Renal Osteodystrophy

Medical Grand Rounds

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The association of various forms of bone disease with chronic renal failure has long been recognized.[1,2] The term renal osteodystrophy has been used to describe this association, since the skeletal abnormalities were presumed to be renal in origin. With the long-term maintenance of end-stage renal failure by hemodialysis, overt skeletal manifestations have become much more prevalent. Renal osteodystrophy has therefore received a major research focus during the past decade.

A considerable progress has already been made pertaining to pathogenesis and management of renal osteodystrophy. Much is now known regarding the physiological basis for the development of bone disease in renal failure, particularly relevant to the deranged metabolism of parathyroid hormone (PTH) and vitamin D. The biochemical and histological profiles of different forms of renal osteodystrophy have been established. Important therapeutic advances were made by the commercial introduction of two vitamin D metabolites, --1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D$) and 24-hydroxyvitamin D_3 (25-OHD).

However, it is apparent that the cause for renal osteodystrophy is multifactorial, involving more than simply PTH excess and/or 1,25-$(OH)_2D$ deficiency. The exact metabolic background responsible for the development of one form of bone disease versus another remains to be clarified. Although the availability of vitamin D metabolites has substantially improved therapeutic outlook, the relative merits of 1,25-$(OH)_2D$ (Rocaltrol) and 25-OHD (Calderol) in the management of renal osteodystrophy remain controversial.

The intent of this review is to critically assess the pathogenetic importance of various factors implicated in renal osteodystrophy, particularly as they might pertain to the development of different forms of bone disease. From the available information concerning deranged vitamin D metabolism and different physiologic actions of various vitamin D metabolites, a scheme has been constructed which could explain the apparent discrepant responses to treatment with 1,25-$(OH)_2D$ from 25-OHD therapy, and which might provide a rational basis for the medical management of renal osteodystrophy.

PATHOGENESIS

Two predominant forms of renal osteodystrophy are osteitis fibrosa and osteomalacia, occurring separately or in combination (mixed). The relative proportion of these conditions vary widely from center to center, region to region, and from one country to another. However, a recent study[3] gave prevalence of osteitis in 54%, osteomalacia in 33% and mixed presentation in 13% among patients with severe renal insufficiency. Even in early renal failure, histologic evidence for osteitis or osteomalacia may be present, even though patients may be asymptomatic. Features of osteosclerosis and osteoporosis may also be found. They will not be considered here, since they are clinically less troublesome, and no major advances have been made regarding their pathogenesis or management.

The pathogenetic background for the osteitis presentation of renal osteodystrophy differs from that of osteomalacia. It is well recognized that the cause of osteitis is secondary hyperparathyroidism (Fig. 1).

Although deranged vitamin D metabolism has frequently ascribed for the development of osteomalacia, other factors have been incriminated as well.

Figure 1. Pathogenesis of Renal Osteodystrophy

Form	Features	Pathogenesis
Osteitis fibrosa	High Osteoclastic resorption Marrow fibrosis High Bone turnover	Secondary hyperparathyroidism
Osteomalacia	Low Mineralization Low Bone turnover	Deranged vit D metabolism Abnormal bone matrix Abnormal bone mineral

PATHOGENESIS OF OSTEITIS

Pathogenetic Role of PTH Excess in Osteitis

The histological picture of bone can be attributed to the excessive action of PTH on bone.[4-6] Thus, osteoclastic resorption is stimulated and marrow fibrosis ensues. Consequent to resorption-formation coupling,[7] osteoblastic activity is augmented as well. However, matrix is formed haphazardly and irregularly. Although mineralization is not disturbed, "woven" rather than lamellar bone results. There is high bone turnover (active bone), reflective of increased activity of both osteoclasts and osteoblasts.

It is apparent that the basis for secondary hyperparathyroidism responsible for osteitis is much more complex than was originally realized. That secondary hyperparathyroidism results from renal failure is suggested by the finding of progressive rise in serum PTH with deteriorating renal function, sometimes to extremely high values,[8,9] and suppressibility of PTH by induced hypercalcemia,[10,11] albeit often not completely to the normal range. Serum PTH rises progressively with deteriorating renal function (reflected by glomerular filtration rate),[9] a finding which suggests that the stimulus for PTH secretion may be present even in mild-moderate renal failure (Fig. 2).

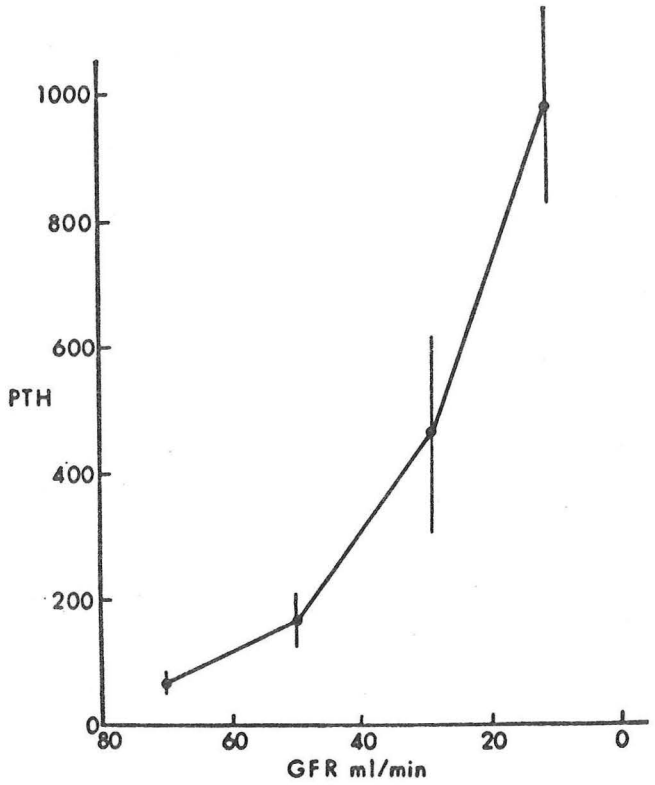


Fig. 2.

The ultimate cause for the parathyroid stimulation is hypocalcemia. Indeed, a decline in the circulating concentration of ionized calcium has been shown in renal failure, even during the mild-moderate stages[12] (Fig. 3). No other direct stimulus for PTH secretion has been implicated in chronic renal failure.

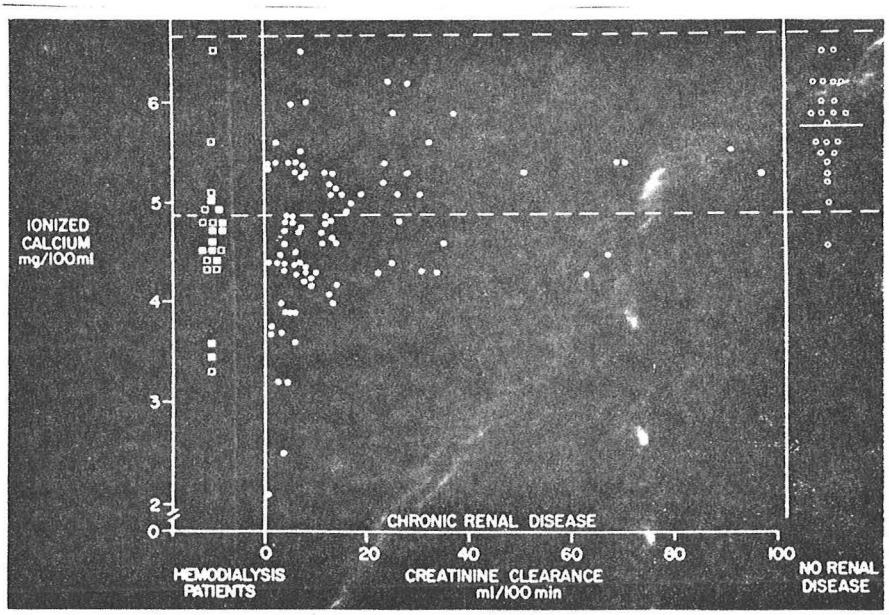


Fig. 3.

Causes of Hypocalcemia Responsible for Parathyroid Stimulation

Several factors contribute to the development of hypocalcemia.[13]

Renal phosphate retention (trade-off hypothesis).[9,14,15] This theory received a wide attention because of its intellectual appeal and potential therapeutic implications. Phosphate retention, resulting from a decline in glomerular filtration rate, was believed to cause hyperphosphatemia, albeit transiently, and to lead to hypocalcemia[9] (Fig. 4). The ensuing parathyroid stimulation restored normal serum phosphorus concentration by stimulating renal phosphate excretion. Thus, the dangers of sustained hyperphosphatemia was "traded off" by the sequelae of hyperparathyroidism. This scheme is supported by the finding of Reiss et al.[16] that an oral phosphate ingestion (1 g phosphorus) increased serum phosphorus concentration, reduced ionized calcium concentration and stimulated PTH secretion in normal subjects.

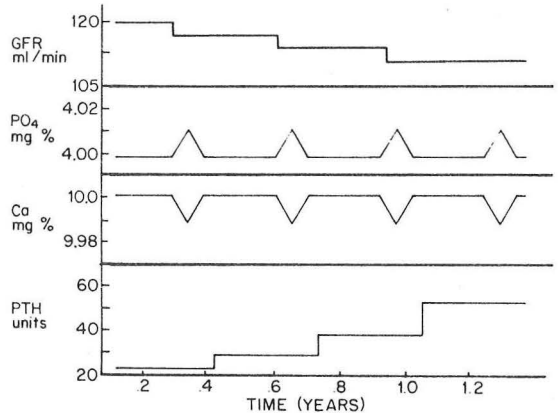


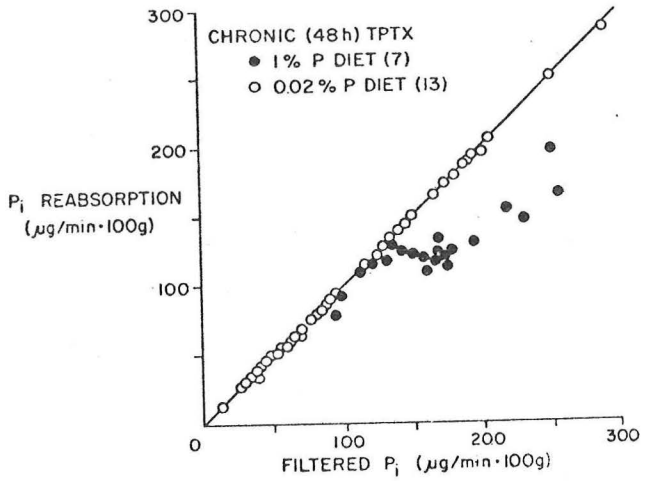
Fig. 4.

