Secondary Hyperparathyroidism in Chronic Renal Failure

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ABSTRACT

The metabolic bone disease associated with chronic renal failure has been described collectively by the terms "renal osteodystrophy" or "renal-glomerular-osteodystrophy" and consists of osteomalacia, osteitis fibrosa, and osteosclerosis. The skeletal abnormalities may occur either alone or in combination with one another. An increased concentration of circulating immunoreactive-parathyroid hormone (i-PTH) is a recognized feature of patients with chronic renal failure, and the values are usually much higher than those found in patients with primary hyperparathyroidism associated with a parathyroid adenoma. It must, however, be recognized that the high circulatory concentrations of parathyroid hormone found in patients with chronic renal failure are of immunoassayable material which may or may not be of biological significance in respect of activity. A disturbance in the homeostatic control mechanism governing parathyroid hormone, the secretion rate, its metabolism, and target organ resistance to its action are of major importance in the pathogenesis of some aspects of the metabolic bone disease in patients with chronic renal failure. The pathogenesis of the secondary hyperparathyroidism of chronic renal failure, however, also involves disturbances in cholecalciferol metabolism, phosphate retention, and the uremic state per se.

Introduction

An understanding of the interrelationships between parathyroid hormone and the various metabolites of vitamin D, the control mechanisms involved in their synthesis and secretion, together with their modes of action, is of prime importance in any consideration of the disturbances of calcium and phosphate homeostasis found in patients with chronic renal failure. The abnormalities that occur in both the metabolism and efficacy of parathyroid hormone and vitamin D are ultimately responsible for the disturbances in calcium and phosphate homeostasis and for the metabolic bone diseases associated with chronic renal failure.

Disturbances in calcium and phosphate homeostasis and the associated metabolic
bone diseases are probably the dominant clinical problem of patients with chronic renal failure. The disturbances commonly take the form of hypocalcemia and hyperphosphatemia, but these changes are not invariable. The metabolic bone disease associated with chronic renal failure has been described collectively by the terms "renal osteodystrophy" or "renal-glo­merular-osteodystrophy" and consists of osteomalacia, osteitis fibrosa, and osteosclerosis. The skeletal abnormalities may occur either alone or in combination with one another. In histological studies it has been reported that, even though clinical evidence may be absent, metabolic bone disease is present in virtually all patients in the terminal phase of chronic renal failure. A disturbance in both the secretion rate and homeostatic control mechanism governing parathyroid hormone are of major importance in the pathogenesis of the metabolic bone disease.

Homeostatic Control

The calcium present in the plasma compartment is divisible into a diffusible and non-diffusible fraction depending on its ability to pass across a semi-permeable membrane. The non-diffusible or "protein-bound" fraction constitutes approximately 40 percent of the total calcium present in plasma and is mainly bound to albumin. The majority of the diffusible fraction is present in the "ionized" form (approximately 50 percent) and the remainder is present as the "complexed" fraction. The latter is bound in a loose complex with bicarbonate, citrate, phosphate, and various other anions. The ionized fraction is considered to be the "active" fraction which triggers the feedback mechanisms for the secretion of parathyroid hormone by the parathyroid glands and the rate of renal synthesis of 1,25-dihydroxycholecalciferol (1,25-DHCC). The interrelationship between the concentrations of the calcium fractions are considered to be dependent on many variables including: (1) alterations in the concentration of the plasma protein fractions, of which albumin is the most important; (2) the concentrations of phosphate, sulphate, citrate, and other anions; and (3) variations in acid-base status in the extracellular fluid compartment. Alterations in any, or all, of these variables are liable to occur in patients with chronic renal failure.

