Serum parathyroid hormone in hypophosphatemic vitamin D-resistant rickets

Serum parathyroid hormone (PTH) was measured in five children with untreated, active hypophosphatemic vitamin D-resistant rickets before, during, and after an infusion of calcium. During the calcium infusion, serum PTH decreased while the tubular resorption of phosphate increased. Although these data clearly indicate that some degree of hyperparathyroidism accompanies the disease, it is apparent that the degree of hyperparathyroidism recorded in these studies is not sufficient to explain the severity of the phosphaturia. One of the basic defects in the disease may involve excessive sensitivity of the renal tubule to the phosphaturic effects of PTH.


The pathogenesis of the phosphaturia and hypophosphatemia that characterizes vitamin D-resistant rickets remains obscure. Two theories dominate current thinking. According to one, the primary defect is malabsorption of calcium by the gastrointestinal tract, which in turn stimulates secondary hyperparathyroidism. Phosphaturia and hypophosphatemia are recognized sequelae of increased secretion of parathyroid hormone (PTH). The second theory assumes the existence of a primary defect in the renal tubular transport system for phosphate resulting in phosphaturia independent of hormonal influences.

The role of secondary hyperparathyroidism has been studied indirectly by intravenous infusions of calcium. The induction of hypercalcemia is known to suppress PTH secretion. Numerous investigators have reported suppression of phosphaturia in vitamin D-resistant rickets during intravenous calcium infusions, and it has been assumed that this decreased phosphaturia is a consequence of inhibition of PTH secretion. However, it is now known that calcium acts directly on the renal tubular transport of phosphate. Hence, there is some doubt whether changes in phosphate excretion during a calcium infusion can be related specifically to changes in PTH secretion.

In this report, we record the results of a
direct study of the role of secondary hyper-
parathyroidism using a highly sensitive radio-
immunoassay for PTH.

MATERIAL AND METHODS

Five children were studied. All had active rickets that failed to respond to oral vitamin D, 5,000 units daily for one month. These patients fulfilled the following additional criteria: (1) elevation of the serum alkaline phosphatase, (2) severe hypophosphatemia, and (3) decreased tubular reabsorption of phosphate. All patients had normal blood urea nitrogen and creatinine values, were able to concentrate their urine to osmolalities greater than 900 mOsm. after fluid deprivation, and responded normally to an ammonium chloride challenge. None had glucosuria. One patient (S. D.) had transient amino-aciduria. Three patients had a family history of rickets. Patient C. B. was an only child but her mother was noted to be bow legged in infancy and had corrective surgery on her legs as an adolescent. Patients M. J. and E. J. are siblings; two other siblings are also known to be hypophosphatemic and to have skeletal deformities of the lower extremities. One female sibling, age 11 months, had a calcium concentration of 9.8 mg. per 100 ml., phosphorus 2.8 mg. per 100 ml., and alkaline phosphatase 24.9 Bodansky units. She concentrated her urine to 870 mOsm. and had normal renal function. The children's mother, age 44 years, had a serum calcium value of 8.9 mg. per 100 ml., phosphorus 2.1 mg. per 100 ml., and alkaline phosphatase of 24.3 Bodansky units. These two patients were not available for calcium infusion studies.

Patients ingested their customary diets. Calcium infusion studies were begun in the morning in the postprandial state. Calcium was infused in the amount of 16 to 24 mg. per kilogram of body weight over a 4 hour period. It was administered in the form of calcium gluconate-glucoheptonate in a solution containing 5 per cent dextrose and 0.2 per cent sodium chloride at a rate of 0.5 to 0.8 ml. per minute. Patients were given 10 ml. of water per kilogram of body weight orally before beginning each study to ensure an adequate rate of urine flow. They were permitted to drink water during the infusion.

Before the infusion was begun, two 1 hour control clearance periods were carried out. During the 4 hour infusion, two 2 hour clearance periods were observed. Following the infusion, two additional 2 hour clearance periods were observed. Blood was drawn at the midpoint of each collection period. Two infants (15 and 20 months of age) were catheterized to ensure complete urine collections; the others voided spontaneously.

