar bundles and woven osteoid requires a degree of structural disorganisation.

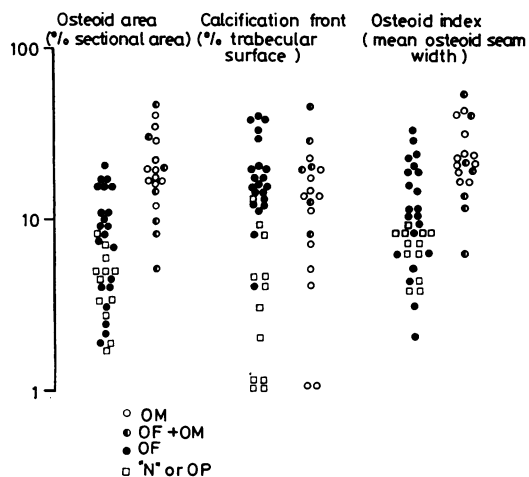


Fig. 1 Histological indices of osteomalacia (OM) in 51 patients with end-stage chronic renal failure. Patients were subdivided according to the presence (right hand columns) or absence (left hand columns) of osteomalacia as judged by the maximum number of osteoid lamellae visible on sections under polarised light. Note the lack of discrimination of the calcification front, the osteoid volume, and the osteoid index in distinguishing patients with and without osteomalacia. Each of the indices discriminates patients with normal bone histology (N or OP) from those with osteomalacia (OF + OM), but discrimination is lost when patients with osteitis fibrosa (OF) are included.

particularly of the ribs, spine, pelvis and femoral neck, occur with a variable frequency and are more common in those dialysis centres with a high prevalence of osteomalacia.

Radiographic features are usually absent and a negative radiographic survey is therefore not helpful in excluding osteomalacia. Looser's zones (Fig. 3) are characteristic of osteomalacia and are most frequently seen in the pelvis, but in dialysis-treated patients are a relatively infrequent finding. Many patients with osteomalacia have radiographic changes which are associated with hyperparathyroidism. These changes include subperiosteal erosions and intracortical porosity. Coarse trabecular markings, periosteal new bone formation and osteosclerosis appear to be more consistently associated with osteomalacia than with osteitis fibrosa.

Children are particularly prone to renal bone disease and may show radiographic features which resemble rickets. A rachitic appearance on x-ray examination does not always mean that osteomalacia is present. Thus, in uraemia there is often no widening of the metaphyseal zone and the width of the growth plate is not as thick as in vitamin D

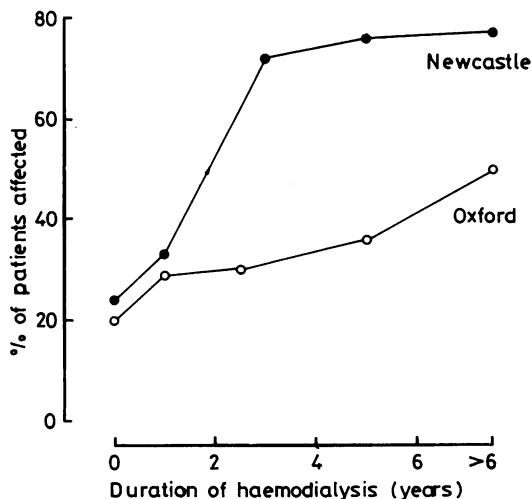


Fig. 2 The prevalence of osteomalacia in patients established on long-term intermittent haemodialysis, as assessed by repeated bone biopsy. Note the large difference in prevalence between Newcastle (a high aluminium area) and Oxford (low aluminium in the dialysate fluid) but a similar prevalence of osteomalacia at the time of starting dialysis. Patients from the Oxford Renal Unit do not invariably develop osteomalacia even after many years of haemodialysis.

deficiency (though it may appear so radiographically because of metaphyseal resorption below the growth plate: Fig. 3). These changes are more likely to reflect secondary hyperparathyroidism than vitamin D deficiency.¹⁴

Few biochemical findings are characteristic of osteomalacia in chronic renal failure. Plasma concentrations of calcium are lower in chronic renal failure than in health, particularly in children, and may be lower in patients with osteomalacia than those without.¹⁵ These differences are still present in patients on intermittent haemodialysis though the differences are less marked (Fig. 4).

A proportion of patients with histologically proven osteomalacia have normal or high concentrations of plasma calcium but without evidence of hyperparathyroidism. In such cases, the bone often shows the absence of active-looking bone cells, which is a characteristic of aluminium-induced bone disease (discussed later).

Plasma phosphate concentrations tend to increase as the glomerular filtration rate falls below 30 ml/min. The level of plasma phosphate is also determined by the diet, the use of oral phosphate-binding agents, and the dialysis regimen in patients with end-stage renal failure. Patients with severe chronic renal failure also malabsorb phosphate and



Fig. 3 Radiographic appearances of renal bone disease. Left: Characteristic radiographic features of osteomalacia in a child. Note the Looser's zone of the tibial shaft, the metaphyseal splaying of the tibia and the increased width of the growth plate. Centre: Appearances resembling rickets at the wrist of a patient with hyperparathyroid bone disease. Note metaphyseal bone resorption. Right: Marked features of hyperparathyroid bone disease of the wrist.

this may be the explanation for the osteomalacia and marked hypophosphataemia seen in some patients not taking phosphate-binding agents. Plasma concentrations of phosphate tend to be lower in patients with osteomalacia but osteomalacia cannot be diagnosed from this alone, since the presence of normal or high plasma concentrations do not exclude osteomalacia (Fig. 4).