Parathyroid Hormone

Parathyroid hormone is a polypeptide that exerts its regulatory role on calcium homeostasis through its actions on bone, kidney, and the gastrointestinal tract. On bone the actions are complex and apparently involve all of the osteogenic cells. The actions on the kidney are also complex and affect the renal tubular handling of calcium, phosphate, magnesium, sodium, hydrogen ion, and water. The actions of parathyroid hormone on the gastrointestinal tract are less well defined than on the other two target organs, but there is evidence that it has an effect on the absorption of calcium. Parathyroid hormone has some regulatory role on the specific activity of the renal 1-hydroxylase for 25-hydroxycholecalciferol (25-HCC) and consequently the production of 1,25-DHCC from cholecalciferol. There is also evidence that the secretion rate of parathyroid hormone is directly influenced by 1,25-DHCC.

Parathyroid hormone is secreted from the glands as a single-chain polypeptide containing 84 amino acids with a molecular weight of 9500; it is stored in the glands as a prohormone with six additional amino acids at the amino terminal end. There is also evidence that parathyroid hormone is probably synthesized as a pre-prohormone which contains 115 amino acids. The pro-hormone appears to undergo two cleavage steps within the gland and a third cleavage step after secre-
tion into the circulation. In the circulation there are three immuno-reactive parathyroid hormone fragments with molecular weights of 9500, 7000 to 7500, and 4000 to 4500 which vary in their biological activity. The activity of the peptidase that catalyzes the conversion of pro-parathyroid hormone to the smaller molecular weight form appears to be regulated by variations in calcium concentration. The concentration of intact hormone in the circulation constitutes less than 10 to 15 percent of the total and the larger proportion of the immuno-reactive hormone present has been reported to be biologically inactive. The latter observations are of considerable importance in the interpretation of assay results for circulating immuno-reactive parathyroid hormone (i-PTH) concentration in clinical situations and particularly in patients with chronic renal failure.

Excess Parathyroid Secretion States

The endogenous secretion rate of parathyroid hormone is normally correlated with the total circulating calcium concentration and, in particular, the ionized fraction. Hyperparathyroidism is by definition an excess or inappropriate serum parathyroid hormone concentration for the prevailing circulating calcium concentration. In primary hyperparathyroidism, the excessive hormone secretion with consequent hypercalcemia is the consequence of the spontaneous development of either an adenoma in one gland, hyperplasia of all four glands, or carcinoma of the parathyroids. In secondary hyperparathyroidism, the excessive hormone secretion is associated with hyperplasia of all four parathyroid glands as a direct result of long-standing chronic hypocalcemic stimulation. The latter may be due either to chronic renal failure or to some primary disease of the gastrointestinal tract with malabsorption of calcium and consequent hypocalcemia. The development of autonomy in the hyperplastic glands, of secondary hyperparathyroidism, with or without the formation of an adenoma, is termed tertiary hyperparathyroidism. In the tertiary state, there can be either normalization of the pre-existing hypocalcemia or "over-swing" up through the normal reference range and hypercalcemia.

An increased concentration of circulating immunoreactive-parathyroid hormone (i-PTH) is a recognized feature of patients with chronic renal failure and the values are usually much higher than those found in patients with primary hyperparathyroidism associated with a parathyroid adenoma. Berson and Yalow reported that although most of the patients they studied were hypocalcemic, there was no "strong correlation" between the degree of hypocalcemia and the concentration of parathyroid hormone, "rather the severity of the uremia seemed to be the more significant factor." It is now established that in patients with untreated chronic renal failure, the elevation in i-PTH is proportional to the degree of failure and correlates significantly with either the blood urea nitrogen or serum creatinine concentration. In patients with chronic renal failure, the mechanism for the development of secondary hyperparathyroidism has been classically regarded as being due to hypocalcemia. It is now recognized that although triggered by hypocalcemia, the clinical state of secondary hyperparathyroidism is associated with phosphate retention, resistance to the actions of parathyroid hormone, and defects in cholecalciferol metabolism. Resistance to the actions of parathyroid hormone in uremia would entail a disproportionately high secretion rate to maintain any given plasma calcium concentration. It must also be recognized that the high circulatory concentrations of parathyroid hormone found in patients with chronic renal failure are of immunoassayable material.
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Secondary Hyperparathyroidism

In patients with chronic renal failure who have excessive demineralization of bone and osteitis fibrosa, the histological and radiological lesions in the bones are indistinguishable from those of primary hyperparathyroidism. In this group of patients, the majority of whom are normocalcemic, the major factor in the etiology of their bone disease is excessive secretion of parathyroid hormone. That the lesions are due to hormonal excess is supported by the fact that after subtotal or total parathyroidectomy, with a consequent removal of excess hormone production, there is an improvement in the bone lesions.