Serum PTH, calcium, and phosphorus, creatinine clearance, and phosphate clearance were measured. Calcium was determined by use of a Perkin-Elmer atomic absorption spectrophotometer. Inorganic phosphorus was determined by the method of Fiske and Subbarow. Creatinine was measured by the method of Natelson and associates, as modified for use on an autoanalyzer. Base-line alkaline phosphatase determinations were performed by the method of King and Jegatheesan. PTH was determined by a highly sensitive radioimmunoassay. Results of the assay are expressed in arbitrary units relating the potency of test sera to that of an arbitrarily selected standard hyperparathyroid serum. The range of normal is the same in children as in adults, 10 to 60 microliter equivalents per milliliter. The coefficient of variation of replicates measured at widely varying dilutions of test sera was 8 per cent.

Control values for tubular resorption of phosphate were determined in 10 children, ages 1 to 15 years, who had no evidence of renal disease, using standard clearance techniques.

RESULTS

The basic data are shown in Table I. A representative study is graphed in Fig. 1.

Base-line serum calcium concentration was normal in all but one child (M. S.), who was slightly hypocalcemic for unknown reasons. In ten normal children studied, the tubular resorption of phosphate was 88.4 ± 1.6 per cent (mean ± 1 S.D.) with a range of 85 to 94. In the patients studied, tubular resorp-
Table I. Basic data before, during, and after calcium infusion

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<th>Patient*</th>
<th>Age (yr.)</th>
<th>Sex</th>
<th>Time period†</th>
<th>Serum Ca (mg./100 ml.)</th>
<th>Serum P (mg./100 ml.)</th>
<th>TRP (%</th>
<th>PTH (µL Equiv./ml.)</th>
<th>Alkaline phosphatase (Bodansky units)</th>
<th>BUN (mg./100 ml.)</th>
<th>Creatinine (mg./100 ml.)</th>
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Normal range: Serum Ca 9.0-10.5 mg. per 100 ml. % tubular resorption of phosphate (TRP) 85-94

*All five patients were Negro.
†Time period: B = Base line; mean of two preinfusion 1 hour periods
1 = First two hours of calcium infusion
2 = Second two hours of calcium infusion
3 = First two hours after infusion
4 = Second two hours after infusion

Interpretation of phosphate was low and was regularly increased during the calcium infusion. Baseline PTH was elevated in all patients, but to a variable degree. With the calcium infusion, suppression of serum PTH was observed in four patients. In Patient M. S. the suppression was equivocal, presumably because the serum calcium level did not rise sufficiently.

**DISCUSSION**

This study shows that serum PTH is increased in vitamin D-resistant rickets, confirming the long-held view that hyperparathyroidism occurs in this disease. By contrast, Arnaud and associates have recently reported normal immunoreactive serum PTH in three of four patients whom they studied.

Interpretation of our results depends critically on the validity of the assay procedure used and on whether the degree of elevation of serum PTH demonstrated is sufficient to explain the severe phosphaturia that characterizes the disease. Assay of serum or plasma PTH in man has proved difficult. Divergent results have been reported from various laboratories. The probable explanation of these differences is that circulating PTH consists not only of the native glandular hormone but also of smaller peptides, which may
be generated either before or after secretion from the parathyroid glands.\textsuperscript{18-20} It is now known that the antiserum used in these studies recognizes at least two distinct smaller peptides in addition to the glandular hormone.\textsuperscript{21} In all probability, various antisera to PTH possess varying affinities for these peptides. Divergent assay results would thus be readily explained. Our assay system has proved exceptionally sensitive in discriminating between normal subjects, patients with primary hyperparathyroidism, and patients with hypoparathyroidism.\textsuperscript{22} The assay results are very well correlated with the expected variations of PTH in response to physiologic changes: Assayable serum PTH is suppressed during hypercalcemia and increased during hypocalcemia.\textsuperscript{23} There is every reason to believe, therefore, that the assay sensitively reflects the secretory activity of the parathyroid glands.

In this study, there was a good temporal correlation between decreasing PTH levels and increasing tubular resorption of phosphate. On completion of the calcium infusions, PTH tended to return toward baseline values despite persistent elevation of serum calcium. The inverse relationship between PTH and tubular resorption of phosphate during calcium infusions suggests that PTH was causally related to the phosphaturia. This simple explanation is not tenable. The elevation of serum PTH was usually small, approximately twice the upper limits of normal. This degree of hyperparathyroidism is in the lowest range for patients with primary hyperparathyroidism. Such patients have only mild phosphaturia. It is evident that in vitamin D-resistant rickets the phosphaturia is disproportionately severe in relation to the mild hyperparathyroidism.