However, bulk of available data do not support the operation of this scheme in patients in whom glomerular filtration rate has not declined below 25% of normal. It has not been possible to show a significant decline in serum calcium concentration or a stimulation of parathyroid function in patients with idiopathic calcium nephrolithiasis treated with orthophosphate (0.5 g phosphorus 3-4 times/day).[17] In patients with moderate renal failure, the rise in serum phosphorus concentration during four hours following an acute ingestion of 1 g phosphorus was not more pronounced than in normal subjects with intact renal function.[15] In fact, long-term treatment with orthophosphate (e.g. of patients with renal stones) has been shown to lower, rather than increase, the serum phosphorus concentration.[17,18] We have found serum phosphorus and renal tubular threshold concentration of phosphorus to be substantially lower during an outpatient setting of higher phosphate intake than during an inpatient setting of limited phosphate intake.[19]

The paradoxical reduction in serum phosphorus during phosphate load cannot be ascribed to the phosphaturic action of PTH, since it was not accompanied by hypocalcemia or parathyroid stimulation. The results could be explained by the PTH-independent renal rejection of phosphate following phosphate loading.[20] It is clear that kidneys may adapt to high phos-

phate load and facilitate its disposal, by reducing renal tubular reabsorption and threshold concentration of phosphorus, even in the absence of PTH[20] (Fig. 5). Thus, in mild-to-moderate renal failure (glomerular filtration > 25% of normal), serum phosphorus concentration is typically maintained within the normal range. The prevention of hyperphosphatemia could be explained by non-PTH-dependent renal disposal of relative phosphate overload (from a decline in filtered phosphorus), without invoking secondary hyperparathyroidism. Before severe renal failure intervenes, the classic trade-off hypothesis would seem to be inadequate to explain either the presence of parathyroid stimulation or the absence of hyperphosphatemia.

Fig. 5.



When the glomerular filtration rate falls below 25% of normal, hyperphosphatemia may develop, because of the limited renal disposal of phosphate[13] (Fig. 6). Phosphate loading has been shown to readily cause hyperphosphatemia and produce a reciprocal fall in serum calcium concentration[12] (Fig. 7). Moreover, serum PTH bears a direct relationship with serum phosphorus concentration[4] (Fig. 8). The results suggest that the phosphate retention theory may be applicable in severe renal failure, and could explain, at least partly, the development of secondary hyperparathyroidism.

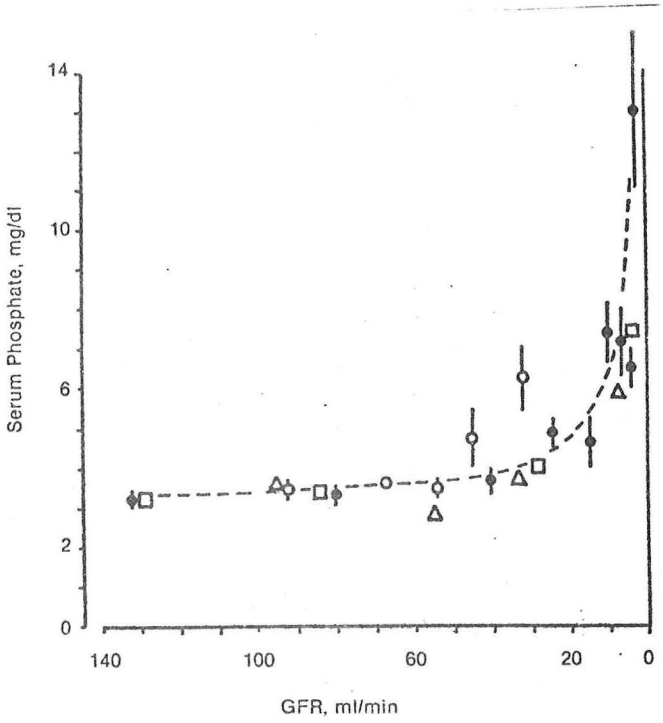


Fig. 6.

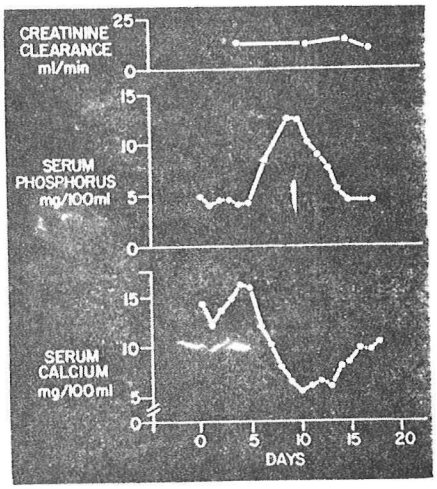


Fig. 7.

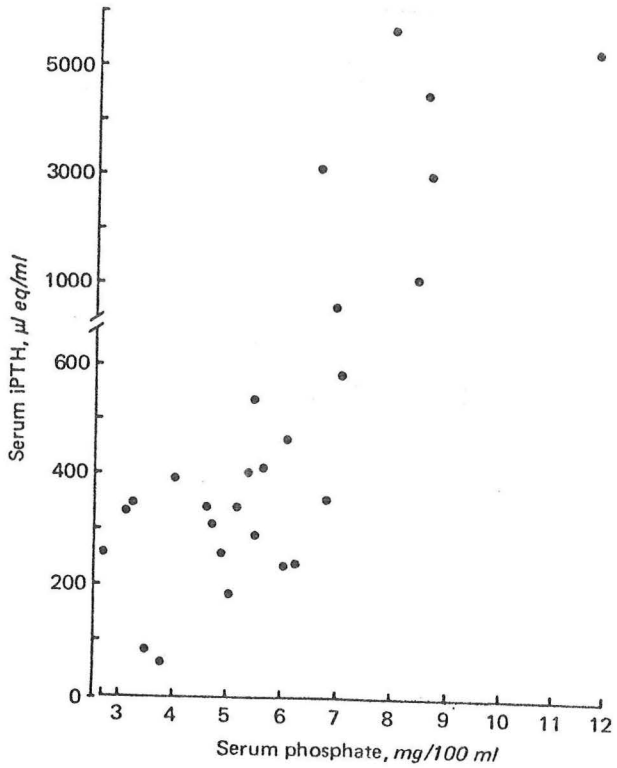


Fig. 8.

The mechanism by which serum calcium concentration declines from the rise in serum phosphorus remains obscure. The physicochemical explanation invoking maintenance of a constant Ca x P solubility product in plasma is inadequate, since it has not been possible to identify a mineral phase in bone with which circulating calcium and phosphorus are in equilibrium.[21] Although soft tissue calcification may accompany hyperphosphatemia, there is no experimental evidence that extraskeletal mineral phase subserves this function. It has been suggested that hyperphosphatemia may lower serum calcium by promoting osteoblastic activity.[22]

Increased complexation of calcium. In severe renal failure, a rise in serum concentration of sulfate as well as that of phosphorus may occur. The ionized calcium concentration may decline from the increased com-

plexation of calcium by phosphate and sulfate.[12,23] In simulated ultrafiltrate of serum, we have found (unpublished observations) that the calculated decrement in ionized calcium concentration was approximately 15% when either serum phosphorus or sulfur was increased from 0-10 mg/dl or 0-30 mg/dl, respectively (Fig. 9 and Fig. 10). Thus, "true" hypocalcemia (reduced ionized calcium concentration) may be present even though the total calcium concentration is normal, if there is an elevated serum concentration of phosphorus and/or sulfur. By this mechanism, the soluble complex formation may contribute to the development of secondary hyperparathyroidism in severe renal failure where the renal retention of phosphate and sulfate is substantial.

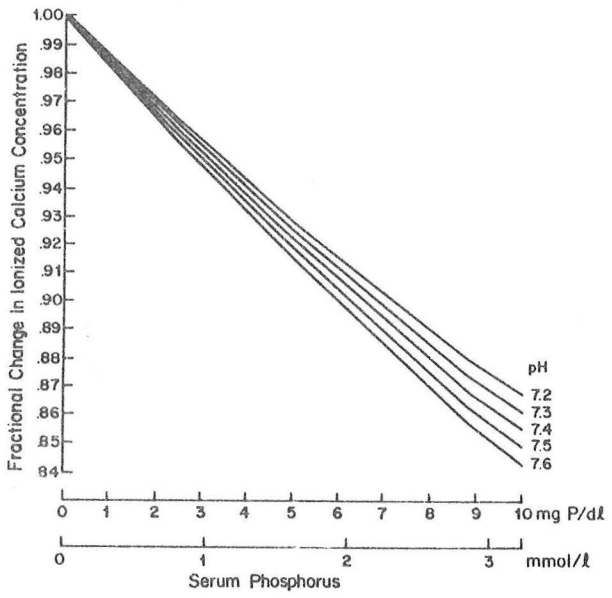


Fig. 9.

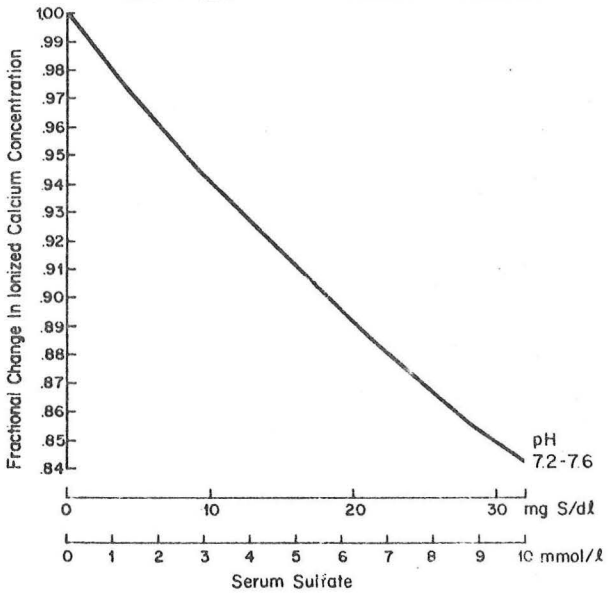


Fig. 10.