The importance of alterations in the functional status of the parathyroid glands in patients with chronic renal failure in relationship to metabolic bone disease was recognized by Katz and his colleagues in a study reported in 1969. They studied 195 patients with advanced chronic renal failure and reported that of those patients who came to autopsy, there were abnormalities in 88 percent of the parathyroid glands and bone specimens examined. The predominant histological change in the parathyroid glands was diffuse chief-cell hyperplasia, while the bones showed changes which were consistent with both osteitis fibrosis and osteomalacia. They also reported that the circulating i-PTH concentration was increased in patients who were suspected on clinical, biochemical or radiological evidence of having secondary hyperparathyroidism. Other workers have subsequently reported that in patients with chronic renal failure, the circulating i-PTH concentration was greater in those with osteitis fibrosa, at any given plasma calcium concentration, than it was in those without bone disease. In their studies, Katz and his colleagues also noted that the increase in circulating i-PTH concentration showed some correlation with the known duration of the disease and closely correlated with the degree of parathyroid hyperplasia at surgical exploration of the neck.

The post-operative fall in serum i-PTH concentration after total parathyroidectomy in patients with chronic renal failure is slower than after the removal of a parathyroid adenoma in patients with primary hyperparathyroidism. Berson and Yalow proposed that the slow post-operative fall in i-PTH concentration in uremic patients suggested that parathyroid hormone in human plasma was immunochemically heterogeneous and that removal of one or more peptides from the circulation may be dependent upon normal renal function. This proposal was confirmed by the studies of Melick and Martin using bovine parathyroid hormone, labelled with 125I, who reported that the rate of disappearance of the hormone was significantly slower in patients with chronic renal failure than it was in normal control subjects. Melick and Martin concluded that a reduction in the destruction rate of parathyroid hormone was one of the factors concerned with maintenance of the hyperparathyroidism of renal failure.

It is now recognized that the kidney plays an important role in the metabolism of parathyroid hormone in vivo, and in chronic renal failure the impairment in renal degradation contributes to the high circulating i-PTH values. Knights et al proposed that polypeptide hormone concentrations may be controlled not only by their rate of synthesis but also by the rate of enzymatic destruction. This concept may be applied to polypeptide hormones other than parathyroid and has many important implications in chronic renal failure. The impairment of parathyroid hormone degradation in chronic renal failure is probably due to enzyme inhibition, as a direct consequence of uremia, rather than
simply owing to a reduction in functional renal mass.

There has been some debate as to whether or not the hyperplastic glands of secondary hyperparathyroidism are autonomous and are no longer responsive to changes in circulating calcium concentration. Autonomy of the glands would account for a high secretion rate, disproportionate to the prevailing calcium concentration. Genuth and his colleagues reported that calcium infusion caused a decrease in circulating i-PTH concentration in six of seven patients with chronic renal failure. They concluded that the glands in secondary hyperparathyroidism were not autonomous and were still responsive to normal feed-back control. Others have reported non-suppressibility after calcium loading but have suggested that the findings, in part at least, were a function of total parathyroid tissue-mass.

