

Renal osteodystrophy: dietary influences and management

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Our concepts of metabolic bone disease in chronic renal failure (CRF) have undergone considerable revision during the last two decades, mainly due to the rehabilitation of patients on dialysis, and to the greater understanding of the metabolism of vitamin D, parathyroid hormone (PTH) and other components of calcium and phosphate homeostasis. Renal osteodystrophy is a pleomorphic disease, the clinical manifestations of which consist of osteomalacia, osteitis fibrosa, osteosclerosis, and osteoporosis. In an individual patient, any one of these lesions may exist alone or in various combinations, with one or the other lesion predominating (Kaye & Silverman, 1965; Ellis & Peart, 1973).

A number of factors have been implicated in the pathogenesis of renal osteodystrophy, including phosphate retention, hypocalcaemia, and secondary hyperparathyroidism (Bricker *et al.* 1969; Arnaud, 1973), vitamin D resistance (Liu & Chu, 1943; Lumb *et al.* 1971), intestinal malabsorption of Ca (Coburn *et al.* 1973; Farrington, Varghese, Newman *et al.* 1979), skeletal resistance to the Ca mobilizing action of PTH (Massry *et al.* 1973; Massry *et al.* 1978), defects in the degradation of PTH (Hruska *et al.* 1975), metabolic acidosis (Cochran *et al.* 1973; Lee *et al.* 1977) and 'uraemic toxins' (Wills *et al.* 1975). Comprehensive reviews of the pathogenesis, clinical assessment and management of renal osteodystrophy have appeared recently (Kleeman & Better, 1973; David, 1975; Avioli, 1978; Pierides, 1978).

The present account makes special reference to dietary factors in the pathogenesis of renal osteodystrophy and its treatment.

Vitamin D metabolism

Liu & Chu (1943) initially proposed the concept of vitamin D resistance in CRF. They also reported that the skeletal lesions in their patients were indistinguishable from those seen in nutritional rickets. Stanbury *et al.* (1969) showed that azotaemic rickets can be cured by vitamin D alone, albeit in pharmacological doses. In untreated patients with renal osteodystrophy, the plasma level of assayable vitamin D has been reported to be normal or low due to dietary restrictions (Lumb *et al.* 1971). In Britain the state of vitamin D nutrition is considered to be only marginally adequate to protect against nutritional rickets and osteomalacia. Hence when chronic renal failure superimposes an increased requirement for vitamin D, British patients are more likely to develop an effective vitamin D deficiency and osteomalacia than patients in the United States, whose vitamin D nutrition is better. Differences in vitamin D nutrition and sunlight exposure may affect the clinical presentation of renal osteodystrophy.

Several mechanisms have been proposed for this vitamin D resistance. These include: failure of endorgan responsiveness due to uraemia (Brickman *et al.* 1974), increased metabolic turnover of vitamin D (Avioli *et al.* 1968), depletion of 25-OHD₃ (Offerman *et al.* 1974) and a deficiency of 1,25-(OH)₂D₃ (Mawer *et al.* 1973; Haussler, 1975). It is now generally agreed that vitamin D₃ must undergo a two-stage metabolic transformation; first in the liver to 25-OHD₃ and then in the kidney to 1,25-(OH)₂D₃ and other metabolites, before it can express its full potential as a steroid hormone (DeLuca, 1973).

Increased hepatic microsomal enzyme induction has been implicated in the depletion of 25-OHD₃ and the pathogenesis of osteomalacia in CRF (Eastwood *et al.* 1976). However, the low levels of 25-OHD found in undialysed patients may well be a consequence of dietary restriction (Mawer *et al.* 1973), and other studies suggest that hepatic metabolism of vitamin D is normal in these patients (Farrington *et al.* 1979). Identification of the kidney as the sole site for the conversion of 25-OHD₃ to its active form—1,25-(OH)₂D₃ has provided an explanation for the nature of 'vitamin D resistance' in CRF. However, some observations are inconsistent with the view that a deficiency of 1,25-(OH)₂D₃ is solely responsible for the pathogenesis of renal osteodystrophy. (Bordier *et al.* 1973.) Recently, Eastwood *et al.* (1979) demonstrated that manifestations of nutritional vitamin D deficiency can occur in the presence of normal concentrations of 1,25-(OH)₂D₃. This is analogous to the situation in anticonvulsant induced osteomalacia (Jubiz *et al.* 1977).

It may thus be that the various metabolites of vitamin D have different roles to perform in the total expression of its biological potential, 25-OHD₃ and 24,25-(OH)₂D₃ may be involved in normal mineralization, whereas 1,25-(OH)₂D₃ has the major influence on intestinal absorption of Ca. There is also evidence that both 24,25-(OH)₂D₃ and 1,25-(OH)₂D₃ may directly influence the parathyroid gland.