Defective intestinal absorption of calcium. The intestinal calcium absorption decreases progressively with deteriorating renal function[24] (Fig. 11). An impairment in calcium absorption has been reported in mild-moderate renal failure. This disturbance could contribute to the development of secondary hyperparathyroidism during all stages of renal failure.

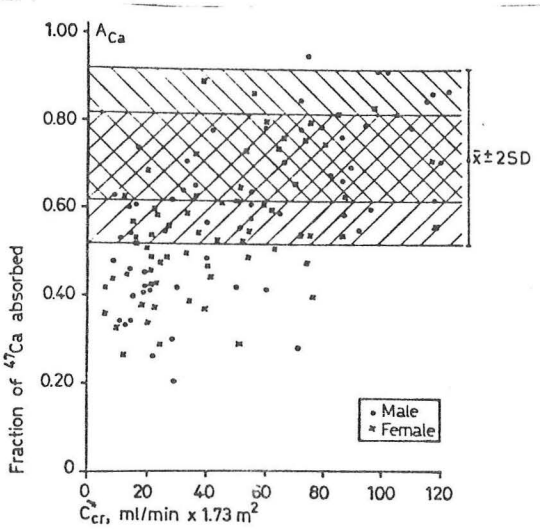


Fig. 11.

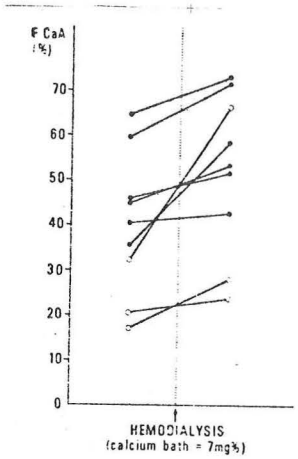


Fig. 12.

The defective intestinal absorption of calcium is probably largely the result of an impaired renal synthesis of 1,25-$(OH)_2D$. In severe renal failure, low serum 1,25-$(OH)_2D$ has been found,[25] because the synthesis of this active vitamin D metabolite is inhibited by the reduced renal mass and hyperphosphatemia.[26] It has been suggested that the renal synthesis of 1,25-$(OH)_2D$ may be inhibited by long-standing acidosis.[27] However, this contention has not been confirmed.[28]

There is some evidence that 1,25-$(OH)_2D$ synthesis may be impaired even in moderate renal failure. Portale et al.[29] found a substantial reduction in serum 1,25-$(OH)_2D$ in patients with a moderate reduction in glomerular filtration rate, even in the absence of hyperphosphatemia. This possibility awaits substantiation.[30]

There is some evidence that the intestinal calcium absorption may be impaired in renal failure, independently of change in vitamin D metabolism. In patients with end-stage renal failure in whom 1,25-$(OH)_2D$ synthesis is expected to be low, the institution of hemodialysis has been shown to significantly augment fractional calcium absorption[31,32] (FCaA, Fig. 12). It has been suggested that "uremic toxin" might interfere with electron transport and oxidative phosphorylation of intestinal mitochondria, and thereby inhibit calcium uptake and release.[33] If mitochondrial calcium transport participates in, or is reflective of, intestinal calcium absorption, the removal of uremic toxins by dialysis could explain the effect on calcium absorption.

The intrinsic defect in calcium absorption could explain the apparent partial resistance of the intestinal tract to 1,25-$(OH)_2D$ action in renal failure. The ability of 1,25-$(OH)_2D$ to stimulate calcium absorption in rats has been shown to be attenuated by nephrectomy.[34]

In summary, intestinal calcium absorption may be depressed in early renal failure, probably consequent to impaired renal synthesis of 1,25-$(OH)_2D$. In end-stage renal failure, both vitamin D-dependent and independent factors contribute to malabsorption of calcium and development of secondary hyperparathyroidism.

Skeletal resistance to PTH. A major cause for the hypocalcemia operative at all stages of renal failure is the impaired calcemic response to PTH. Massry et al. found that the increment in serum calcium following exogenous PTH administration was substantially lower in moderate (glomerular filtration rate 52±6 SE ml/min) and advanced renal failure (glomerular filtration rate <20 ml/min)[35] (Fig. 13). In mild renal failure (glomerular filtration rate 65±5 SE ml/min), a prolonged delay in restoration of normal serum calcium concentration was reported following induced hypocalcemia with ethylenediaminetetracetate infusion, despite a more marked increase in serum PTH than in the control group.[36]

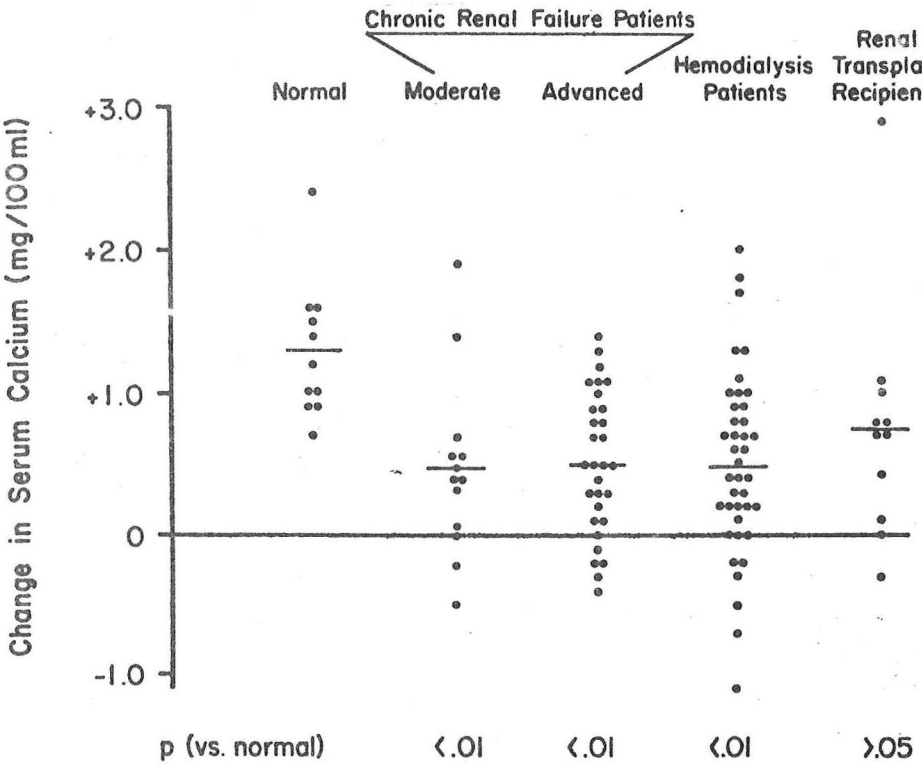


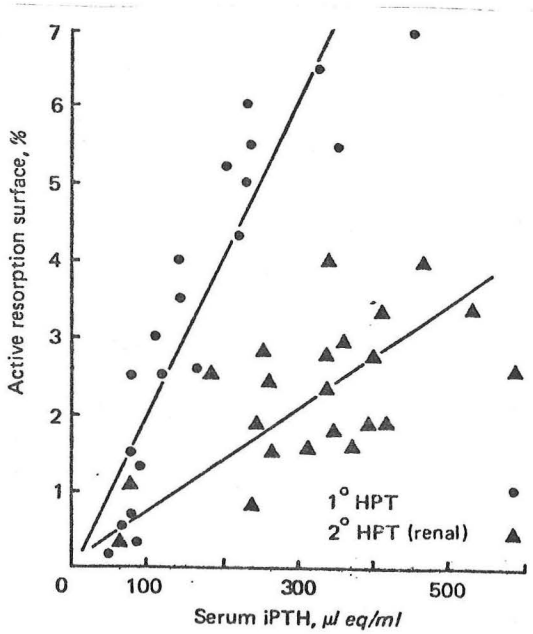
Fig. 13.

The basis for the blunted calcemic response is partly the impaired 1,25-$(OH)_2D$ synthesis. Supplementation by 1,25-$(OH)_2D$ has been shown to restore normal calcemic response.[37] In our recent study (unpublished), normal calcemic response to PTH was restored following renal transplantation commensurate with the return of serum 1,25-$(OH)_2D$ toward the normal range.

Although the functional role of osteocytes has been disputed, the postulated stimulatory role of 1,25-$(OH)_2D$ on osteocytic resorption[22] could explain the blunted calcemic response to PTH in renal failure. Since exogenous PTH probably does not increase serum 1,25-$(OH)_2D$ significantly in renal failure, changes in osteocytic resorption and in serum calcium would be expected to be subnormal.

There is some evidence that osteoclast-stimulating activity of PTH may also be defective in renal failure. Uremic serum was shown to inhibit PTH-induced bone resorption in vitro.[38] Although a direct linear relationship was found between serum PTH and active resorption surface in renal failure, the slope describing this relationship was less steep than in primary hyperparathyroidism, a finding indicating that an equivalent circulating value PTH was less effective in stimulating osteoclastic resorption in renal failure[4] (Fig. 14). However, a delayed disposal of PTH fragments in renal failure could have accounted for the results, since the radioimmunoassay for PTH in the study had utilized antiserum directed at the carboxy-terminal portion of the PTH molecule (see next section).

Fig. 14.



It is also recognized that skeletal mobilization of calcium may be impaired in renal failure because of abnormal mineral phase of bone. Bone mineral in renal failure is rich in pyrophosphate,[39] a potent inhibitor of calcium phosphate dissolution.[40]

The available evidence therefore suggests that, in both early and late renal failure, calcium mobilization from bone may be impaired because of blunted cellular responsiveness to PTH and of inhibitory action of pyrophosphate. These disturbances undoubtedly contribute to the development of hypocalcemia and exaggerate secondary hyperparathyroidism. However, their role in the development of bone disease is less certain, since the augmented PTH secretion is the consequence of the skeletal resistance to PTH.