Plasma alkaline phosphatase and plasma hydroxyproline are commonly raised in chronic renal failure. An increase in alkaline phosphatase activity may not always be due to an increase in bone-derived phosphatase but may be due to increased activities of the gut and liver isoenzymes. In population studies, plasma activities of alkaline phosphatase correlate well with histological indices of bone cell activity—for example, osteoblast counts. Hence, alkaline phosphatase activity is usually increased in patients with osteomalacia combined with secondary hyperparathyroidism, but is normal or low in many patients with osteomalacia alone (Fig. 4).

Since osteomalacia can rarely be diagnosed without histological assessment of bone, studies of its pathogenesis and the assessment of treatment regimens must include the study of biopsy material, and require a critical awareness of the meaning of the histological variables measured.

PATHOGENESIS OF OSTEOMALACIA IN CHRONIC RENAL FAILURE

Many factors are thought to be important in the pathophysiology of osteomalacia (Table 3). The evidence incriminating these factors is frequently circumstantial but their consideration is valuable in devising strategies for treatment.

Metabolism of vitamin D

Deficiency of vitamin D in man retards skeletal growth and results in defective mineralisation of matrix produced both by chondrocytes and by osteoblasts. Reversal of these abnormalities by vitamin D provides convincing evidence for the importance of vitamin D in skeletal homeostasis. However, it is not yet clear whether formation and mineralisation of bone and cartilage are direct actions of vitamin D metabolites or whether these processes are secondary to the actions of vitamin D at non-skeletal sites of calcium and phosphate transport such as the gut and kidney. In addition, vitamin D metabolites may regulate the secretion of other hormones such as parathyroid hormone and calcitonin, which themselves modify calcium and phosphate concentrations and bone metabolism.

In the past decade the major thrust in vitamin D research has been directed to studies of its metabolism

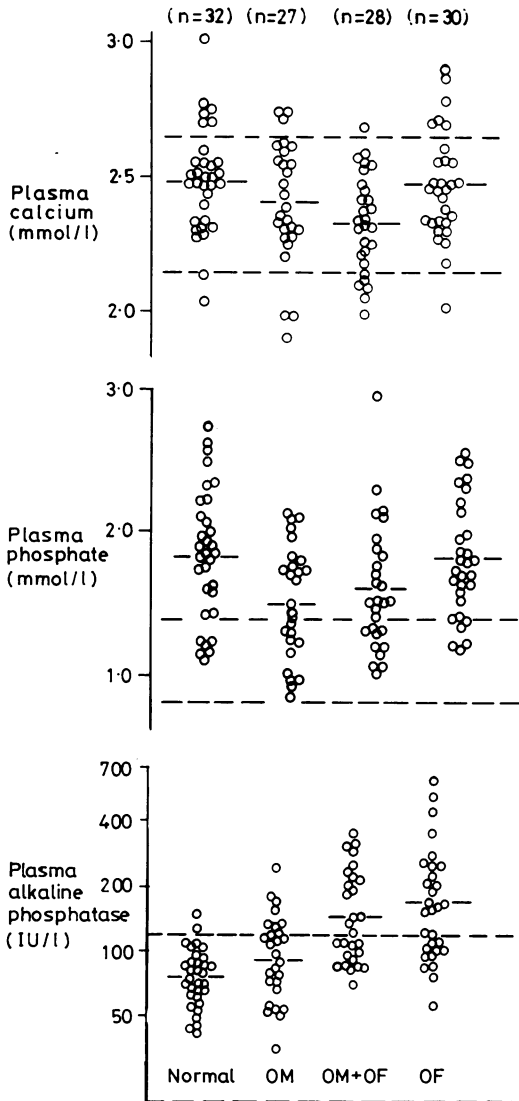


Fig. 4 Biochemical findings in plasma (predialysis values) in patients on dialysis treatment. Patients have been grouped according to the type of bone disease. OM = osteomalacia, OF = osteitis fibrosa. The broken lines denote the limits of the normal range.

to active products.¹⁶⁻¹⁸ The kidney is involved critically in this process since it is the major site of production of 1,25-dihydroxy vitamin D₃ (1,25(OH)₂-D₃) and 24,25(OH)₂-D₃.