The assessment of parathyroid suppressibility in response to a calcium challenge, on the basis of the assay of circulating i-PTH concentration, must also take into consideration the immunoassay technique. Goldsmith and his colleagues measured the concentrations of two immuno-reactive species of circulating parathyroid hormone in patients with chronic renal disease. Basal values of the smaller molecular weight species (i-PTH-7) were invariably raised while those of the larger molecular weight species (i-PTH-9) were normal. In response to calcium infusions, the concentrations of i-PTH-9 decreased on every occasion, but there were variable responses in i-PTH-7 concentration. It was concluded that the circulating concentration of i-PTH-9 reflected primarily the moment-to-moment secretory status of the glands while i-PTH-7 reflected more closely the chronic status.

Changes in Plasma Phosphate Concentration

In chronic renal failure, there is an increase in the plasma phosphate concentration. Plasma inorganic phosphate is derived from the diet and may be liberated from organic compounds such as phospholipids and nucleoproteins in catabolic states. The increase in plasma phosphate concentration in renal failure is not simply due to a reduction in functional renal mass. In progressive chronic renal disease, although there is a decrease in phosphate clearance, the rate of fall is proportionately less than that of glomerular filtration. The average rate of phosphate excretion in the surviving nephron units increases as the total nephron population is decreased. Parathyroid hormone plays a major role in the control mechanisms involved in the changes in the pattern in phosphate excretion in this situation.

A high plasma phosphate concentration in uremia in itself is not known to produce biochemical disturbances, although it may be of importance in the development of resistance to parathyroid hormone. In the classical concept of bone disease in chronic renal failure, phosphate is considered to have a secondary effect by lowering the plasma calcium concentration. According to the classical concept, changes in the plasma calcium concentration follow, or are secondary to, those in the plasma phosphate concentration; therefore, it might be expected that the plasma calcium concentration would be low in all patients with chronic renal failure. Such, however, is not the case. The plasma calcium concentration may remain normal despite considerable increases in the plasma phosphate concentration; alternatively, it may be low in the presence of only small changes in the phosphate concentration.

An explanation for these findings was proposed by Stanbury and Lumb who considered that the plasma calcium concentration in chronic renal failure is determined by factors other than the plasma phosphate concentration. Their view was based on their own personal experiences of a large series of patients with renal osteodystrophy. They suggested that in pa-
tients with chronic renal failure there was a continuous spectrum of changes in which those with osteomalacia, or defective mineralization, and those with pure osteitis fibrosa, or excessive decalcification, represented the two extremes. They divided their patients into two groups. In group one, who had evidence of osteomalacia or defective mineralization, the plasma calcium concentration was below normal. In the second group, the patients had no evidence of defective mineralization but had evidence of osteitis fibrosa, and in these the plasma calcium concentrations were normal. An increase in the parathyroid hormone secretion rate, in this second group, would account for the osteitis fibrosa.

In the pathophysiology of osteitis fibrosa in patients with uremia, Bricker\textsuperscript{10} proposed that the retained phosphate ion played a "unique role." In his concept he proposed that as the plasma phosphate concentration increased, there was a reciprocal fall in the ionized calcium concentration with consequent stimulation of parathyroid hormone secretion. The increase in parathyroid hormone secretion would, in this concept, through its dual actions on bone and kidney, effect an increase in the plasma calcium and a fall in the plasma phosphate concentration, and so maintain steady state conditions. Bricker considered that this "on-off" oscillation in parathyroid gland activity would maintain normal plasma concentrations of calcium and phosphate until the glomerular filtration rate fell below a value of 25 to 30 ml per minute, at which stage hyperphosphatemia with presumably hypocalcemia would ensue. This concept has been termed the "trade-off hypothesis" and postulates that the dietary phosphate intake is potentially the all important factor.\textsuperscript{14} In this hypothesis, a proportional reduction in dietary phosphate intake and, hence, solute load in direct relation to the decrease in glomerular filtration rate, would prevent initiation of the sequence of events. In experimental animals, this hypothesis has been confirmed and secondary hyperparathyroidism prevented by using a proportional reduction in dietary phosphate intake as the glomerular filtration rate was reduced.\textsuperscript{45,46}

The rarity of renal osteodystrophy in Israel in patients with chronic renal failure has been attributed to their naturally lower dietary phosphate intakes.\textsuperscript{6} In studies on experimental animals with renal failure, it was reported that the degree of hyperparathyroidism was influenced by variations in the dietary intakes of calcium, phosphorus, and hydrogen ion.\textsuperscript{50} Kaye reported that the dietary phosphate intake was linearly related to parathyroid gland size.