False Secondary Hyperparathyroidism from Impaired PTH Clearance

Recent elucidation of PTH metabolism has disclosed that the native molecule composed of 84 amino acids, upon release by the parathyroid glands, is rapidly cleaved in peripheral tissues into carboxy-terminal and amino-terminal fragments. Renal clearance is normally responsible for the disposal of biologically inactive carboxy-terminal fragments. In the presence of renal failure, the plasma half-life of carboxy-terminal fragments is considerably prolonged[41] (Fig. 15). Thus, radioimmunoassay for PTH, employing antiserum directed at the carboxy-terminus, may yield "falsely" high values for PTH in renal failure, because of the accumulation of the biologically inactive fragments. For the appropriate interpretation of the assay, the extent of the elevation of PTH resulting from retention of carboxy terminal fragments in plasma should be estimated.

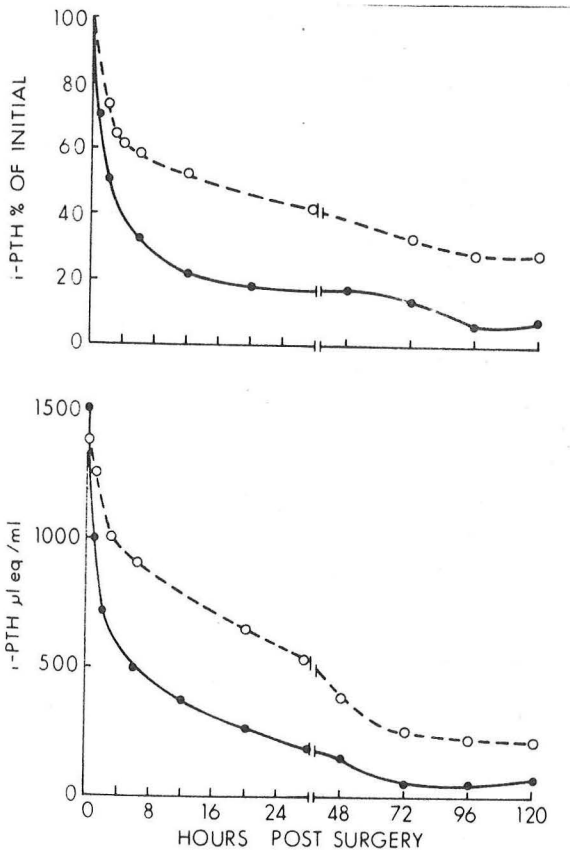


Fig. 15.

Changes in Immunoreactive Parathyroid Hormone (i-PTH) in Case 3 after Renal Transplantation (● — ●) as Compared with Values after Parathyroidectomy (O - - - O) in Case 2 on Dialysis.

Results are expressed as a per cent of the preoperative values in the upper panel and in absolute values in the lower panel.

PATHOGENESIS OF OSTEOMALACIA

The histological picture of osteomalacia is characterized by a defective mineralization of matrix.[4,6,42] Mineral apposition rate is markedly delayed and the percentage of osteoid surface showing mineralization is greatly reduced. Thus, both osteoid volume and width are increased. In advanced osteomalacia uncomplicated by osteitis, both osteoblastic and osteoclastic activity may be reduced (low bone turnover). Although osteomalacia of renal osteodystrophy has been attributed commonly to deranged vitamin D metabolism, it is apparent that other factors may participate in its pathogenesis (Fig. 1).

Deranged Vitamin D Metabolism

Impaired synthesis of 1,25-$(OH)_2D$ in renal failure has already been discussed. Serum concentration of 1,25-$(OH)_2D$ is significantly reduced in end-stage renal failure, and is very low or undetectable in anephric state.[25,29] These findings are not unexpected since kidneys are the principal site of 1,25-$(OH)_2D$ synthesis. Despite report to the contrary,[30] there is some evidence that 1,25-$(OH)_2D$ synthesis may be disturbed even in early renal failure.[29] Reduced serum 1,25-$(OH)_2D$ has been reported in children with moderate renal failure[29] (MRI, Fig. 16). The intestinal Ca absorption progressively declines with deteriorating renal function (Fig. 11). The calcemic response to exogenous PTH, which may partly reflect the functional activity of 1,25-$(OH)_2D$, is blunted even in mild renal failure.[35]

		1,25$(OH)_2D$ (pg/ml)
Normal controls	(3-15 yrs)	54.9 ± 5.8 (17)
MRI, GFR 41 ± 3.0	(3-13 yrs)	30.9 ± 3.7 (7)*
Chronic dialysis	(7-15 yrs)	10.1 ± 2.3 (7)

*VS controls $p<0.02$

Fig. 16.

The synthesis of other biologically active vitamin D metabolites, 25-OHD and 24,25-dihydroxyvitamin D (24,25-$(OH)_2D$), may be impaired as well in renal failure. Reduced circulating concentration of both these metabolites in the anephric state has been reported[43] (Fig. 17). The low serum 25-OHD may partly reflect a facilitated microsomal P-450-dependent hepatic clearance of this sterol,[44] or an impaired hepatic mitochondrial 25-hydroxylation. This defect could explain the relative resistance to treatment by parent compounds (vitamin D_2 or vitamin D_3) in renal osteodystrophy. The reduced serum 24,25-$(OH)_2D$ is not unexpected, since its principal though not the sole locality of synthesis is the kidneys, and as its substrate (25-OHD) concentration is reduced. No systematic study has been done to determine if 25-OHD or 24,25-$(OH)_2D$ is deficient in early renal failure.

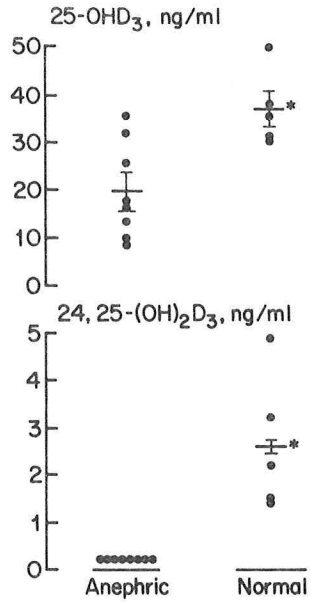
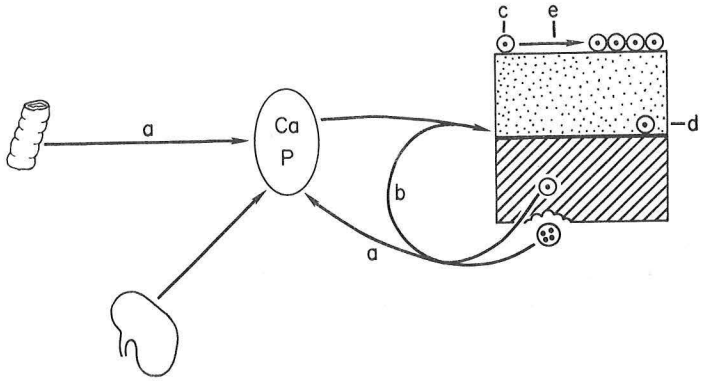


Fig. 17.

Pathogenetic role of deficiency of vitamin D metabolites in osteomalacia. The etiologic role of deranged vitamin D metabolism in osteomalacia was discussed in previous grand rounds. The exact mechanism remains obscure and needs to be elucidated.

Taken in general context, vitamin D deficiency may cause osteomalacia in renal failure by (a) a reduction in circulating concentration of calcium from impaired calcium absorption and reduced skeletal calcium mobilization, (b) a reduced availability of calcium and phosphate to sites of mineralization, because of impaired vitamin D-dependent bone resorption and mineral "recycling" from areas of resorption to formation areas, (c) a defective osteoblast function, resulting in synthesis of abnormal matrix of poor "mineralizability", (d) an impairment in mineralization because of the loss of presumed direct role of vitamin D metabolites, and (e) a deficient recruitment of new osteoblasts for matrix synthesis (Fig. 18).

Fig. 18.



It is clear that the deficiency of any one of three metabolites ($1,25\text{-}(OH)_2D$, 25-OHD, $24,25\text{-}(OH)_2D$) could theoretically lead to osteomalacia[45-48] via one or more mechanisms enumerated above. Certainly, $1,25\text{-}(OH)_2D$ is not the only metabolite pathogenetically implicated in osteomalacia.[48,49] Osteomalacia has been encountered in $1,25\text{-}(OH)_2D$ deficiency[45] or resistance,[48] 25-OHD deficiency,[46,48] and in $24,25\text{-}(OH)_2D$ lack.[47] However, the severity of osteomalacia and the relative role of various factors (enumerated above) leading to defective mineralization of bone matrix may depend on the exact metabolite implicated. A brief review of comparative physiological actions of vitamin D metabolites is pertinent, since it may help to clarify the etiologic role of their deficiency in the development of osteomalacia.

Physiological actions of vitamin D metabolites. Available data suggest that $1,25\text{-}(OH)_2D$, 25-OHD and $24,25\text{-}(OH)_2D$ differ from each other in their physiological actions not only quantitatively, but qualitatively as well. Quantitative differences are generally not important pathogenetically, if the relative potency of various vitamin D metabolites parallels their normal physiological concentrations in circulation in reverse order. For example, although $1,25\text{-}(OH)_2D$ may be 1000-fold more potent than 25-OHD in stimulating intestinal calcium absorption or bone resorption,[50] its circulating concentration is approximately 1/1000 that of 25-OHD (Fig. 19). Thus, at their physiological concentrations in circulation, the two metabolites probably exert equivalent biological activity with respect to these actions.