It has been recognised for a long time that large doses of vitamin D may increase the intestinal absorption of calcium and heal osteomalacia and osteitis fibrosa in patients with renal failure.¹⁹ The

Table 3 Some factors thought to be important in the pathogenesis of osteomalacia in chronic renal failure

Disturbed vitamin D metabolism
Inadequacy of intake of vitamin D or exposure to UV light
Defective production of 1,25(OH) ₂ -D ₃
Excessive urinary losses of 25-OHD (nephrotic syndrome)
? Defective production of 24,25(OH) ₂ -D ₃
Accelerated metabolism of 25-OHD (anticonvulsants etc)
Toxic effects on bone
Aluminium intoxication—dialysate and ? aluminium-containing phosphate-binding agents
? Fluoride
Anticonvulsants (target organ resistance to vitamin D metabolites)
Availability of calcium and phosphate
Low plasma phosphate (malabsorption, hyperparathyroidism, steroids, phosphate-binding agents, lengthy dialysis schedules)
Very low calcium diets
Uncertain
Total parathyroidectomy
Uraemic inhibitors (? pyrophosphate)
? Acidosis

bone disease in renal failure is "vitamin D-resistant" in the sense that the doses of vitamin D required to produce a biological response are greater than those required to satisfy physiological needs in normal individuals. There is now considerable evidence that this resistance in renal failure is due to a defect in the metabolism of vitamin D.¹⁷

The first step in the metabolism of vitamin D₃ is its conversion to 25-hydroxy vitamin D₃ (25-OHD₃) which occurs mainly in the liver (Fig. 5). Is renal bone disease due to defective production, accelerated metabolism, or impaired action of this metabolite? Certainly plasma concentrations of 25-OHD (D₂ and D₃) may be low in patients with the nephrotic syndrome and be associated with bone disease.²⁰ Apart from this exception, there is little evidence that low concentrations of 25-OHD are due to defects in vitamin D metabolism, despite suggestions to the contrary. Certain drugs, such as anticonvulsants and barbiturates, induce hepatic microsomal enzymes, and might, therefore, increase the metabolism of 25-OHD to inert products, but there is little direct evidence for this. A more important effect of anticonvulsants may be to block the action of vitamin D metabolites on gut and bone.²¹ Low concentrations, when present, may therefore be due either to inadequate diet or reduced exposure to sunlight and might be expected to contribute to osteomalacia particularly when the degree of renal failure is modest. The usual experience is that, when anticonvulsants are avoided and patients allowed to eat normal diets (for example on dialysis treatment), plasma 25-OHD concentrations are normal.⁵

It is commonly thought that most of the actions of vitamin D₃ are mediated by metabolism of 25-OHD₃

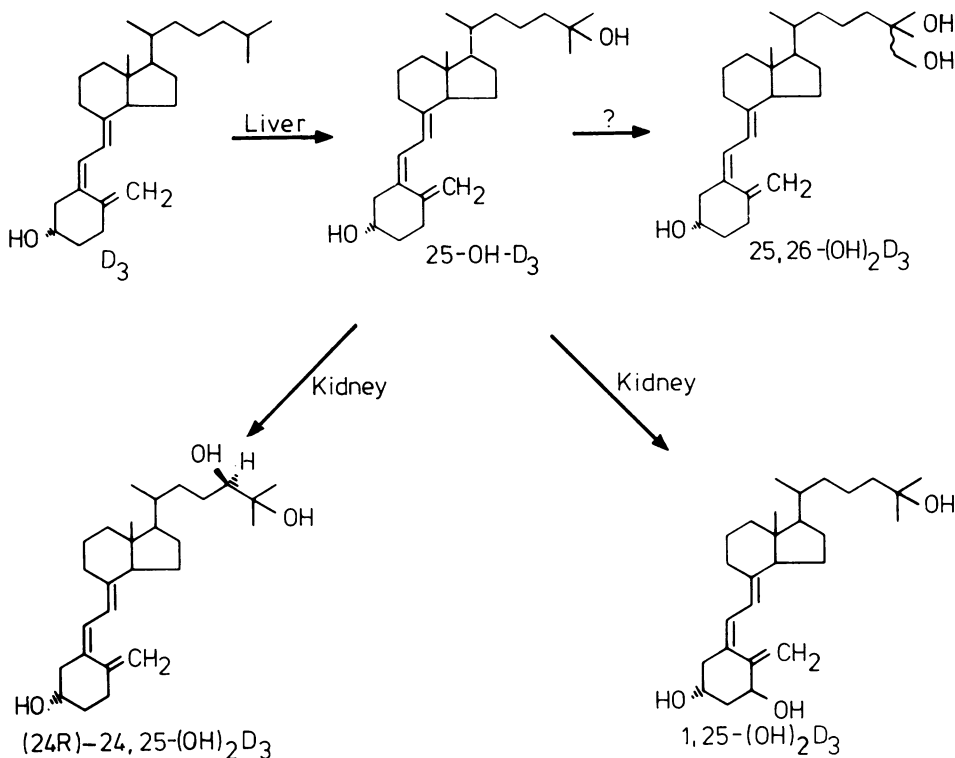


Fig. 5 Some of the major steps in the metabolism of vitamin D.

to 1,25(OH)₂-D₃. Since the kidney is probably the sole site of synthesis of 1,25(OH)₂-D₃ (apart from the placenta in pregnancy), the development of osteomalacia and its resistance to vitamin D and to 25-OHD may result from impaired production of 1,25(OH)₂-D₃ due to loss of renal tissue and perhaps also to the inhibitory effects of hyperphosphataemia on the renal 1- α hydroxylase.¹⁶⁻¹⁸