Ca malabsorption

Decreased 1,25-(OH)₂D₃ synthesis causes decreased intestinal absorption of Ca. Abnormal Ca absorption is further aggravated by low dietary Ca intake (Coburn *et al.* 1973; Varghese *et al.* 1973), although uraemic subjects can absorb Ca in similar amounts to normal subjects on normal diets when dietary Ca intake is elevated to 4–10 g/d (McDonald *et al.* 1964). These observations suggest that there is a loss of normal adaption of Ca absorption and a lack of normal compensatory modulation to the skeletal needs for Ca. This adaption appears to be mediated by vitamin D. The factors responsible for reduced Ca absorption in chronic renal failure may be multiple, but reduced net Ca absorption may have an important role in the pathogenesis of renal osteodystrophy.

Phosphate retention and secondary hyperparathyroidism

Phosphate retention is considered to play an important role in causing hypocalcaemia. Bricker *et al.* (1969) proposed that 'secondary hyperparathyroidism in chronic progressive renal disease begins with the destruction of the first nephron'. Their hypothesis suggests that loss of nephrons

leads to phosphate retention which in turn reduces the plasma Ca concentration and causes an increase in the secretion of PTH. This results in an increase in phosphate excretion and normalization of plasma phosphate level and a stepwise increase in PTH with every decrement in renal function.

Several observations support this hypothesis (Slatopolsky *et al.* 1972). Berlyne *et al.* (1973) attributed the lower incidence of renal osteodystrophy in undialysed CRF patients in Israel to their low-phosphate diet. It has also been shown that the decrease in plasma phosphate concentration obtained during treatment with phosphate binding agents is usually associated with a fall in the level of circulating i-PTH (Hill *et al.* 1973). In patients with severe osteitis fibrosa PTH itself by its effect on bone reabsorption can exacerbate hyperphosphataemia and render it refractory to treatment. The development of secondary hyperparathyroidism thus appears to begin early and progresses in severity with advancing renal failure (Fig. 1).

Additional factors

Although hyperphosphataemia plays a major role in the pathogenesis and progression of renal osteodystrophy, there is now an increasing awareness that phosphate depletion may aggravate bone disease and cause osteomalacia. This may be due to over-treatment with phosphate binders (Baker *et al.* 1974) but in other instances is due to factors such as severe phosphate malabsorption, poor dietary intake and excessive dialysis losses (Ahmed *et al.* 1976).

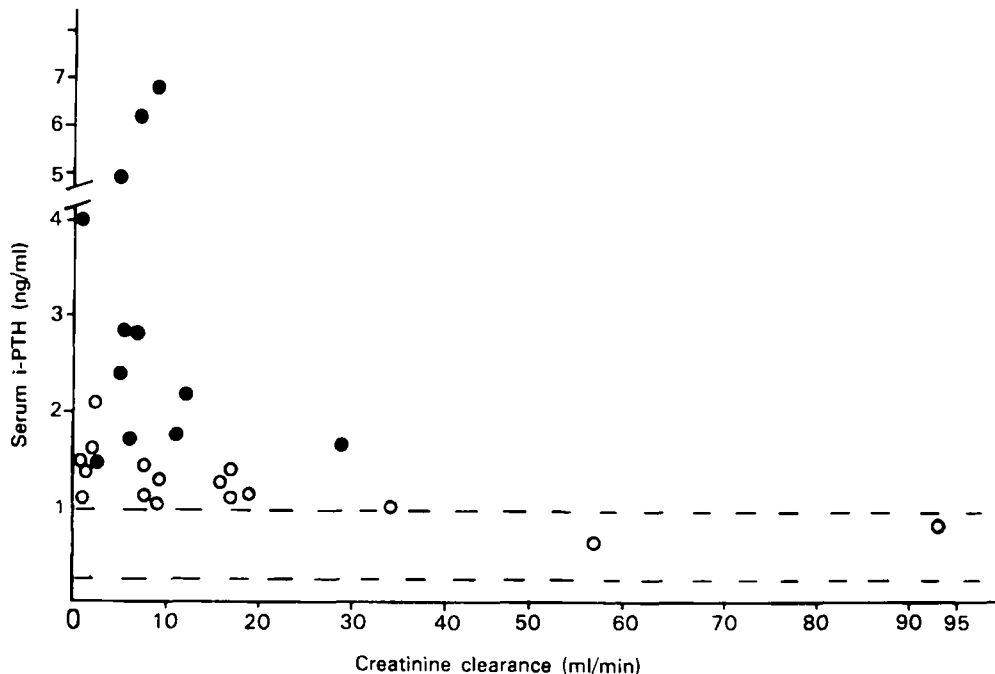


Fig. 1. Relationship between creatinine clearance and serum with PTH values in non-dialysed CRF patients with (●) and without (○) subperiosteal erosions (Arnaud, 1973).