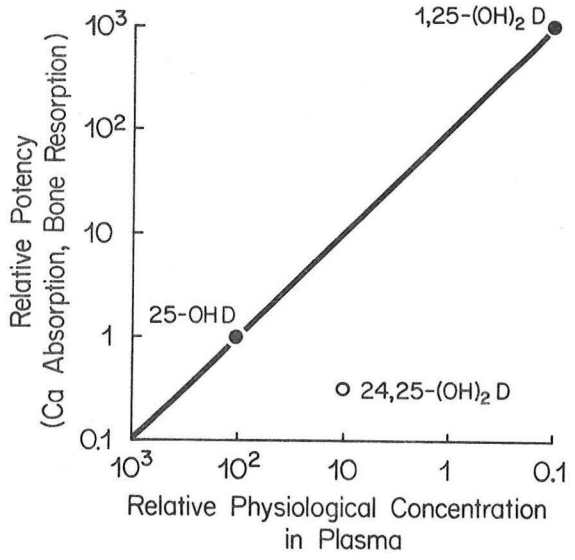
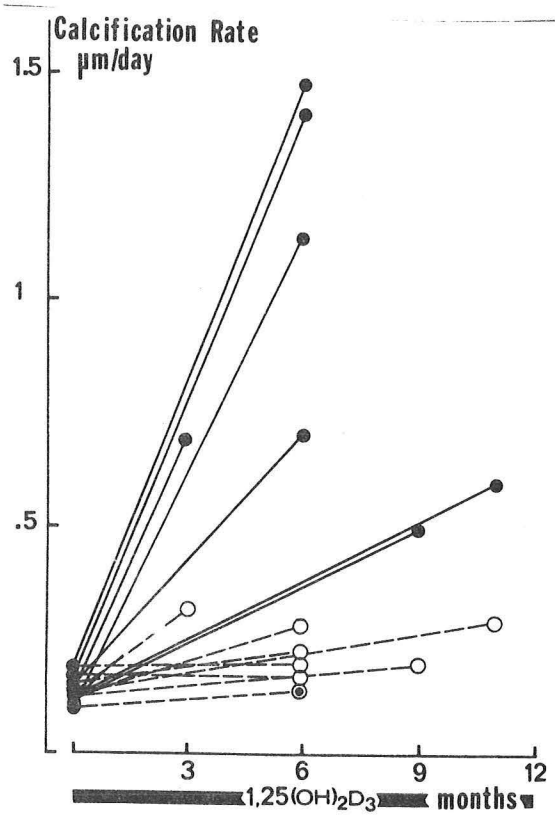


Fig. 19.

In contrast, actions of vitamin D metabolites at their physiologic circulating concentrations may differ from one another, if (a) there is no inverse parallelism between relative potency and circulating concentrations, and (b) if there are qualitative differences in biological activity among the metabolties. Although 24,25-$(OH)_2D$ is less active than 25-OHD in stimulating intestinal calcium absorption or bone resorption,[50] its normal circulating concentration is approximately 1/10 that of 25-OHD (Fig. 19).[43] Thus, 24,25-$(OH)_2D$ is not expected to exert any significant biological activity with respect to these actions under normal circumstances.

There is evidence that all three metabolites are capable of promoting mineralization of bone matrix. That 24,25-$(OH)_2D$ may stimulate mineralization is suggested by a substantial decline in serum calcium in the face of increased calcium absorption and a decline or no change in urinary calcium excretion.[51-53] Confirmation by histomorphometric analysis of bone is lacking. 24,25-$(OH)_2D$ has also been shown to inhibit PTH secretion.[51,54] The promotion of mineralization by 25-OHD is more firmly established. It has been shown to be selectively localized to areas of new bone formation. 24,25-$(OH)_2D$, though not 1,25-$(OH)_2D$ was also shown to localize to calcifying callus tissue.[56] 25-OHD has been shown to promote maturation of bone collagen and mineral phase.[57] Bone collagen in renal osteodystrophy has been shown to have enhanced solubility in 0.5 M NaCl and ethanol-ether,[58] indicative of reduced cross-linking. This immaturity may interfere with deposition of calcium phosphate, since the mineral phase fails to show normal transformation to hydroxyapatite.[59,60] Although other metabolites have not been tested, 25-OHD has been shown to correct this defect.[57] Finally, 25-OHD has been shown to augment calcification front and to reduce osteoid volume on histomorphometric analysis.[61]

Although the prevailing view indicates lack of action of 1,25-$(OH)_2D$ on mineralization, a recent study of Meunier et al.[62] has clearly shown that this metabolite also shares this action. The calcification rate adjacent to osteoblastic layers was significantly enhanced by 1,25-$(OH)_2D$ though not that adjacent to osteoid surfaces lacking osteoblasts[62] (Fig. 20). On the basis of available data, it is difficult to assign relative importance of the three metabolites in promoting mineralization at their physiological concentrations under normal circumstances.



Changes in calcification rate (CR) induced by 1,25-$(OH)_2D_3$.
● CR along osteoblastic layers
○ CR without the presence of osteoblasts

Fig. 20.

The most important difference in action of the three metabolites with respect to the pathogenesis of osteomalacia concerns their effects on osteoblastic cellular proliferation. 25-OHD has been shown to augment osteoblastic bone formation surface, whereas the remaining metabolites have been shown to reduce it[61] (Fig. 21). Thus, the action of 25-OHD may be qualitatively different from that of dihydroxy-metabolites, since 25-OHD may stimulate the formation of additional osteoblasts for matrix synthesis for eventual mineralization. Unlike other metabolites, 25-OHD may not only cause mineralization of matrix, but also increase the amount of calcifiable matrix via recruitment of new osteoblasts.

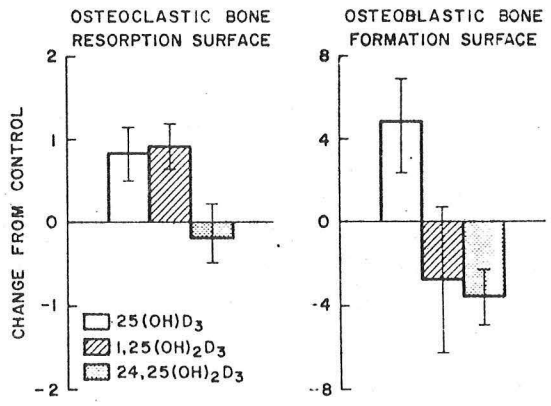


Fig. 21.

Another qualitative difference pertains to the effects on PTH secretion. Though still controversial, 24,25-$(OH)_2D$ may inhibit PTH secretion[51,54] unlike other metabolites. In experimental animals, infusion of 24,25-$(OH)_2D$ into cranial thyroid artery has been shown to reduce PTH concentration in the thyroid venous effluent as well as in the peripheral venous blood.[54] Orally administered, 24,25-$(OH)_2D$ reduced serum PTH despite a fall in serum calcium.[51] Similar studies have not yet been performed in man.

Scheme for development of osteomalacia. On the basis of above known or speculated actions of vitamin D metabolties (Fig. 22), the following scheme may be constructed for the development of osteomalacia of renal osteodystrophy from the deficiency of various metabolites.

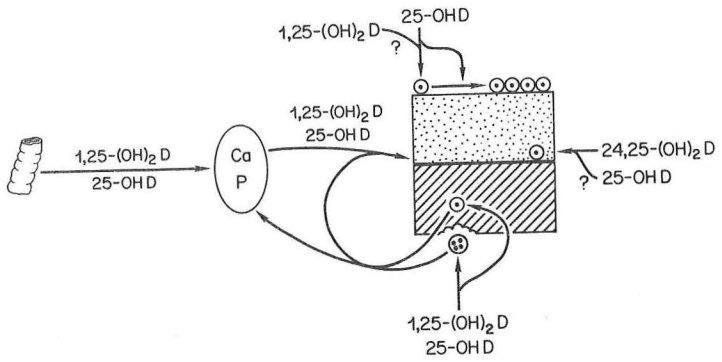


Fig. 22.

The deficiency of 1,25-$(OH)_2D$ probably causes osteomalacia largely indirectly by reducing the availability of calcium and phosphorus at sites of bone formation, because of impaired intestinal calcium absorption and reduced skeletal calcium mobilization. The deficiency of 24,25-$(OH)_2D$ may result in osteomalacia mainly because of the lack of direct action on matrix mineralization. Osteomalacia may result from 25-OHD deficiency via both factors enumerated above. In addition, the presumed reduction in number and function of osteoblasts may accentuate mineralization defect. This theme will be developed under therapeutic considerations.

Abnormal Bone Matrix and Mineral

The presence of abnormal bone matrix of poor mineralizability in renal osteodystrophy has already been discussed.[58] Although it was suggested that vitamin D deficiency may be responsible for the defective collagen

maturation,[57] the role of other factors associated with uremic state has not been excluded.

Bone mineral is also abnormal in renal osteodystrophy.[59,60] It is characterized by a preponderance of amorphous mineral fraction of low density, a finding indicative of disturbance in maturation into hydroxyapatite. While abnormal bone matrix could contribute to this defect, it is equally likely to have resulted from the accumulation of inhibitors of calcification in bone in the uremic state.

Bone mineral in renal failure is characterized by a high content of pyrophosphate[63-65] and magnesium.[66] The accumulation of pyrophosphate has been attributed to defective renal excretion and inactivation (from inhibition of pyrophosphatase by hyperphosphatemia). Impaired renal excretion and ingestion of magnesium-containing antacids probably account for the retention of magnesium.

Pyrophosphate is a potent inhibitor of nucleation and growth of calcium phosphate and of transformation of amorphous calcium phosphate to apatite.[67,68] Magnesium may share these actions, albeit to a lesser extent.[69] Thus, these inhibitors may interfere with matrix calcification by a direct physicochemical action on bone mineral. This contention is supported by the complication of osteomalacia during long-term treatment with diphosphonate, a synthetic analog of pyrophosphate.[70]

It is noteworthy that an increased prevalence of bone disease simulating osteomalacia has been described in patients undergoing hemodialysis using water of high aluminum content.[71-74] However, the effect of aluminum on bone mineral has not been clarified.

It is not known whether the skeletal content of pyrophosphate or magnesium is increased in early renal failure. Moreover, there is no evidence that the mineral maturation defect is confined to the osteomalacia presentation,[60] or that the skeletal accumulation of pyrophosphate and magnesium is more pronounced in osteomalacia than in osteitis. In the latter form of bone disease, the potential role of pyrophosphate toward development of skeletal resistance to PTH was previously discussed. The foregoing remarks indicate that these inhibitors may contribute to but do not solely account for the development of osteomalacia.