The evidence for a causal relation between vitamin D resistance, defective 1- α hydroxylation, and osteomalacia, is based on several observations. Firstly, plasma concentrations of 1,25(OH)₂-D₃ and its rate of formation decrease when the glomerular filtration rate is less than 40 ml/min, and 1,25(OH)₂-D₃ is usually undetectable in end-stage chronic renal failure.¹⁷ Secondly, x-ray and histological appearances of renal bone disease have features which resemble nutritional vitamin D deficiency. Thirdly, administration of 1,25(OH)₂-D₃ or its synthetic analogue 1- α hydroxy vitamin D₃, reverses many of the biochemical and radiographic features of osteomalacia. Moreover, the doses of 1,25(OH)₂-D₃ required to maintain remission (0.25-0.5 μ g daily) are close to its estimated daily

endogenous production rate in health, suggesting that target organs are sensitive to physiological amounts of 1,25(OH)₂-D₃ in contrast to 25-OHD.^{13,22}

The view that lack of 1,25(OH)₂-D₃ is the major cause of osteomalacia in renal failure may be an oversimplification. Thus not all patients with severe chronic renal failure have osteomalacia, and its incidence does not invariably increase with time on dialysis despite defects in the metabolism of vitamin D.²³ The incidence of osteomalacia varies widely between dialysis units (Fig. 2) suggesting the importance of dialysis-related factors in its aetiology. Moreover, the prevalence of osteomalacia is not increased markedly in anephric patients, and in some such patients the rates of mineralisation and bone formation are normal. Treatment with 1- α hydroxylated metabolites may improve radiographic and biochemical indices of osteomalacia, but this is not invariable, particularly when histological indices of response are used.^{13, 22, 23} Radiographic criteria of healing may be inadequate, particularly in children where the so-called rachitic appearances of the epiphyses may be due to hyperparathyroidism rather than to osteomalacia. These data suggest that factors

other than defective production of $1,25(\text{OH})_2\text{-D}_3$ must contribute significantly to the osteomalacia of chronic renal failure.

The production of $24,25(\text{OH})_2\text{-D}_3$ may also be deficient in renal failure since the kidney has an enzyme system capable of converting 25-OHD_3 to this metabolite. In chronic renal failure, plasma concentrations of $24,25(\text{OH})_2\text{-D}_3$ are, in some patients, lower than would be predicted from the circulating concentration of 25-OHD_3 .^{24,25} Preliminary observations suggest that patients with renal failure and osteomalacia may have the lower concentrations of $24,25(\text{OH})_2\text{-D}_3$.²⁵ The administration of $24,25(\text{OH})_2\text{-D}_3$ alone in doses sufficient to restore plasma concentrations to normal has metabolic effects but does not heal osteomalacia (unpublished observations). There is increasing evidence that both $1,25(\text{OH})_2\text{-D}_3$ and $24,25(\text{OH})_2\text{-D}_3$ are required for the actions of vitamin D on bone to be complete.^{26,27} However, the relation between decreased synthesis of $24,25(\text{OH})_2\text{-D}_3$ and osteomalacia in chronic renal failure will be clarified only when we know whether or not the kidney is the sole site of production of this metabolite (a controversial issue) since nephrectomy does not appear to aggravate renal bone disease.²³

Calcium and phosphate metabolism

It is possible that the skeletal effects of vitamin D are not dependent upon direct actions of the metabolites on bone itself but are due to consequent changes in the plasma concentration of calcium, phosphate and parathyroid hormone. One of the reasons why this question remains open is the difficulty in studying mineralisation *in vitro*, while the effects of vitamin D metabolites *in vivo* are complex.

In many disorders, including renal failure, the level of plasma phosphate appears to be an important determinant of osteomalacia. The concentration of plasma phosphate in dialysis-treated patients has been shown to correlate inversely with the degree of osteomalacia, such that those patients with normal amounts of osteoid have the higher plasma phosphate concentrations (Fig. 6).²³ It may be relevant that phosphate concentrations in such patients are considerably higher than the upper limit of normal in health, and hyperphosphataemia may therefore protect the patient from osteomalacia, despite defective vitamin D metabolism. If such a protective mechanism exists, hyperphosphataemia may mask the true importance of disturbed vitamin D metabolism in renal bone disease.

The case for the phosphate effect on mineralisation is greater than for calcium. Calcium deficiency in some experimental models leads to osteoporosis rather than to osteomalacia. However, it has been

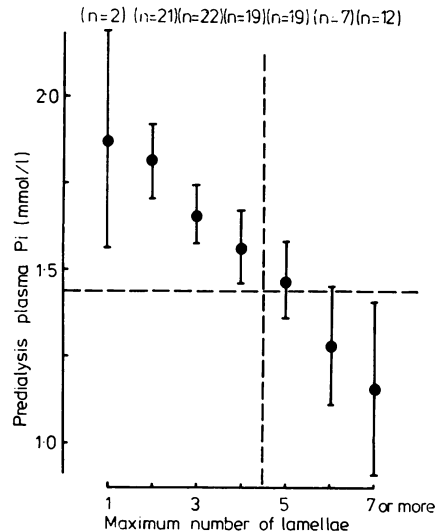


Fig. 6 Relation between plasma phosphate (P_i ; mean of values taken immediately before dialysis treatment \pm SEM) and the number of osteoid lamellae seen in histological sections. Osteomalacia (five or more lamellae) was uncommon in patients with high concentrations of plasma phosphate. Evidence of osteomalacia was commonly noted in patients whose plasma phosphate concentration lay below the upper limit of the normal range (indicated by broken lines).