Other dietary factors may also be important in the development of renal osteodystrophy. Water-soluble vitamins are scarce in the diet of uraemic subjects (Kopple & Swendseid, 1975) and it has also been shown that protein restriction may aggravate the deficiency of vitamin C and pyridoxine. Vitamin C, vitamin D and pyridoxine are essential cofactors in the formation and maturation of collagen, and a normal collagen matrix is essential for normal skeletal function. Elevated serum vitamin A levels occur in uraemic subjects (Kopple & Swendseid, 1975). This may be aggravated by the indiscriminate use of multivitamin preparations. Vitamin A may stimulate the parathyroid gland, and directly or indirectly cause Ca release from bone (Chertwo *et al.* 1974).

Dialysis osteodystrophy

Haemodialysis does not completely correct the uraemic state and does not restore plasma Ca and phosphate homeostasis to normal. The deficiency of $1,25\text{-(OH)}_2\text{D}_3$ persists (Haussler & McCain, 1977). Gastrointestinal absorption of Ca and phosphate, though variable, usually remains defective (Fig. 2). However, it is wrong to assume that metabolic bone disease developing in patients on MHT is necessarily similar to that found in non-dialysed chronic renal failure patients. Despite the histological similarities, the two diseases have different clinical courses, different rates of progression, and different prevalences (Moorhead *et al.* 1974).

The main component of dialysis osteodystrophy is osteitis fibrosa; osteomalacia being relatively uncommon. Bone disease in MHT patients progresses despite the maintenance of plasma Ca, and magnesium and their fractions at concentrations which in a normal subject would be unlikely to be associated with either osteomalacia or hyperparathyroidism. (Varghese *et al.* 1973.) Dialysis patients may encounter numerous additional factors (Table 1) some of which may be outside the normal influence of the metabolic regulators of Ca and phosphate homeostasis.

Table 1. *Special factors in dialysis osteodystrophy*

1. Dialysate calcium
2. Dialysate magnesium
3. Phosphate depletion
 - (a) Use of phosphate binders
 - (b) Loss during dialysis
 - (c) Severe phosphate malabsorption
 - (d) Poor dietary intake
4. Impurities in the water or chemicals used in the preparation of dialysis fluid
 - (a) Fluoride
 - (b) Aluminium
 - (c) Other contaminants
5. Type and frequency of dialysis
6. Drugs
 - (a) The influence of enzyme inducing drugs on vitamin D metabolism, e.g. barbiturates
 - (b) Drugs modifying PTH secretion, e.g. β blockers, cimetidine, vitamin A
 - (c) Heparin