CLINICAL AND BIOCHEMICAL PRESENTATIONS

Clinical Presentation (Fig. 23)[75,76]

Symptoms clearly associated with renal osteodystrophy may not be present despite biochemical, radiological or histological evidence for bone disease. Some of the symptoms are independent of the nature of the underlying bone disease. The most common symptom is probably bone pain, affecting hips, back and ribs, and occasionally knees, shoulders and heels. Varying degrees of muscle weakness may be found. The weakness is usually more prominent in the proximal musculature, and may affect ambulation and use of arms. Though less common, there may be weakness of distal musculature, disclosed by reduced grip strength. Patients with renal osteodystrophy are at increased risk for skeletal fractures, particularly of the ribs. Healing is generally slow.

Certain symptoms are more characteristic of the particular form of underlying bone disease. In osteitis fibrosa with high serum Ca x P pro-

duct (>70 $(mg/dl)^2$),[75] extraskeletal calcification in bursae and periarticular regions may cause painful joints. Conjunctival and corneal calcifications may cause watery, itchy eyes. Severe pruritis may be present. In renal osteodystrophy where osteomalacia is the predominant presentation, there may be tenderness of bone, particularly in the rib cage, iliac crest and tibia. It is our impression that muscle weakness is more severe in osteomalacia than in osteitis. It has been suggested that PTH may be a "uremic toxin".[77] It is expected that such toxicity would be more prominent in osteitis. In patients with mixed bone disease, all of above symptoms are expected.

Figure 23. Clinical Presentation

	Renal Osteodystrophy		
	Osteitis Fibrosa	Osteomalacia	Mixed
Bone pain	+	+	+
Muscle weakness	+	++	+
Fracture	+	+	+
Extraskeletal calcification	+	-	+
Pruritis	+	-	+
Bone tenderness	-	+	+

The radiologic picture of osteitis fibrosa resulting from renal osteodystrophy is often much more severe than that which is encountered in primary hyperparathyroidism. Subperiosteal resorption of fingers begins with irregularity of lateral margins, progresses to scalloped erosions on the sides of phalanges, and in severe cases cause dissolution of terminal phalanx, resulting in "pseudoclubbing". Other common sites of resorption are distal clavicles. Cortical striations may be prominent in the phalanges and metacarpals. Less common presentations are "salt and pepper" appearance of the calvarium and brown tumors. Pseudofractures are the only clearly recognizable presentation of osteomalacia. However, they are uncommonly encountered in chronic renal failure.

Biochemical Presentation

A recently completed study indicates that certain biochemical presentations distinguish patients with "active bone" from those with "inactive bone"[78] (Fig. 24). Patients with active bone had histological manifestations of secondary hyperparathyroidism (osteitis), whereas those with inactive bone exhibited derangement in mineralization (osteomalacia). The osteitis group was characterized by higher values for serum phosphorus, alkaline phosphatase activity and serum immunoreactive PTH (by assays using antiserum directed at carboxy terminus (C-terminal assay) or intact molecule (N-terminal assay)). In osteomalacia, on the other hand, serum PTH was within normal limits when "N-terminal" assay was used, and only moderately elevated by the "C- terminal" assay. Serum calcium was normal and not significantly different between the two groups.

Figure 24. Biochemical Presentation

	Renal Osteodystrophy		
	Osteitis Fibrosa	Osteomalacia	Normal Range
Serum Ca, mg/dl	9.48±0.15 SE	9.71±0.25	8.9-10.1
Serum P, mg/dl*	4.85±0.25	3.79±0.38	3.2±4.3
Alkaline phosphatase, IU*	94.5±18.9	31.3±5.0	26±7 (SD)
Magnesium, mg/dl*	2.89±0.09	3.30±1.7	1.7-2.1
iPTH (C-term), µl eq/ml**	1586±239	278±44	<40
PTH (intact), pg eq/ml*	1444±361	293±35	255±46 (SD)

*$p<0.05$, **$p<0.01$ between patient groups

A similar conclusion was reached by Brickman et al.[79] A surprising finding in that study was the biochemical presentation in the mixed group (osteitis plus osteomalacia). Serum calcium was found to be low (7.2 mg/dl), and serum alkaline phosphatase was more markedly increased than in "pure" presentations. Serum PTH was moderately increased, though less than the level found in the osteitis group.

THERAPEUTIC CONSIDERATION

Ultimate goals of treatment are to (a) halt further progression of, or reverse, the bone disease after it has appeared, and (b) institute prophylactic measures to retard or inhibit development of bone disease. Because of major therapeutic advances made recently, the first goal will be discussed in detail.

TREATMENT WITH VITAMIN D METABOLITES

It has long been known that vitamin D or dihydrotachysterol may be useful in the management of renal osteodystrophy. A favorable response has been usually encountered, especially to dihydrotachysterol.[80] The recent interest generated by the commercial introduction of 1,25-$(OH)_2$D (Rocaltrol) and 25-OHD (Calderol) stems from possibilities that (a) these vitamin D metabolites are safer to use because of shorter biological half-lives and greater predictability of action, (b) they might be more effective therapeutically, and (c) and their use is more rational because it represents replenishment of naturally-occurring compounds which are depleted in renal osteodystrophy.

Despite numerous reports of successful therapeutic trials with these metabolites, it is clear that they may be ineffective sometimes, the response to the two compounds might differ, and their use may be attendant with complications. This discussion will attempt to provide physiological basis for the apparent discrepant responses to the two compounds, and will suggest indication for use of each vitamin D metabolite.

Current Status on Relative Efficacy of 1,25-$(OH)_2D$ and 25-OHD

There is general agreement that both 1,25-$(OH)_2D$ and 25-OHD are effective in correcting secondary hyperparathyroidism and osteitis. Both compounds have been shown to increase serum calcium concentration, and reduce the circulating concentration of immunoreactive PTH (Fig. 25 and Fig. 26).[81,78]

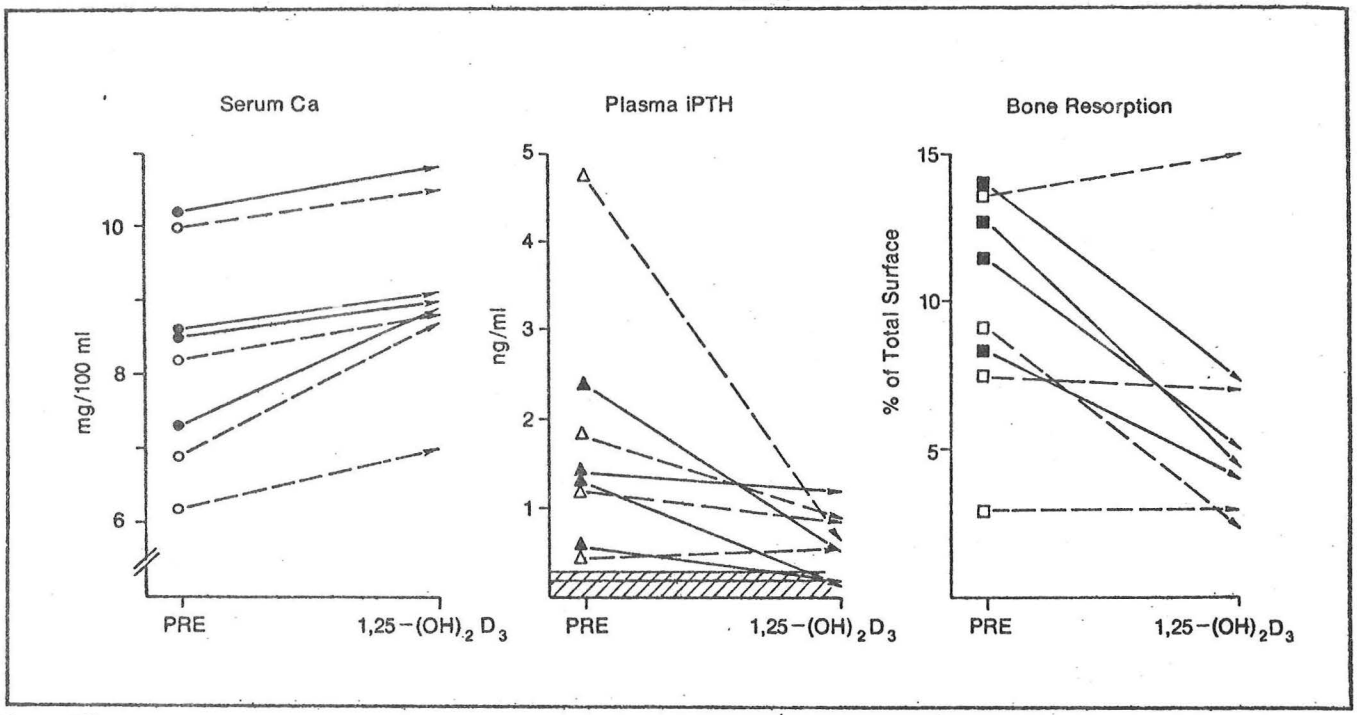


Fig. 25 Representative levels of serum calcium (Ca), parathyroid hormone (iPTH), and % bone surface showing resorption before (PRE) and following treatment with 1,25-$(OH)_2D_3$. Solid symbols and arrows are patients with bone lesions of hyperparathyroidism; open symbols with interrupted arrows, patients with osteomalacia.

Mean Changes in Biochemical Parameters During 25-OHD Therapy

Serum Parameter	25-OHD Therapy 17 Weeks	89 weeks
Calcium, mg/dl	+1.21±0.27**	+0.24±0.24
Phosphorus	+0.03±0.27	+0.30±0.29
Alkaline phosphatase, IU/dl	-37.9±8.8**	-95.2±33.4*
PTH (C-terminal), µlEq/ml	-294±157	-797±688
PTH (Intact), pg Eq/ml	-631±234*	-1199±383**
25-OHD, ng/ml	+187.7±26.9**	+157.8±40.9**

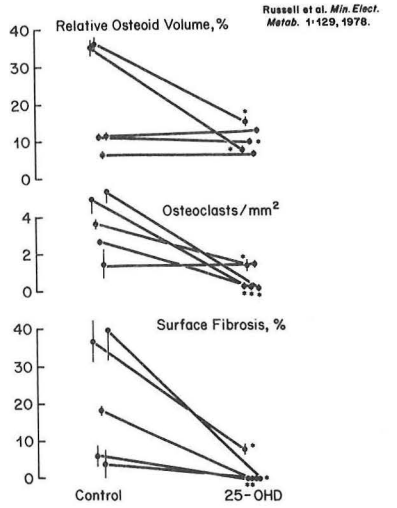
*$p<0.05$; **$p<0.01$

After Frost et al. Metabolic Bone Disease and Related Research. 1981.