shown recently that the delayed rate of osteoid maturation in D-deficient rats is correctable when hypocalcaemia is reversed by dietary calcium supplements.²⁸ There is controversy as to whether calcium deficiency alone in the presence of adequate vitamin D nutrition can cause osteomalacia in man. The most convincing demonstration of calcium deficiency rickets is in Bantus who have normal vitamin D status.²⁹ In chronic renal failure it has been reported that severe calcium deficiency may render the patient unresponsive to $1,25(\text{OH})_2\text{-D}_3$, whereas healing of osteomalacia occurs when the diet is adequately supplemented with calcium.³⁰

Trace elements and water contaminants

A number of trace elements accumulate in chronic renal failure due either to impaired excretion or to absorption from the dialysate. These include arsenic, strontium, molybdenum, magnesium, manganese, copper, aluminium and fluoride, but, with the possible exception of fluoride and aluminium, their role in the evolution of dialysis bone disease is unclear. Patients with osteomalacia do not respond uniformly to treatment with $1,25(\text{OH})_2\text{-D}_3$ or its synthetic analogue, $1\text{-}\alpha\text{-OHD}_3$ ^{13,22} despite

adequate control of plasma phosphate concentrations and the administration of calcium supplements. Indeed the failure to respond to $1,25(\text{OH})_2\text{-D}_3$ may be one method of separating patients in whom osteomalacia is due to other causes. It is also the impression of many groups that osteomalacia more commonly fails to respond to vitamin D treatment in patients on intermittent haemodialysis than in patients managed conservatively, and this has led to renewed interest in the possibility that disturbances induced by haemodialysis itself may give rise to osteomalacia.

The possible role of fluoride has been the most extensively studied. Fluoride accumulates in chronic renal failure during haemodialysis and is deposited in bone. It is also known that high doses in man induce the formation of excessive amounts of osteoid. Several groups have attempted to find a correlation between fluoride and bone disease whereas others have looked at the effects of reducing the fluoride content of the dialysate. However, there is no consensus view to be obtained from the many studies performed³¹ and it is now recognised that the bone disease attributed to fluoride may have been due to other factors not recognised at the time.

There is an increasing body of evidence that aluminium retention may be an important factor in the pathogenesis of osteomalacia in dialysis-treated patients. A form of osteomalacia associated with a high incidence of bone pain and fractures is common in certain geographical locations with a high aluminium content in the water (Fig. 2), and its incidence appears to decrease with deionisation of the water. There is also a good correlation (in the UK) between osteomalacia associated with fractures and the aluminium content of the water used for dialysis.^{32,33} Flendrig *et al.*³⁴ showed that the incidence of fractures (and of dialysis dementia) in their unit was associated with a source of aluminium in the dialysate lines whereas other patients using the same tap water did not develop this complication. This suggests that either aluminium or some factor associated with aluminium is responsible for the high prevalence of osteomalacia seen in some centres.

The question arises whether or not phosphate-binding agents containing aluminium salts may give rise to aluminium toxicity, since there is good evidence that oral aluminium is absorbed.³⁵ One of the difficulties of investigating this problem is that skeletal retention of aluminium may remain for many years after the source has been withdrawn and aluminium toxicity may take many years to develop. Thus, it is difficult to assess the relative importance of oral and water-borne aluminium. The evidence to date suggests that water-borne, rather than oral aluminium, is most commonly the major source of

skeletal aluminium.

Acidosis

The role of acidosis in contributing to renal bone disease has been advocated for many years. It has been suggested that bone acts as a buffer by releasing alkaline bone salts and this is supported by the finding of a decrease in the bicarbonate content of bone from uraemic patients.³⁶ The acute administration of acid loads to normal man results in a negative calcium balance³⁷ and it has been noted that the rate of mineralisation increases acutely when alkalis are administered to acidotic patients with osteomalacia.³⁸ The long-term effects of metabolic acidosis on bone are, however, less clear and it has not been regarded as a major factor, since the correction of acidosis appears to influence renal bone disease in only a minority of patients.³⁹ Chronic acidosis in the absence of uraemia or hypophosphataemia—for example, chronic respiratory disease, diabetes mellitus, Gaucher's disease, is not characterised by osteomalacia.

Parathyroidectomy

Total parathyroidectomy may be associated with the development of osteomalacia when osteitis fibrosa has healed.^{1,10} It is interesting that, apart from patients with aluminium toxicity, a high proportion of patients with recognised osteomalacia and renal disease who fail to respond to treatment with vitamin D metabolites have had previous parathyroidectomies.^{13,22} In some instances this lack of response may be related to persistent hypophosphataemia, but this is not invariably the case. The relative ease with which woven osteoid, present in hyperparathyroidism, calcifies in the absence of vitamin D (compared with lamellar osteoid) may explain the appearance of osteomalacia only after parathyroidectomy when lamellar bone is laid down. A corollary is that osteitis fibrosa may protect against osteomalacia.

