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## Serum Parathyroid Hormone Levels and Renal Handling of Phosphorus in Patients with Chronic Renal Disease

MORDECAI M. POPOVTZER, WULF F. PINGGERA, MARTIN P. HUTT,  
 JOHN ROBINETTE, CHARLES G. HALGRIMSON, AND THOMAS E. STARZL

*Departments of Medicine and Surgery, University of Colorado Medical Center, Denver, Colorado*

**ABSTRACT.** In eight patients with advanced renal insufficiency (inulin clearance 1.4–9.1 ml/min), concentrations of serum calcium (S[Ca]) and phosphorus (S[P]) were maintained normal (S[Ca] > 9.0 mg/100 ml, (S[P] < 3.5 mg/100 ml) for at least 20 consecutive days with phosphate binding antacids and oral calcium carbonate. The initial serum levels of immunoreactive parathyroid hormone (S-PTH) were elevated in three (426–9230 pg/ml), normal in four (one after subtotal parathyroidectomy), and not available in one. The initial fractional excretion of filtered phosphorus ( $\frac{C_p}{C_{IN}}$ ) was high in all and ranged from 0.45–1.05. Following sustained normocalcemia and normo-phosphatemia, S-PTH was reduced below control levels in all patients; being normal in six and elevated in two.  $\frac{C_p}{C_{IN}}$  decreased below

control levels in all patients; it remained high in six (of which five had normal S-PTH) and was normal ( $\frac{C_p}{C_{IN}} = 0.01$ ) in two (of which one had elevated S-PTH). The observed relationship between S-PTH and  $\frac{C_p}{C_{IN}}$  could either reflect the inability of the radioimmunoassay for PTH employed to measure a circulating molecular species of PTH which was present in which case the actual levels of S-PTH were higher than those measured, and/or it could be indicative of the presence of additional important factor(s) (other than S-PTH) which inhibit tubular reabsorption of phosphorus in advanced chronic renal failure. (*J Clin Endocrinol Metab* 35: 213, 1972)

**T**HE DECREASED fractional tubular reabsorption of phosphorus in patients with chronic renal disease has been attributed to concurring secondary hyperparathyroidism (1–3). However, the persistence of high fractional excretion of phosphorus after parathyroidectomy (4–6), even with demonstrable normal serum level of immunoassayable parathyroid hormone (6), supports the notion that additional factors other than secondary hyperparathyroidism may play an important role in the regulation of tubular reabsorption of phosphorus in patients with advanced chronic renal insufficiency.

The fall in the fractional excretion of

phosphorus following calcium infusion has been generally interpreted as resulting from inhibited secretion of parathyroid hormone (7–9). Calcium infusion has been shown to induce a fall in circulating parathyroid hormone from a high to a lower or to a normal level in patients with advanced renal insufficiency (10–13); however, no significant change in the fractional excretion of filtered phosphorus could be demonstrated following the infusion (14).

Sustained normo-phosphatemia and normocalcemia, accomplished with phosphate restriction and the administration of large doses of vitamin D in 6 patients with chronic renal failure, was associated with an increase in fractional reabsorption of phosphorus to normal levels (3). These findings were interpreted by the authors as consistent with suppression of parathyroid hyperactivity. However, the above assumption was not

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substantiated by measurements of parathyroid hormone levels at the beginning and at the end of the study. In addition, the administration of vitamin D *per se* could have directly enhanced the tubular reabsorption of phosphorus irrespective of the variations in the level of circulating parathyroid hormone (15-18).

In the present study, normo-phosphatemia and normo-calcemia were accomplished with the administration of aluminum hydroxide gel and calcium carbonate without any supplementary vitamin D. The changes in the fractional excretion of filtered phosphorus were correlated with the levels of immunosassayable parathyroid hormone.

### Materials and Methods

Eight patients with advanced chronic renal disease of diverse etiology were studied (Table 1). The patients were not receiving diuretics or supplementary vitamin D and were not treated with dialysis. Patient H.L. showed mild radiographic changes of osteitis fibrosa cystica. Patient RI had severe osteoporosis documented by a bone biopsy with multiple rib fractures and had been subjected to subtotal parathyroidectomy four months prior to the study.