Fig. 26.

Commensurate with these changes, improvement in histological manifestation of osteitis fibrosa has been observed, including reduction in osteoclastic resorption (Fig. 25 and Fig. 27)[81,82] and in endosteal fibrosis (Fig. 27).[82] The results suggest that these vitamin D metabolites had attenuated the skeletal effects of PTH-excess (osteitis) by reducing the degree of secondary hyperparathyroidism.

Fig. 27.



However, there is disagreement regarding the relative effectiveness of the two compounds in the management of uremic osteomalacia.[83] Bordier et al., for example, claimed that 1,25-$(OH)_2D$ was ineffective in restoring normal matrix mineralization,[61] since osteoid volume remained high and calcification front remained low (Fig. 28).[84] Others have shared this view.[83,85] On the other hand, Malluche et al.[86] found improvement in mineralization in the majority of cases. Their conclusion was supported by others.[81,87] In contrast, it is generally believed that 25-OHD treatment is effective in promoting mineralization[61,83,88] (Fig. 27).[82] Thus, a notion has emerged suggesting that 25-OHD may be more useful than 1,25-$(OH)_2D$ in the treatment of osteomalacic presentation of renal osteodystrophy.[83]

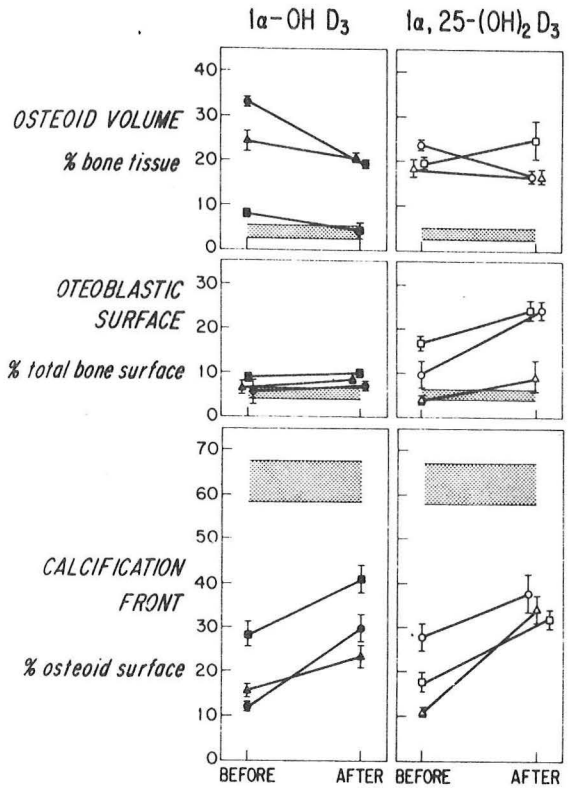


Fig. 28

A recent study[79,89] has provided some clarification. Patients with uremic osteomalacia were separated into those with pure osteomalacia and those with mixed presentation (osteomalacia and osteitis). The response to treatment with 1,25-$(OH)_2$D was found to be poor in patients with pure osteomalacia with normal serum PTH. However, positive response was typically found in those who displayed evidence of both osteomalacia and osteitis with high serum PTH.

Resolution of Controversy

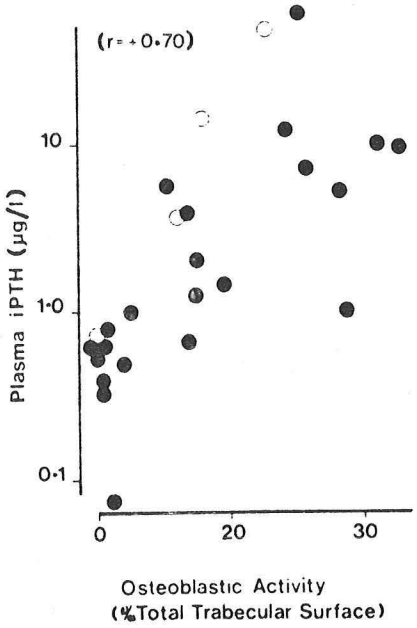
Questions to be resolved are: (a) Why is 25-OHD apparently more effective than 1,25-$(OH)_2$D in the management of uremic osteomalacia? (b) Why is 1,25-$(OH)_2$D apparently ineffective in pure osteomalacia whereas it may be effective in mixed osteomalacia and osteitis? Recent advances in the mode of action of these vitamin D metabolites, discussed under Pathogenesis, permits formulation of a hypothetical scheme which may provide answers to these questions.

Three assumptions, derived from available data, were made in this formulation,--that both 1,25-$(OH)_2$D[62] and 25-OHD[61] promote mineralization of available calcifiable matrix, that 25-OHD but not 1,25-$(OH)_2$D recruits new osteoblasts for matrix synthesis,[61] and that PTH increases the number and activity of osteoblasts.[7]

It is well known that PTH increases osteoclast population, and by coupling raises the number of osteoblasts.[7] In renal osteodystrophy, a direct correlation has been found between circulating PTH concentration and osteoblastic activity (Fig. 29).[90] The importance of PTH in maintaining bone formation in uremia was stressed by Teitelbaum et al.[91] It is

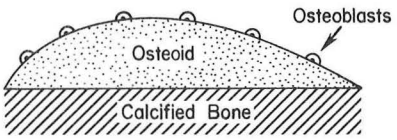
therefore expected that osteoblastic activity would be increased in mixed osteomalacia and osteitis where secondary hyperparathyroidism is present. In contrast, osteoblastic activity may be low in pure osteomalacia, where serum PTH is not increased and essential vitamin D metabolites may be lacking. This conclusion is supported by the finding of increased bone turnover in osteitis and low turnover in osteomalacia.[78] Thus, the amount of calcifiable matrix adjacent to active osteoblasts may be adequate in mixed presentation, whereas it is probably low in pure osteomalacia. A recent study of Frost et al.[78] found active osteoid surface, or the percentage of total trabecular perimeter covered by osteoid which is in contact with osteoblasts, to be 13.5% in osteitis and only 1.3% in pure osteomalacia.

Fig. 29.

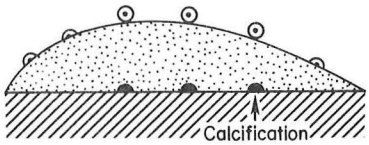


The histologic picture in pure osteomalacia is schematically shown in Fig. 30. Most of osteoid surface is not covered by osteoblasts. Osteoblasts are few in number and flat in appearance, indicative of reduced activity. Treatment with 1,25-$(OH)_2D$ is presumed to increase the activity of osteoblasts and stimulate the mineralization of osteoid adjacent to them. However, the number of osteoblasts remains low. Thus, the percentage of osteoid showing mineralization continues to be low. In contrast, 25-OHD may increase the number and activity of osteoblasts, albeit not completely to normal. Since it is also presumed to promote mineralization, both the osteoid adjacent to activated preexisting osteoblasts as well as that formed by newly recruited osteoblasts would undergo calcification. Thus, the percentage of osteoid surface undergoing mineralization would be expected to be greatly increased.

Pure Osteomalacia
(Normal PTH, Vitamin D Deficiency)



$1,25\text{-}(OH)_2$ D Therapy



25-OH D Therapy

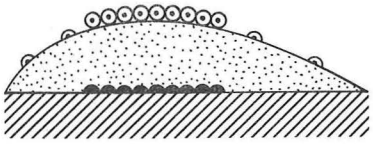
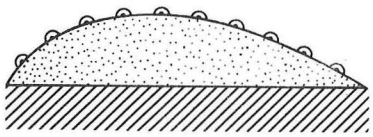


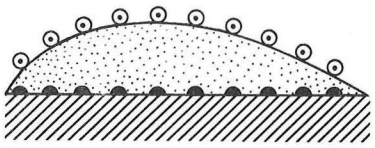
Fig. 30.

Fig. 31.

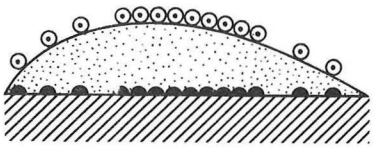
Mixed Osteomalacia and Osteitis
(High PTH, Vitamin D Deficiency)



$1,25\text{-}(OH)_2$ D Therapy



25-OH D Therapy



The situation in mixed bone disease (osteomalacia and osteitis) is schematically presented in Fig. 31. Because there is secondary hyperparathyroidism, more osteoblasts are present. However, osteoblasts are flat in appearance indicative of low activity, presumably due to vitamin D deficiency. Treatment with 1,25-$(OH)_2$D may stimulate the activity of osteoblasts and promote mineralization of osteoid adjacent to them. Since the number of osteoblasts are already high to begin with, the proportion of total osteoid surface undergoing calcification may be substantial. Histological improvement in osteomalacia may thus ensue. Treatment with 25-OHD is presumed to also activate osteoblasts and promote mineralization of osteoid adjacent to them. It may initially increase the number of osteoblasts, further enhancing mineralization. However, the osteoblast number may actually decrease with continued treatment because of amelioration of secondary hyperparathyroidism.

A potentially important advantage of 25-OHD has been discerned in our preliminary study of vitamin D metabolism following 25-OHD treatment. Treatment of patients with end-stage renal failure with 25-OHD has been shown to increase, not only the circulating concentration of 25-OHD, but that of 24,25-$(OH)_2$D as well. As similar finding has been observed in patients with osteoporosis.[92] Thus, 25-OHD treatment offers the beneficial effects of both 25-OHD and of 24,25-$(OH)_2$D.