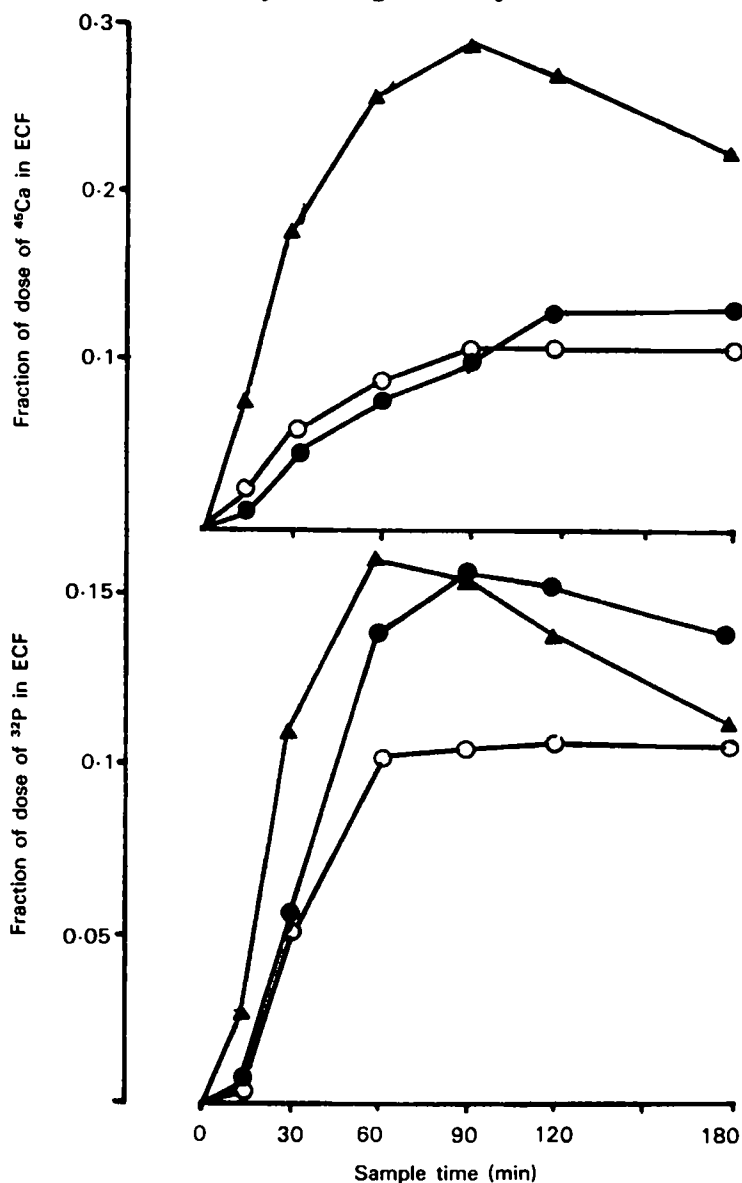


Fig. 2. Plasma activity of calcium and phosphate during 3 h absorption tests. (▲), controls; (●), CRF patients on dialysis; (○), non-dialysed CRF patients.

Management

Despite the progress in the understanding of the pathogenesis of renal osteodystrophy there is still no unified approach to treatment. However, from an understanding of the pathogenesis several therapeutic measures are possible. The

aims of these are to normalize plasma phosphate and Ca concentration, to suppress parathyroid glands, to normalize skeletal metabolism, and to avoid metastatic calcification. It is of importance to monitor the renal function in non-dialysed CRF patients, to ensure that the agents used (vitamin D compounds, and Ca supplements) have no adverse effect on residual renal function (Farrington *et al.* 1978).

Phosphate binders

Although it has been claimed that a proportional reduction of dietary phosphate with decline in renal function may delay the development of secondary hyperparathyroidism early in renal failure, this is not practicable. In severe renal failure phosphate binders are used with careful monitoring of phosphate levels. Increasing duration and frequency of dialysis may also aid control of plasma phosphate.

Oral Ca supplements

Because of the co-existence of poor dietary intake of Ca and Ca malabsorption, supplements should be given to increase the total dietary intake to approximately 1.5–2.0 g/d. Fletcher *et al.* (1963) reported that external Ca balance in renal failure could be made positive by increasing the oral Ca intake, but this had no beneficial effect in correcting osteomalacia. This is in agreement with the observations of Eastwood *et al.* (1974).

Dialysate Ca

Raising the concentrations of Ca in the dialysing fluid (approximately 6.0 mg/100 ml) is another way to keep the patients in a positive Ca balance. It has been suggested that bone disorders associated with secondary hyperparathyroidism can be prevented by the use of high dialysate Ca (Goldsmith *et al.* 1971). A number of studies have indicated short-term benefit from such strategies (Moorhead *et al.* 1975). However, Tatler *et al.* (1973) found no significant changes in the progressive development of bone reabsorption and vascular calcification when they used dialysate Ca concentrations of 6.5–7.5 mg/100 ml. Although there is no definite recommendation regarding the optimum concentrations of Ca in the dialysate, a concentration between 6.5–7.5 m/100 ml seems to be desirable.

Vitamin D compounds

Since the pathogenesis of renal osteodystrophy suggests an effective vitamin D deficiency state, vitamin D and related compounds have a definite place in the treatment of renal osteodystrophy and this is specially important in patients with predominant osteomalacia, hypocalcaemia and after parathyroidectomy. Currently the forms of vitamin D compounds available for clinical use include vit D₂, vit D₃, DHT, 1 α -OHD₃, and clinical trials are being done with other compounds 25-OHD₃, 1,25-(OH)₂D₃ and 24,25-(OH)₂D₃. There is little evidence to indicate

that vitamin D₂ differs in activity from vitamin D₃ in man. Pharmacologic doses of vitamin D₃ have been found to be effective in treating renal osteomalacia (Lumb *et al.* 1971). The individual requirement for vitamin D₂ may vary widely from 0.1 to 5 mg/d, and the dosage needs to be adjusted during the course of treatment. This dosage is far in excess of the daily normal adult requirement (1.9 µg/d) and a real danger of toxicity exists. Dihydrotachysterol has been used in the treatment of renal osteodystrophy since the original observation of Liu & Chu (1943). DHT has obvious structural similarities to 1,25-(OH)₂D₃, because of the possibility of rotating the 'A' ring through 180° bringing the 3β hydroxyl group into a pseudo 1 position (Hallick & DeLuca, 1972). This may explain why DHT is more effective than vitamin D₂ or vitamin D₃ in patients with chronic renal failure. Our experience of treating CRF patients with some of these compounds is given in the next sections.