Inulin clearances were measured in all patients at the beginning and at the termination of the study. The clearance studies were conducted in a fasting state between 8 AM and 11 AM. An oral water load was given prior to the study (15 ml/kg bwt tap water). A priming dose of inulin based on the bwt was injected iv and was followed by a sustaining dose. The latter

was infused with a Sigma-motor pump delivering 1 ml of normal saline per min with inulin in an amount calculated on the basis of the presumptive glomerular filtration rate. Forty-five min were allowed for equilibration before three timed urine collections were obtained. Each urine collection lasted 30 min and a blood sample was drawn at its midpoint. The patients remained supine during the clearance study with the exception of assuming an upright position for voluntary voiding. All serum and urine specimens were assayed for creatinine, inulin, phosphorus, and calcium. Inulin (19) and creatinine (20) were determined by a Technicon Auto-Analyzer. Inorganic phosphorus was measured utilizing the methodology developed by American Monitor Company (21). Calcium was determined with the Norelco Unicam Atomic Absorption Spectrophotometer. All samples and standards were diluted with lanthanum chloride to prevent phosphate and protein interference. In addition, serum concentrations of creatinine, phosphorus and calcium, and urinary excretion of phosphorus and creatinine, were measured daily through the study.

Following the initial clearance determinations, the patients were treated with 30 ml aluminum hydroxide gel (Amphojel) every hour. As the serum concentration of phosphorus approached the normal range (serum phosphorus 2.5-3.5 mg/100 ml), the dose of Amphojel was reduced whereas calcium carbonate was started in an initial amount of 2.5-5.0 g every hr. The dose of calcium carbonate was adjusted to maintain the serum calcium concentration in excess of 9.0 mg/100 ml. This level of serum calcium and a serum phosphorus concentration below 3.5 mg/100 ml were recorded in each patient for at

TABLE 1. Clinical data of all patients

Patient	Age	Sex	Diagnosis	C <sub>IN</sub> (ml/min)	C <sub>Cr</sub> (ml/min)	Osteitis fibrosa
PR	45	F	Polyc. K.	1.4	2.3	—
DD	35	M	K-W	4.3	8.0	—
RI	45	F	Chr. PN.	3.4	6.2	—
VF	40	F	Chr. GN.	5.3	8.0	—
MS	21	F	Chr. PN.	5.4	8.2	—
HL	35	F	Chr. GN.	9.1	12.0	+
MU	34	M	K-W	4.9	7.6	—
MC	54	M	Med. C.	4.0	4.5	—

Abbreviations: C<sub>IN</sub>—inulin clearance; C<sub>Cr</sub>—endogenous creatinine clearance; F—female; M—male; Chr. GN.—Chronic glomerulonephritis; Polyc. K.—polycystic kidney disease; K-W—diabetic nephropathy; Chr. PN—chronic pyelonephritis; Med. C.—medullary cystic kidney disease.

least 20 consecutive days before the second clearance study was performed.

Serum levels of parathyroid hormone were measured by a radioimmunoassay (Hawker, C.D., and R.D. Utiger, Radioimmunoassay of Parathyroid Hormone, in preparation) at the beginning of the study and after 3 weeks of sustained normo-calcemia and normophosphatemia. In patient PV, only the final level of serum parathyroid hormone was available. The radioimmunoassay procedure for parathyroid hormone employed pure bovine parathyroid hormone (22) as standard and as labeled hormone. An antiserum was prepared by immunizing guinea pigs against partially purified bovine parathyroid hormone (prepared by gel filtration). Dextran-coated charcoal was used to separate the antibody-bound labeled hormone complex from the free-labeled hormone. The validity of the assay was established by demonstration that the line obtained with multiple dilutions of a hyperparathyroid serum was parallel to the line obtained with multiple concentrations of the bovine standard PTH. All unknown serum samples were run at three dilutions (each in duplicate) and the results for each unknown serum were compared with the results for standard hyperparathyroid and normal sera which were included in each experiment. The results for unknown sera

were accepted only when the slopes for their lines were not significantly different from the slopes of the lines for the standard sera. The results were expressed as picograms per ml (pg/ml) compared to the bovine parathyroid standard. Normal subjects ( $N = 61$ ) had a mean parathyroid hormone value of 255 pg/ml and SD of 82 pg/ml. Ninety-five percent of the sera of all normal subjects were within the range of mean  $\pm 2$  SD. Values in excess of mean  $+ 2$  SD (419 pg/ml) were considered as elevated. The antiserum employed in the present study was evaluated for its affinity for different immunoreactive forms of parathyroid hormone. It has been found that the antiserum combines with both, the large mol wt (9500) and the small mol wt (5500-7500) species of immunoreactive parathyroid hormone, however, its affinity for the former is 10-fold greater than for the latter. It is therefore possible that because of the relatively low sensitivity for the low molecular wt species, the radioimmunoassay could underestimate the concentration of the total immunoreactive parathyroid hormone in the serum.