If PTH plays a role in the pathogenesis of the phosphaturia of the disease, excessive renal sensitivity to the phosphaturic effects of the hormone would have to be assumed. This possibility has received some support by the clinical trials of Riggs and associates\textsuperscript{23} who obtained a cure of severe osteomalacia by parathyroidectomy in a patient with vitamin D-resistant rickets who had failed to respond to very vigorous medical management.

The pathogenesis of vitamin D-resistant rickets remains obscure, and treatment remains unsatisfactory. With the discovery that abnormal vitamin D metabolism occurs in this disease,\textsuperscript{24} it was hoped that treatment with the active metabolite of vitamin D, 25-hydroxycholecalciferol, would provide effective control. To date, this hope has not been fulfilled.\textsuperscript{25} Possibly the new active metabolite recently discovered by Gray and associates\textsuperscript{26} will prove effective. It is known that raising the serum phosphorus concentration to normal, by whatever means, effects cure of the rickets.\textsuperscript{27, 28} For this reason, oral phosphate supplements that increase the serum phosphorus concentration have received extensive clinical trials. This therapy carries with it the theoretic danger of inducing more severe hyperparathyroidism.\textsuperscript{29} There is some evidence that this in fact occurs.\textsuperscript{13, 28, 30} The oldest therapy, massive
doses of vitamin D, cures the bone disease only at the expense of some degree of hypercalcemia and is associated with the constant threat of severe vitamin D intoxication.

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Editorial comment

THE BASIS FOR the intractable hypophosphatemia in primary hypophosphatemic vitamin D-resistant rickets has been the subject of discussion since the first detailed report of this disorder by Albright and associates.\(^1\) As the result of experimental studies of renal tubular reabsorption of phosphate by Harrison and Harrison,\(^2\) it was proposed that hypophosphatemia was due to reduced renal tubular reabsorption of phosphate; this was seconded by Robertson and associates\(^3\) who studied phosphate clearances in a patient with "refractory rickets." It remained uncertain whether the low tubular resorption of phosphate in primary hypophosphatemia was the result of a primary defect in the phosphate transport system of the renal tubule, of secondary hyperparathyroidism with inhibition of phosphate transport by high levels of circulating parathyroid hormone, or of a block in a possible direct effect of vitamin D upon renal tubular phosphate transport. The late Fuller Albright supported the secondary hyperparathyroidism concept and this was generally accepted, but a clear-cut test of this hypothesis was not possible until methods for determining parathyroid hormone concentration in plasma became available. Such determinations are now possible by immunologic methods and there are now two reports of immunoreactive parathyroid hormone concentrations in the plasma of patients with untreated primary hypophosphatemic vitamin D-resistant rickets. In the first, Arnaud and associates\(^4\) reported that the immunoreactive parathyroid hormone concentrations in such patients were within normal limits unless they were treated with high phosphate loads. In the preceding paper by Lewy and associates, the results are somewhat at variance, but as the authors point out there are still uncertainties in the methodology; apparent heterogeneity of polypeptide molecules of parathyroid origin may be recognized to a different extent by the various antibody preparations used in the determination. Even with this variance, Lewy and associates agree that the moderate increase in immunoreactive parathyroid hormone concentrations found in their laboratory could not account for the extreme block in tubular resorption of phosphate, thus placing the locus for the defect in the renal tubule.

Since this paper was accepted for publication, the possibility that vitamin D or a metabolite of vitamin D might act directly on the renal tubule has been resurrected. This idea was originally propounded by us,\(^2\) but it was difficult to separate the effects of secondary hyperparathyroidism from those of vitamin D deficiency. Puschett and associates\(^5\) have found that 25-OH cholecalciferol, a metabolite of vitamin D, increases tubular reabsorption of phosphate by kidneys of parathyroidectomized dogs. Now that the secondary hyperparathyroidism basis for the hypophosphatemia of primary hypophosphatemic vitamin D-resistant rickets has become unlikely, the remaining possibilities are a primary defect of a specific renal tubule function or an error of vitamin D metabolism. If an error of vitamin D metabolism, it cannot be failure of 25-hydroxylation because 25-OH cholecalciferol is not specifically effective in the treatment of the hypophosphatemia of these patients. However, there are other metabolites of vitamin D, one of which is a product of kidney metabolism,\(^6\) and there is still a possibility that a specific vitamin D-induced factor controls tubular transport of phosphate. We can expect renewed interest in the study of this transport system in our continued efforts to understand and treat more effectively this metabolic problem.

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