Dihydrotachysterol (DHT)

Fifteen CRF patients were treated with 0.25 mg DHT/d for 18 months. Thirteen patients were on haemodialysis and the remaining two had end stage CRF (creatinine clearance (C.Cr) 6 ml/min). In addition to DHT they were given 4 g Ca CO₃/d. Plasma phosphate was controlled by aluminium hydroxide therapy. There was no significant increase in plasma phosphate during the course of this study (Fig. 3). There was a gradual rise in plasma Ca and it became statistically significant from the second month ($P < 0.025$). However, at no point did the patients become hypercalcaemic. Plasma hydroxyproline showed a significant ($P < 0.02$) fall from the first month, even before there was a significant change in plasma Ca. Plasma alkaline phosphate only showed a significant change ($P < 0.01$) 5 months after starting treatment. This response in alkaline phosphatase was slower than that which was seen with either 1α-OHD₃ or 1,25-(OH)₂D₃. Iliac crest bone biopsies were available in ten patients before and after treatment (Fig. 4). These showed a marked reduction in osteoid volume in all patients. However, improvement in mineralization front was seen in only five patients. There was a reduction in active reabsorption surfaces in seven patients.

1α-OH cholecalciferol

Eleven patients with CRF (mean C.Cr 11.8 ± 8.8 ml/min) were treated for periods of 6 to 15 months with oral doses of 1α OHD₃ (0.25 µg–1 µg/d, mean dose 0.4 µg/d). The starting dose was 0.25 µg/d increasing up to 0.5 or 1 µg/d. Oral Ca carbonate (up to 2.5 g/d) and aluminium hydroxide preparations were also prescribed.

Ca absorption was increased in direct proportion to the dose of 1α-OHD₃ used (Fig. 5) though there was no over-all effect of phosphate absorption on any dose level. This may reflect a fundamental difference in the control mechanism of intestinal Ca and phosphate transport, as previously suggested (Farrington *et al.* 1979). Plasma Ca increased significantly in response to treatment, but there was no effect on plasma phosphate levels (Fig. 6); Alkaline phosphatase decreased

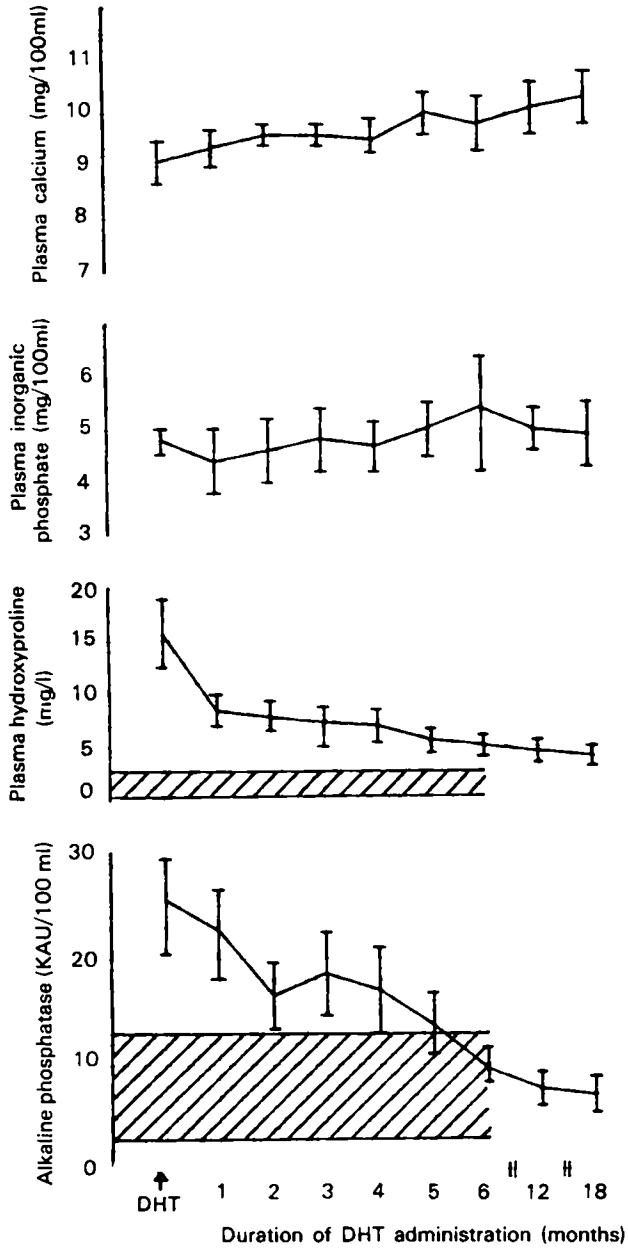


Fig. 3. Biochemical responses to treatment with dihydrotachysterol (DHT).