Other factors

A number of years ago Yendt *et al.*⁴⁰ noted that uraemic plasma contained a factor which inhibited the calcification of rat cartilage. The nature of this uraemic factor has not been elucidated. One candidate might be pyrophosphate which is an inhibitor of calcium phosphate nucleation *in vitro*. Increased concentrations are found in patients with hypophosphatasia and in patients with chronic renal failure, and it is conceivable that these might cause failure of mineralisation in both conditions. In population studies there does not appear to be a clear relation between histological indices of osteomalacia and plasma pyrophosphate⁴¹ but this

does not necessarily exclude a regulatory role for pyrophosphate or other inhibitors of skeletal metabolism.

TREATMENT OF OSTEOMALACIA IN CHRONIC RENAL FAILURE

The strategy of treatment should be based not only on the presence of osteomalacia or associated symptoms but also on a careful assessment of the other skeletal abnormalities present, the other consequences of disturbed mineral metabolism (Table 1), and the mechanisms responsible for the disorder. The proposed management of the chronic renal disease itself should also be considered since, for example, therapeutic approaches may depend on the probability of subsequent transplantation.

There are a number of preventative measures which should be considered in all patients with advanced renal impairment. It is probable that the severe restriction of dietary protein, as sometimes practised, is a greater factor in inducing morbidity than it is in achieving beneficial effects. Though low protein diets restrict the amount of phosphate, this is better achieved with the use of phosphate-binding agents. Protein-deficient diets also tend to restrict the intake of vitamin C and pyridoxine which both act as essential cofactors in the formation and maturation of collagen. The relation between deficiency of these factors and osteomalacia is unclear and they may be more important in the pathogenesis of osteoporosis. Both vitamin C and vitamin B₆ should be given as dietary supplements.

Treatment of disturbed phosphate metabolism

Despite compensatory decreases in tubular reabsorption of phosphate, plasma phosphate concentrations are nearly always markedly increased in patients with severe renal impairment (Fig. 4). The value of lowering plasma phosphate concentrations in preventing hyperparathyroid bone disease in man is uncertain but the control of plasma phosphate is important in the management and prevention of extraskeletal calcification,⁴² and is usually achieved by the use of phosphate-binding agents, such as aluminium hydroxide. Calcium carbonate also binds phosphate in the gut, and has potential advantages in that it corrects acidosis, increases the dietary calcium load, and enables the ingestion of aluminium to be avoided; but in practice the amounts of calcium carbonate required are large.

In order to avoid extraskeletal calcification, predialysis concentrations of plasma phosphate should be less than 2.4 mmol/l.⁴² Factors which influence the dose required of the phosphate-binding agent include the dietary intake of phosphate, concurrent treatment with vitamin D and its ana-

logues or metabolites, and the haemodialysis treatment schedule prescribed. Profound hypophosphataemia should also be avoided since it is associated with osteomalacia.⁴³ If the relation between predialysis concentrations of phosphate and histological indices of osteomalacia is causal (Fig. 6), it is important to note that the concentrations of plasma phosphate below which osteomalacia may be induced are considerably higher than those associated with impaired mineralisation in patients with normal renal function. Thus the plasma phosphate concentrations which best balance the risks of metastatic calcification and osteomalacia probably lie between 1.4 and 2.4 mmol/l in dialysis-treated patients.

Phosphate therapy has been advocated as a method of treating osteomalacia in chronic renal failure. This is not without risk and should only be attempted, and then cautiously, in patients with tubular disorders. The infusion of phosphate during the dialysis treatment does not appear to improve osteomalacia and indeed may aggravate osteitis fibrosa.⁴⁴

Treatment of disturbed calcium metabolism

Unlike the net intestinal absorption of phosphate which is largely dependent on the dietary load, the net absorption of calcium is more critically dependent on the presence of the vitamin D metabolites, particularly 1,25(OH)₂-D₃. Nevertheless, net intestinal transport of calcium can be augmented by large amounts of calcium carbonate (5-20 g daily) and this may improve osteomalacia.⁴⁵ It is often more practicable to give vitamin D or one of its metabolites, but net intestinal absorption of calcium cannot be greatly augmented if the diet is severely deficient in calcium. Moreover, marked calcium deficiency appears to impair the response to 1,25(OH)₂-D₃.³⁰ It is important, therefore, to ensure a normal dietary intake of calcium with the use of calcium supplements if necessary.

The dialysis membrane provides a site for the loss of calcium or its incorporation into the body, but there is no evidence that the dialysate calcium concentration influences the natural history of osteomalacia.