Vitamin D "Resistance"; Cholecalciferol Metabolism

Hypocalcemia and the consequent defective mineralization of bone in patients with chronic renal failure may be regarded as the direct consequence of a reduction in intestinal calcium absorption. A reduction in calcium absorption from the gastro-intestinal tract has been recognized as a feature of chronic renal failure for many years. In the past, the view was held that in chronic renal disease there was an acquired insensitivity or "resistance" to the actions of vitamin D and that this accounted for the reduction in intestinal calcium absorption.

The renal steroid hormone 1,25-dihydroxycholecalciferol (1,25-DHCC) is the dominant factor in the intestinal absorption of calcium.\textsuperscript{48} Calcium is absorbed throughout the length of the small intestine, but absorption is greater in the duodenum and proximal jejunum than in the ileum.\textsuperscript{47} Calcium absorption in the duodeno-jejunal segment is by an active carrier-mediated energy-dependent process.\textsuperscript{2} It is at this site by inducing the synthesis of the specific calcium-binding transport protein that 1,25-DHCC plays its dominant role in intestinal calcium ab-
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sorption. In chronic renal disease, with a reduction in functional renal mass, a failure of formation of 1,25-DHCC would result in a decrease in the intestinal mucosal content of the calcium-binding protein. This has been reported in experimental animals and in man. The findings are, however, controversial as it has also been reported that intestinal calcium-binding protein was normal in activity, quantity, and affinity for calcium in malabsorbing uremic patients when compared with normal control subjects. These latter findings would suggest that the defect in intestinal calcium absorption in uremia is unrelated to a disturbance or deficiency of intestinal calcium-binding protein.

Although 1,25-DHCC deficiency is undoubtedly a major factor that accounts for the calcium malabsorption of chronic renal failure, there is evidence that other factors may play contributory roles. This view is based on the observations that plasma concentrations of 1,25-DHCC are not necessarily low in all patients with end-stage chronic renal failure, some of whom have low concentrations of plasma 25-hydroxycholecalciferol (25-HCC). In his recent review of the controversies regarding uremia and the acquired defects in cholecalciferol metabolism, Avioli proposed that additional information is required not only on the 1,25-DHCC and 25-HCC metabolites but also on other metabolites such as 24,25-dihydroxycholecalciferol. In experimental animals with uremia, the metabolism and tissue distribution of radioactive cholecalciferol and its metabolites after injection has been reported to be only slightly different from that in normal animals. Von Herrath and his colleagues concluded that target organ resistance probably played a role in uremia. In support of this conclusion are the observations that uremia per se decreased the intestinal absorption of calcium in experimental animals. Target organ resistance could be due to a uremic inhibitory effect on intestinal micro-villar alkaline phosphatase activity.

The “resistance” to or the defect in metabolism or formation of 1,25-DHCC in chronic renal failure has important consequences. It not only accounts for the hypocalcemia and defective bone mineralization but also, because of its interrelationships with parathyroid hormone, plays a role in the resistance to the actions of that hormone seen in patients with uremia.

Parathyroid Hormone Resistance

In patients with chronic renal failure, there is target organ resistance to the actions of exogenous parathyroid extract after its administration. It can be assumed that this also reflects resistance to the actions of endogenous hormone. The classical concept of parathyroid hormone resistance in hypocalcemic states, with osteomalacia, was that the presence of an envelope of unmineralized osteoid prevented the exchange of calcium ions between bone and the extracellular fluid compartment. In the acute calcemic response to exogenous parathyroid hormone, in vitamin D-deficient animals, there is some experimental evidence that supports this concept. In view, however, of the known actions of parathyroid hormone on the organic phase of bone, this concept, although perhaps tenable in the acute experimental calcemic response situation, cannot account for the resistance to parathyroid hormone seen in patients with chronic renal failure.