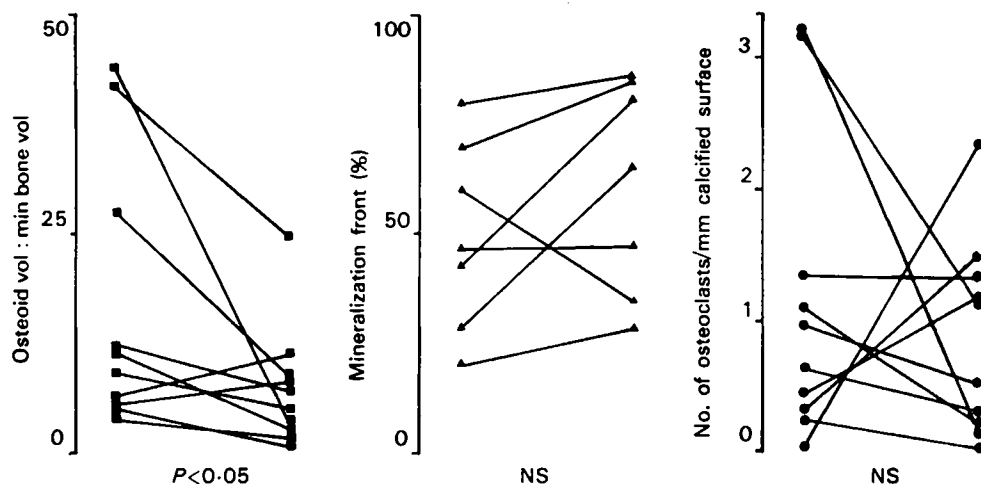


Fig. 4. Changes in histological measurements in response to treatment with dihydrotachysterol (DHT). NS, not significant.

significantly. A significant reduction in bone turnover occurred, as indicated by significant reductions in osteoid volume and active surfaces (Fig. 7). However, there was no significant effect on mineralization front as assessed by single tetracycline labelling. This supports the suggestions of Bordier *et al.* (1978) that other metabolites of vitamin D such as 25-OHD₃ and 24,25-(OH)₂D₃ may be important in the reversal of the mineralization defects in this condition.

1,25-(OH)₂ cholecalciferol

Oral 1,25-(OH)₂D₃ (0.5 µg/d) and 4 g of Ca carbonate/d were given to five CRF patients for 4–16 months. This treatment was found to be effective in correcting intestinal Ca malabsorption in all patients. Plasma alkaline phosphatase, plasma hydroxyproline and i-PTH concentrations showed significant reductions. The fall in i-PTH concentration seen was independent of changes in the plasma Ca, suggesting a direct action of 1,25-(OH)₂D₃ on parathyroid glands. Bone histology showed marked improvements (Ahmed *et al.* 1978).

Parathyroidectomy

With increasing time on dialysis a growing number of patients may develop persistent hypercalcaemia, progressive elevations in the concentration of plasma phosphate, alkaline phosphatase, hydroxyproline and i-PTH, and radiological and histological evidence of severe osteitis fibrosa. These patients require subtotal or total parathyroidectomy.

Hyperparathyroidism in dialysis patients thus appears to be of a progressive nature (Fig. 8) in spite of the short-term control obtained by phosphate binders, oral Ca supplements, high dialysate Ca and vitamin D compounds. This eventual 'escape' from control may not be obvious from short-term studies.