Use of vitamin D and related compounds

A variety of vitamin D compounds is available for use in chronic renal failure. These include vitamin D₂, D₃, 25-OHD₃, dihydrotachysterol (DHT), 1,25(OH)₂-D₃ and 1- α -OHD₃. A great deal of clinical interest has focused on 1,25(OH)₂-D₃ and its synthetic analogue 1- α -OHD₃ since they bypass the metabolic block caused by uraemia, but DHT is also biologically active without the necessity for 1- α -hydroxylation by the kidney. DHT and

1- α -OHD₃ undergo hepatic hydroxylation and the 25-OHDHT or 1,25(OH)₂-D₃ so formed are the major circulating forms of these agents. It has been suggested that anticonvulsants interfere with the hepatic production of these metabolites and these drugs should therefore be avoided for this reason. The clinical evidence for this is not clear though it should be remembered that anticonvulsants probably also interfere with the target organ actions of all the vitamin D compounds.

All the vitamin D-like compounds available are effective in relieving symptoms of bone pain and muscle weakness, in increasing plasma calcium concentrations, and in the majority of patients they suppress raised plasma activities of alkaline phosphatase and correct radiographic abnormalities (Figs. 7 and 8).^{13 19 22} Skeletal deformity in the young can probably be prevented and growth partly restored.^{46 47}

The histological response to treatment is often disappointing, particularly in patients maintained on intermittent haemodialysis, where factors other than disturbed vitamin D metabolism presumably play a dominant role in the pathophysiology. Osteomalacia

appears to respond more readily when associated with osteitis fibrosa. Once again this may be related to the different pathogenic mechanisms.

Although most patients with end-stage chronic renal failure have histological evidence of bone disease, they are often symptomless. In patients on dialysis treatment, considerable differences exist in the incidence and natural history of osteomalacia between renal units. Whether to treat asymptomatic patients with vitamin D metabolites will therefore depend on several factors. Our own policy at present is not to treat those patients with abnormal bone histology unless they have symptoms, marked hypocalcaemia or radiographic or biochemical evidence of bone disease. Several trials are currently underway to evaluate the efficacy of 1- α -OHD₃ or 1,25(OH)₂-D₃ in preventing the development of overt bone disease and this view may therefore require modification.

Doses of the various agents required to maintain the plasma calcium concentration within the normal range and to reverse bone disease are indicated in Table 4. In general, the maximal dose which avoids hypercalcaemia decreases with time (Fig. 7). The

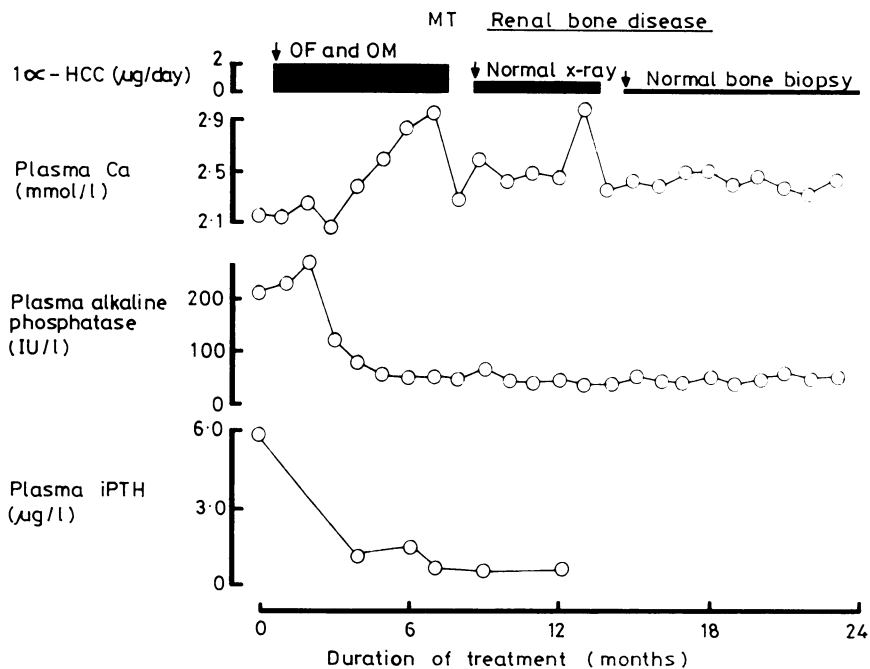


Fig. 7 Long-term treatment of osteomalacia (OM) with 1- α -hydroxy-vitamin D₃ (1- α -HCC) in a dialysis-treated patient. Healing of osteomalacia occurred within 15 months. Episodes of hypercalcaemia occurred suddenly and the dose of 1- α -HCC tolerated decreased progressively once plasma alkaline phosphatase had fallen to normal activities. Remission from bone disease was maintained using a dose of 1- α -HCC of 1 μ g thrice weekly. OF = osteitis fibrosa, iPTH = immunoreactive parathormone.