Indications for treatment with vitamin D metabolites

From the preceding discussion, the following recommendations may be made concerning the use of specific vitamin D metabolites in renal osteodystrophy. Their use should be entertained only after hyperphosphatemia has been controlled with low phosphate diet and phosphate binding antacids. Otherwise, serious complications of soft tissue calcification may ensue during treatment with vitamin D metabolites. The prophylactic value of these metabolites in the prevention of development of osteodystrophy has not yet been ascertained. Thus, these suggestions pertain to the management of established renal osteodystrophy.

Osteitis fibrosa with serum Ca <10 mg/dl, P <5 mg/dl. This condition is characterized by radiological evidence of osteitis, high serum alkaline phosphatase, and elevated serum PTH (typically >20-fold upper limit of normal by carboxy-terminal assay).

Either 1,25-$(OH)_2$D or 25-OHD has been shown to be effective in this situation. The aim of treatment is to increase the serum concentration of calcium sufficiently to suppress PTH secretion, but not so high as to invite dangers of extraskeletal calcification. Initial dose of 1,25-$(OH)_2$D is 0.25 to 0.5 µg/day and that of 25-OHD is 50 µg/day. The dose should be carefully adjusted to raise serum Ca, but not above 11 mg/dl. During initial period of treatment, serum alkaline phosphatase may increase, and serum calcium and phosphorus may decrease, probably consequent to "remineralization" of the skeleton. Later, changes in these chemistries in reverse order may be encountered upon completion of remineralization. However, individual responses vary too wide to make this general pattern a useful guide in treatment. There is no substitute for a careful follow-up and adjustment of dosage according to serum chemistries. A closer follow-up may be required during 1,25-$(OH)_2$D treatment, because

the fluctuation in serum calcium is probably greater than during treatment with 25-OHD.

In patients with significant hypocalcemia (<7.5 mg/dl), calcium supplements (e.g. as calcium carbonate, not containing phosphate, equivalent to 1 g calcium in divided doses/day) may be advisable.

Mixed osteomalacia and osteitis fibrosa (serum P<5 mg/dl). As in osteitis fibrosa, there may be roentgenological evidence of osteitis and serum PTH is substantially elevated. However, serum Ca is typically lower and alkaline phosphatase higher than in the previous group.[89]

Positive response has been reported with both 1,25-$(OH)_2$D and 25-OHD. 25-OHD might be slightly superior to 1,25-$(OH)_2$D in promoting overall mineralization.

Pure osteomalacia (serum P<5 mg/dl). This condition is characterized by normal or slightly increased serum PTH (N-terminal assay), and only moderately high serum PTH (<8-fold, by C-terminal assay). Symptoms of bone tenderness and muscle weakness may be present.

25-OHD is clearly the treatment of choice. In patients with serum calcium >10 mg/dl, a low calcium diet may be useful, in order to permit sufficient dose of 25-OHD to be administered without provoking significant hypercalcemia (>11 mg/dl).

Osteitis fibrosa with serum Ca >11 mg/dl. Treatment with either 1,25-$(OH)_2$D and 25-OHD is contraindicated because of the dangers of hypercalcemia. This group was considered to be "treatment failures" to 1,25-$(OH)_2$D by Brickman et al.[79,89] The failure was probably due to early withdrawal of treatment because of the onset of hypercalcemia and not the result of the inability of vitamin D metabolite(s) to suppress PTH secretion.

This is the group where parathyroidectomy might be indicated. However, it may be speculated that 24,25-$(OH)_2$D when it becomes available may have a unique therapeutical role. Its hypocalcemic action[51,52] may obviate the danger of hypercalcemia. The PTH-excess may be attenuated by its direct inhibition of PTH secretion.[51,54]

Osteitis fibrosa with marginal hypercalcemia. In patients with serum calcium concentration ranging between 10-11 mg/dl, a judicious use of vitamin D metabolites may be indicated. 25-OHD may be preferable to 1,25-$(OH)_2$D because it may be less likely to cause an abrupt rise in serum calcium. An increase in serum calcium up to 12 mg/dl may be attempted, provided there is a careful monitoring for potential side effects. A vigorous attempt should be made with dietary means and phosphorus binding antacids to maintain serum phosphorus within the normal range.

Myopathy. In patients with severe muscle weakness, both 1,25-$(OH)_2$D and 25-OHD have been shown to produce a marked subjective and objective improvement. The exact cause for the muscle weakness and the mode of action of vitamin D metabolites have not been elucidated. Prevailing data suggest that vitamin D deficiency interferes with cellular phosphate influx, synthesis of high energy phosphates, and with uptake of calcium by the sarcoplasmic reticulum.[93-95] Treatment with 1,25-$(OH)_2$D has been reported to correct the defect in calcium transport in sarcoplasmic reticulum,[95] and to reduce the amount of electrical activity recorded at given load on electromyograph.[96] 25-OHD stimulates phosphate influx[97] and restores normal histological picture in affected musculature.

Side-effects of treatment with vitamin D metabolites. Dangers of treatment are largely the result of hypercalcemia (already discussed) and hyperphosphatemia. Recent study[98] by segmental intestinal technique has unequivocably demonstrated the ability of 1,25-$(OH)_2$D to stimulate intestinal phosphate absorption. The enhanced phosphate absorption may increase serum phosphorus concentration, especially after initial remineralization period. Treatment with vitamin D metabolites should not be undertaken in patients with hyperphosphatemia (>6 mg/dl).

Intestinal perfusion studies have also disclosed the ability of 1,25-$(OH)_2$D to augment magnesium absorption.[99] Thus, skeletal retention of magnesium may be exaggerated (see Pathogenesis).

It has been reported that 1,25-$(OH)_2$D treatment accelerates deterioration of residual renal function in patients with glomerular filtration ranging from 9-35 ml/min.[100] Although this study has been criticized,[101] it is not surprising that such a complication had occurred, because of the frequent development of hypercalcemia during 1,25-$(OH)_2$D therapy.[100,102]

CONSERVATIVE TREATMENT PROGRAMS

The most important adjunct therapy is the control of hyperphosphatemia. Phosphate restriction and prevention of hyperphosphatemia may help to preserve residual renal function,[103] prevent development of secondary hyperparathyroidism and osteitis,[104,105] and avoid complications of soft-tissue calcification.[75,105]

Serum phosphorus concentration should preferably be kept below 5.0 mg/dl by dietary phosphate restriction and use of phosphate-binding antacids. Ingestion of dairy products should be discouraged because of their high phosphate content. If calcium supplementation is required, it may be provided as calcium salts (free of phosphate). Magnesium containing antacids should not be used, because of their potential aggravation of skeletal magnesium retention, and since they possess weak phosphate-binding capability.

Other conservative programs include maintenance of a normal acid-base status, and avoidance of unnecessary treatment with anticonvulsants,[106] tranquilizers and steroids which might adversely affect the state of bone.

Propranolol and cimetidine. The use of these drugs is based on the finding that they may reduce serum concentration of immunoreactive PTH. In chronic renal failure, patients taking propranolol (for hypertension or angina) were found to have lower values for serum immunoreactive PTH and alkaline phosphatase than a separate group of patients not taking this drug.[107] Unfortunately, no prospective study in the same patients was performed. Cimetidine was shown to significantly reduce serum PTH in patients undergoing hemodialysis.[108,109] However, this finding could not be confirmed.[110] Moreover, serum calcium concentration was not reduced by cimetidine.[108-110]

Treatment with these modalities should not be undertaken for the control of secondary hyperparathyroidism of renal failure without further clarification.

SURGICAL MANAGEMENT OF RENAL OSTEODYSTROPHY

Parathyroidectomy may be indicated in patients with hypercalcemic osteitis fibrosa in whom treatment with vitamin D metabolites is contraindicated or is expected to elicit poor response. Surgery may also be considered in those with osteitis in whom hyperphosphatemia cannot be adequately controlled, especially if they have soft tissue calcification. Total parathyroidectomy with parathyroid autotransplantation[111-113] may be advantageous to subtotal parathyroidectomy,[114,115] because it may obviate the reexploration of the neck for recurrent parathyroid hyperplasia.

It is expected that successful renal transplantation would eliminate much of the pathogenetic factors responsible for the development of renal osteodystrophy. Indeed, normal renal phosphate disposal,[116] restoration of serum 1,25-$(OH)_2D$[117] and suppression of serum PTH typically ensues.[41,118] However, some patients may develop hypercalcemia[116,118,119] or hypophosphatemia, and complications of long-term steroid therapy may ensue.

Serum PTH may remain elevated following renal transplantation because of the delay in hyperplastic parathyroid tissue to return to the normal state despite lack of stimulus. Hypercalcemia probably results from the restoration of normal skeletal responsiveness to PTH and from increased intestinal calcium absorption. Renewed synthesis of 1,25-$(OH)_2D$ by the transplanted kidney[117] probably contributes to the changes in skeletal and intestinal responses. Hypophosphatemia may be accounted for by the phosphaturic action of PTH, and use of phosphate-binding antacids sometimes used in conjunction with steroid therapy. It has been reported that azathioprine may cause phosphaturia and contribute to the hypophosphatemia.[120] In patients with hypercalcemia post-renal transplantation, orthophosphate supplementation (1.5-2 g P/day) should be attempted before considering parathyroidectomy.[116,119]

CONCLUSION

It is apparent that much progress has been made regarding pathogenesis and management of osteodystrophy. Sufficient information is now available to characterize the physiological background, clinical presentation and biochemical picture of three principal forms of renal osteodystrophy,--osteitis fibrosa, osteomalacia, and mixed osteitis and osteomalacia. Therapeutic outlook has improved substantially with the introduction of vitamin D metabolites. From the available data concerning the mode of vitamin D action and control of bone cell metabolism, it has been possible to construct a scheme for defining specific indications for each vitamin D metabolite.

However, many questions remain to be elucidated. Serum "vitamin D profile" during different stages of renal failure and in different forms of uremic bone disease needs to be better delineated. The basis for the apparent rise in intestinal calcium absorption following hemodialysis requires clarification. The effects of oral phosphate load and the definition of parathyroid function and vitamin D metabolism during different stages of renal failure in man should be better defined. The prophylactic value of vitamin D metabolites in the prevention of renal

osteodystrophy requires exploration. Finally, the potential development of bone disease post-renal transplantation should be anticipated, the nature of bone disease characterized and appropriate therapeutic or prophylactic program developed.

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