### Results

The serum levels of calcium and phosphorus, the clearances of inulin and phos-

TABLE 2. Changes in renal handling of phosphorus and in serum levels of parathyroid hormone following sustained normo-calcemia and normo-phosphatemia

Patient	$S_{Ca}$ (mg/100 ml)	$S_P$ (mg/100 ml)	$C_{IN}$ (ml/min)	$T_P$ ( $\mu$ g/min)	$\frac{C_P}{C_{IN}}$	$S_{PTH}$ (pg/ml)
C	7.8	8.0	1.4	-5.6	1.05	—
PR N	11.2	2.4	1.2	4.6	0.84	309
C	8.0	7.1	4.3	24.4	0.92	2168
DD N	10.5	3.1	5.5	44.3	0.74	511
C	7.8	7.6	3.4	51.7	0.80	393
RI N	10.7	2.9	3.3	38.2	0.59	250
C	7.0	5.9	5.3	125.0	0.60	426
VF N	10.0	3.0	4.8	83.5	0.42	266
C	8.5	6.2	5.4	143.9	0.57	293
MS N	10.2	3.4	5.8	112.4	0.43	234
C	8.5	5.3	9.1	226.7	0.53	9230
HL N	10.5	2.4	8.0	190.0	0.01	520
C	6.0	7.4	7.2	293.0	0.45	279
ML N	9.0	2.1	5.8	120.6	0.01	262
C	8.3	8.2	4.9	76.3	0.81	382
MV N	9.7	2.9	4.6	46.7	0.65	165

Abbreviations:  $S_{Ca}$ —serum calcium concentration;  $S_P$ —serum phosphorus concentration;  $C_{IN}$ —inulin clearance;  $T_P$ —tubular reabsorption of phosphorus;  $C_P$ —phosphorus clearance;  $S_{PTH}$ —serum concentration of parathyroid hormone; C—control, N—after sustained normo-calcemia.

phorus and the serum levels of immunoreactive parathyroid hormone before treatment and after 20 or more days of sustained normo-calcemia and normo-phosphatemia, are shown in Table 2. Only two patients showed a substantial decrease in the fractional excretion of phosphorus (HL and ML). This decrease probably occurred within less than one week after starting the treatment, as judged from daily measurements of endogenous creatinine and phosphorus clearances and using the former as a rough estimate of

GFR. This early fall in  $\frac{C_p}{C_{CR}}$  was noticed as serum phosphorus reached low values (<2.5 mg/100 ml) before serum calcium increased to normal levels. The other six patients showed variable decreases, but in all the fractional excretion remained above 0.40. In

all six patients the lowest values for  $\frac{C_p}{C_{CR}}$  were observed during the maximal fall in serum phosphorus concentration even in the presence of abnormally low serum levels of calcium. A modest fall in fractional excretion of phosphorus following phosphate deprivation (without substantial changes in serum calcium concentration) was also reported by Slatopolsky *et al.* (3).

The initial serum levels of immunoassayable parathyroid hormone were elevated above normal in three patients, and were within the normal range in the remaining four. One of the latter group, patient RI, had had subtotal parathyroidectomy before the study. No significant correlation could be found between the fractional excretion of phosphorus and the level of immunoreactive hormone at the onset of the study. After sustained normo-calcemia and normo-phosphatemia, the serum level of immunoreactive parathyroid hormone decreased in all patients. In one patient, PR, the initial value was not available; however, the final one was within the normal range. In two patients with highest initial values, the decrement in

serum parathyroid hormone was most striking although the final values were still in the abnormally high range. Six patients who had normal parathyroid hormone levels at the end of the study, all except for one (ML), had fractional excretion of phosphorus in excess of 0.40. Of the two remaining patients with elevated parathyroid hormone levels, at the end of the study the fractional excretion of filtered phosphorus was normal (0.01) in one and remained elevated in the other. No correlation could be demonstrated between the level of the hormone and the fractional excretion of phosphorus at the end of the study. Likewise, there was no significant correlation between the decrements in the hormone level and the decreases in fractional excretion of phosphorus.