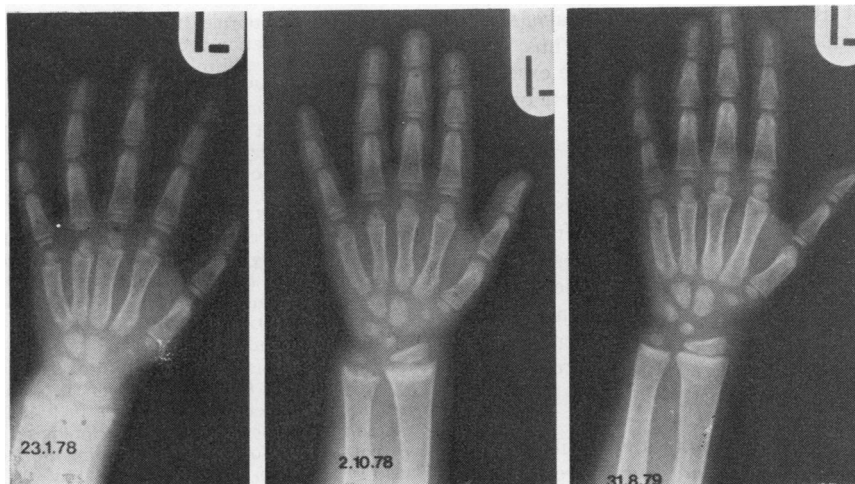


Fig. 8 Radiographic responses to treatment of osteomalacia with large doses of vitamin D.

Table 4 Usual dose requirements of vitamin D₃ (or vitamin D₂), dihydrotachysterol (DHT), 1 α -OHD₃, and 1,25(OH)₂-D₃ in dietary deficiency rickets and in vitamin D resistance due to chronic renal failure. Note that, though larger amounts of DHT than vitamin D are required to treat simple rickets, for the treatment of renal bone disease only slightly higher doses of DHT (or 1 α -OHD₃ or 1,25(OH)₂-D₃ up to \times 4) are required in contrast to the much larger doses of vitamin D₃ (up to \times 400) that are required

	D ₃	DHT	1 α -OHD ₃	1,25(OH) ₂ -D ₃
Approximate daily dose required to treat or prevent rickets (μ g)	2.5-25	up to 200	up to 1.0	up to 0.5
Potency relative to vitamin D ₃	100	10	250	500
Approximate daily dose required to treat renal bone disease (μ g)	750-10 000	200-1000	0.5-2.0	0.25-2.0
Potency relative to vitamin D ₃	100	1000	500 000	500 000

Note 1 μ g D₃ or 1,25(OH)₂-D₃ is equivalent to approximately 40 IU.

greatest risks of hypercalcaemia occur at the start of treatment, particularly in patients who respond poorly to treatment (aplastic osteomalacia), and later when biochemical responses are nearing completion. Plasma calcium concentrations should be monitored frequently during these risk periods. It is also important to note that these agents increase the absorption of phosphate and the requirements for phosphate-binding agents may be increased.

Despite advocates to the contrary, there is no clinical evidence that 1,25(OH)₂-D₃, 1-alpha-OHD₃ or DHT have any particular therapeutic actions not also possessed by other agents such as 25-OHD₃ or vitamin D.^{13 48} The advantages of the 1-alpha-hydroxylated metabolites of vitamin D lie in the ease with which doses are titrated according to requirements and the speed with which toxic effects are reversed on withdrawal of treatment.⁴⁹

Treatment with vitamin D or its metabolites is not without risk. Prolonged raised plasma calcium and phosphate concentrations give rise to extraskeletal calcification. Patients with pre-existing hypercalcaemia and osteomalacia should be treated

cautiously, if at all, since such patients often respond poorly to treatment. Prolonged hypercalcaemia may also impair renal function, sometimes irreversibly, and there has been recent interest in the suggestion that vitamin D compounds may themselves be nephrotoxic.⁵⁰ It is difficult, however, to be sure how much any deterioration of renal function reflects the natural history of the disorder or the effects of the hypercalcaemia or hyperphosphataemia,⁵¹ and others have not noted such adverse effects when plasma calcium and phosphate are well controlled. These considerations nevertheless re-emphasise the need for close control of plasma calcium and phosphate, and the serial measurement of plasma creatinine in patients not yet established on dialysis treatment.

Aluminium toxicity

This severely disabling condition does not respond to treatment with vitamin D or its metabolites. It may respond slowly to transplantation or adequate removal of aluminium from the dialysis fluid. This slow response probably reflects the prolonged skeletal retention of aluminium and the difficulty

with which it is removed by haemodialysis, and indicates the importance of prophylaxis. Thus, where aluminium concentrations in the dialysate exceed 20 µg/l, the water should be treated by reverse osmosis or possibly by deionisation.³³

Parathyroidectomy

Surgical removal of parathyroid glands is the most effective and rapid method of treating hyperparathyroid bone disease. The place for parathyroidectomy is beyond the scope of this review, but the occurrence (or unmasking) of osteomalacia following total parathyroidectomy is one of the reasons why partial parathyroidectomy may be preferred.

Renal transplantation

Theoretically renal transplantation would be the treatment of choice for patients with osteomalacia. This rapidly restores the capacity to form 1,25(OH)₂-D₃ and of course reverses uraemia. Osteomalacia is often slow to reverse, particularly when associated with aluminium retention. Bone disease, including osteomalacia, may arise de novo in the transplanted population. There is a high incidence of hypophosphataemia in the transplant population⁵² and this may be partly related to phosphate depletion by the use of antacids, to the persistence of hyperparathyroidism which is slow to regress after transplantation, and to the effects of corticosteroids in decreasing renal tubular reabsorption of phosphate.

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