The primary action of parathyroid hormone on both renal and skeletal tissue appears to be the activation of adenyl cyclase with a consequent increase in the intracellular concentration of cyclic 3',5'-adenosine monophosphate (AMP). As there is a critical requirement for calcium ions in the action of cyclic 3',5'-AMP, it could be postulated that in hypocalcemic chronic renal failure the resistance to parathyroid hormone seen in those early reports was directly attributable to the hypocalcemia. Although
hypocalcemia may play a role in parathyroid hormone resistance, it is probably not a major factor, as it has been reported that the calcemic response to parathyroid extract in renal failure was unrelated to the initial plasma calcium concentration. These studies suggest that factors other than hypocalcemia must be invoked in the mechanism of resistance to the actions of parathyroid hormone seen in the patients with chronic renal failure.

The actions of parathyroid hormone on some of its target organs appear to involve the biologically active metabolites of cholecalciferol. The diminution in 1,25-DHCC production in chronic renal failure could, therefore, be an important factor in the resistance to parathyroid hormone seen in these patients. On the kidney it has been reported that there was no phosphaturic response after the administration of parathyroid extract to hypocalcemic patients with chronic renal failure. The lack of a phosphaturic response in this situation could be due to the fact that the renal tubules were already under maximal stimulation from high circulating concentrations of endogenous parathyroid hormone. This concept is supported by the observations that there is a relative resistance to the phosphaturic action of parathyroid extract in patients with chronic renal failure. The actions of parathyroid hormone on both bone and the gastro-intestinal tract would, however, appear to be dependent, in part at least, on the presence of 1,25-DHCC. The interrelationships between these two hormones on these two organs probably involve cyclic 3',5'-AMP as a final common pathway.

It is also possible that other factors play a role in the mechanism of resistance to parathyroid hormone in chronic renal failure. Amongst these are uremia per se and phosphate retention. Serum from uremic patients collected prior to hemodialysis has been shown to exert an inhibitory effect in vitro on parathyroid extract-induced bone resorption in organ culture while post-dialysis serum from the same patients had no such inhibitory effect. These findings are consistent with the view that the accumulation of uremic metabolites plays a role in the parathyroid hormone resistance of chronic renal failure. It would seem likely, however, that the effect is a cumulative one in vivo, as the individual metabolites studied were not inhibitory at concentrations known to occur in uremic serum. A high phosphate concentration in bone organ culture medium is also recognized to have an inhibitory effect on parathyroid extract-induced resorption. These latter observations could be relevant in the clinical in vivo situation of phosphate retention in chronic renal failure. Autoantibodies that block the binding of parathyroid hormone to membrane receptors for the hormone have been reported in sera from 49 of 50 uremic patients with secondary hyperparathyroidism. The autoantibodies were detected in the serum IgG fraction, were species-specific, and were not affected by dialysis. If these findings are confirmed, secondary hyperparathyroidism could be classified as an example of a receptor-antibody disease.

Conclusion

Secondary hyperparathyroidism and osteitis fibrosa is one of the major forms of metabolic bone disease found in patients with chronic renal failure. Metabolic bone disease is probably the major clinical, and frequently disabling, problem in patients with chronic renal failure. It is present and often severe on histological examination in virtually all patients with end-stage disease even though clinical evidence of its presence may be absent. The major biochemical factors involved in the pathogenesis of the metabolic bone disease are, without doubt, the disturbances
in calcium and phosphorus homeostasis and the associated secondary hyperparathyroidism. The pathogenesis of the secondary hyperparathyroidism, however, also involves the disturbances in cholecalciferol metabolism and the uremic state per se.

References