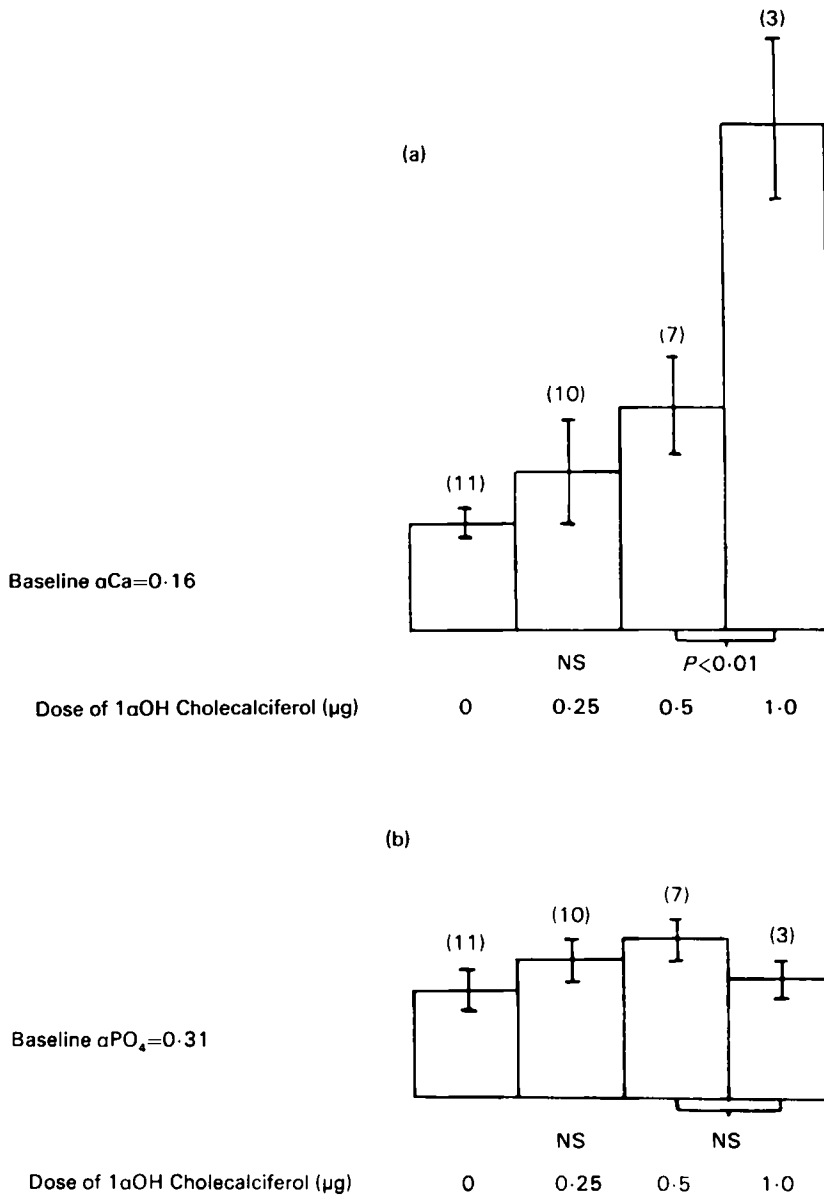


Fig. 5. Calcium (a) and phosphate (b) absorptions in response to treatment with $1\alpha\text{OH}$ cholecalciferol. Number of observations in parentheses. Vertical bars represent SEM.

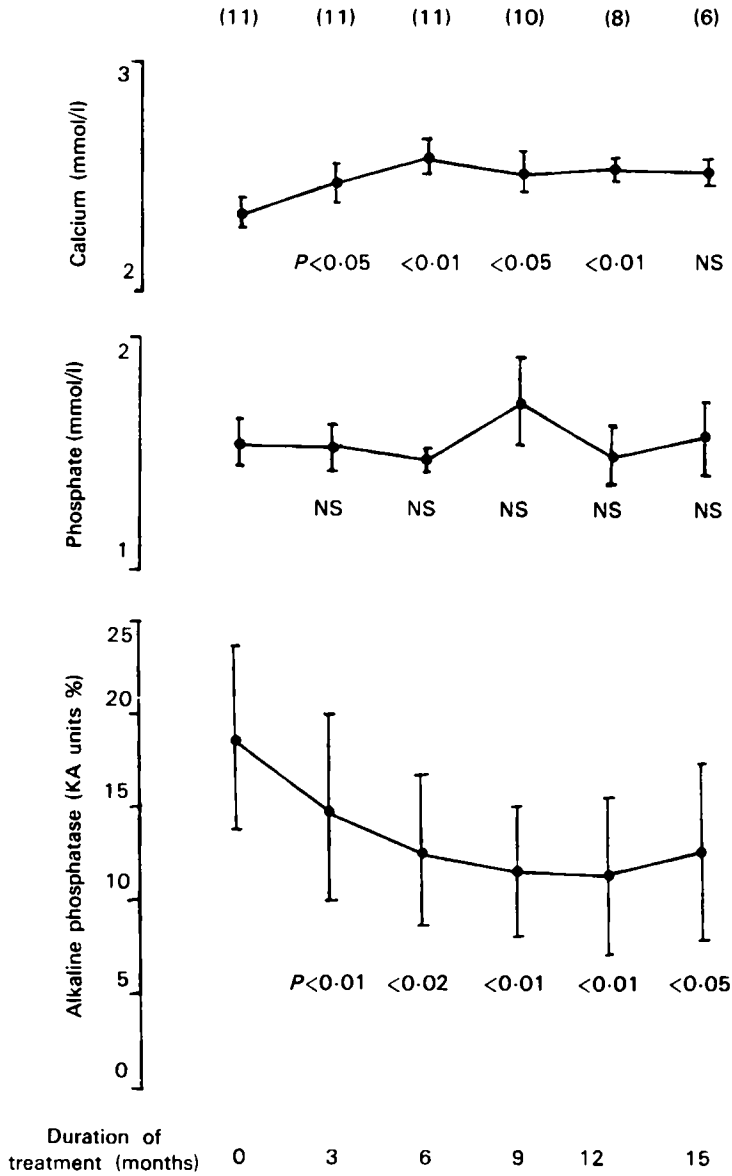


Fig. 6. Biochemical responses to treatment with 1 α OH cholecalciferol. Points are mean values with their SEM represented by vertical bars; number of patients in parentheses.