### Discussion

The present study demonstrated that the level of circulating parathyroid hormone as determined by our radioimmunoassay was not the principal determinant responsible for the depressed tubular reabsorption of phosphorus in 7 out of 8 patients with advanced chronic renal failure. The observed high fractional excretion of phosphorus in 5 patients with normal levels of parathyroid hormone and normal serum phosphorus concentrations on the one hand, and the normal fractional excretion of phosphorus in a patient with an elevated hormone level on the other at the end of the study leads to the following two possible alternatives.

1. The radioimmunoassay measured only a portion of the total circulating immunoreactive parathyroid hormone yielding lower values than those that actually were present. This possibility does not provide an explanation for the elevated hormone level and normal  $\frac{C_p}{C_{IN}}$  in patient HL.

The explanation for the finding of normal initial control levels of immunoassayable parathyroid hormone in 3 patients (MS, ML and MV) in the present study is not

apparent; however, normal levels were also reported previously in similar patients by other investigators (11–13). It is possible that the “normal” levels represent only a portion of the total circulating hormone because the radioimmunoassay was measuring primarily one of the two species of immunoreactive parathyroid hormone known to circulate in human plasma (23).

2. In advanced chronic renal failure factor(s) other than the level of circulating parathyroid hormone also play an important role in the diminished tubular reabsorption of phosphorus. Intrinsic tubular damage has been shown to be responsible for decreased tubular reabsorption of phosphorus in experimental unilateral acute renal failure (24). Tubular leak of phosphate has not been shown to be present in unilateral chronic kidney disease in experimental animals (1) and in humans (3). However, this is not necessarily true for all patients with chronic renal disease. Dissociation between the variations in the level of immunoreactive parathyroid hormone and the fractional excretion of filtered phosphorus has been reported in 6 kidney homograft recipients in which, following calcium infusion, suppression of parathyroid hormone secretion did not correlate with the changes in tubular reabsorption of phosphorus (25). In these patients with renal homografts residual tubular damage could be responsible for persistent phosphaturia.

The fact that extracellular volume expansion activates mechanisms which depress both the tubular reabsorption of sodium and phosphorus (26) raises the possibility that also in chronic renal failure similar association between sodium and phosphorus may exist and the same mechanism(s) may be responsible for both depressed tubular reabsorption of sodium and phosphorus (27). Moreover, recently, Weber *et al.* (28) have demonstrated, with a micropuncture technique using parathyroidectomized rats, the presence of natriuretic and phosphaturic

factor(s) in the serum of a totally parathyroidectomized uremic patient.

The difference between our results and those reported by Slatopolsky *et al.* (3), who found a uniform increase in the fractional tubular reabsorption of phosphorus to normal levels in 6 patients that maintained normal serum levels of calcium for comparable periods of time, is not readily explicable. The major difference in the procedure was the use of vitamin D in the latter study which could at least partly be responsible for the augmented tubular reabsorption of phosphorus (15–18). Also, the degree of hypophosphatemia which was attained in the latter study was more striking than in our study.

The observed decrease in the level of immunoassayable hormone in all patients is consistent with the contention that in most patients with chronic renal insufficiency, the hyperfunction of the parathyroid gland is not autonomous and is responsive to varying levels of serum calcium. Similar observations were made by other workers who demonstrated a decrease in the level of immunoreactive parathyroid hormone during calcium infusion (10–13), and with hemodialysis utilizing high calcium or high magnesium concentrations in the dialysate (29, 30). It appears, therefore, that all above-mentioned procedures may be of certain therapeutic benefit in the prevention and the treatment of secondary hyperparathyroidism in patients with chronic renal disease. However great caution should be exercised in interpreting the results of immunoreactive parathyroid hormone assays in patients with chronic renal failure. The immunological heterogeneity of circulating parathyroid hormone (31) warrants careful definition of the specificity of the antiserum employed. Furthermore, one has to be aware of the interpretive hazards amounted with the assumption that biological and immunological activities are identical if it has not, in fact, been established experimentally.

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