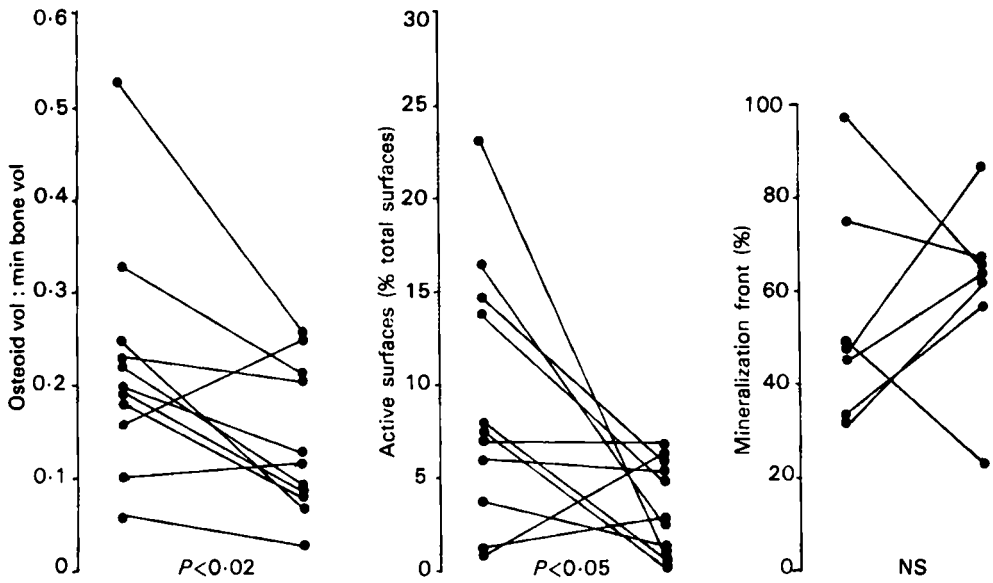


Fig. 7. Changes in histological measurements in response to treatment with $1\alpha\text{OH}$ cholecalciferol. Active surfaces refer to the sum of active resorption and active formation surfaces.

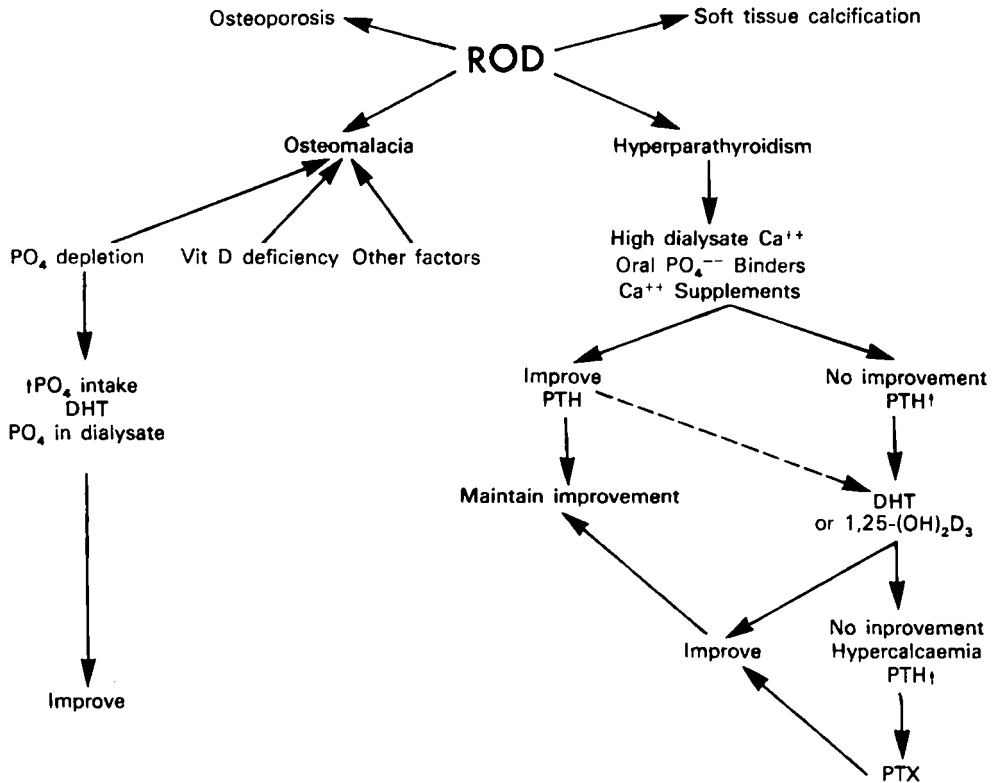


Fig. 8. Schematic representation of the responses of haemodialysis patients to various therapeutic interventions for controlling metabolic bone disease. Escape from the therapeutic control and the progression of the bone disease on dialysis is also shown.

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