Kidney International, Vol. 54 (1998), pp. 2140–2145

Effect of serum phosphate on parathyroid hormone secretion during hemodialysis

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Background. Recent studies have demonstrated that a high concentration of phosphate directly stimulates parathyroid hormone (PTH) secretion. High serum levels of phosphate are usually observed in patients with end-stage renal disease. The aim of the present study was to evaluate whether serum phosphate concentration had an acute effect on PTH secretion in hemodialysis patients. The levels of serum phosphate were manipulated during the hemodialysis session by using a phosphate free dialysate or a dialysate with a high content of phosphate.

Methods. Ten stable hemodialysis patients with PTH values above 300 pg/ml were included in the study. A PTH-calcium curve was obtained during both high phosphate and phosphate free hemodialysis.

Results. The serum phosphate concentration remained high (2.17 ± 0.18 mM) throughout the high phosphate hemodialysis and decreased progressively to normal levels (1.02 ± 0.06 mM) during the phosphate free hemodialysis. The serum PTH levels at maximal inhibition by hypercalcemia (minimal PTH) were greater during the high phosphate than the phosphate free hemodialysis (413 ± 79 vs. 318 ± 76 pg/ml, $P < 0.003$). In all patients the values of minimum PTH were greater during the high phosphorus than the phosphorus free hemodialysis. The values of maximally stimulated PTH during hypocalcemia and the set point of the PTH-calcium curve were similar during the high phosphate and the phosphate free hemodialysis.

Conclusion. The maintenance of high serum phosphorus levels during hemodialysis prevented, in part, the inhibition of PTH secretion by calcium, which strongly suggests that in hemodialysis patients high serum phosphate contributes directly to the elevation of PTH levels despite normal or high serum calcium concentration.

Hyperparathyroidism is a common finding in patients with renal insufficiency. Calcitriol deficiency and phosphate retention together with hypocalcemia are the main factors involved in the pathogenesis of secondary hyperparathyroidism [1]. Phosphate retention is considered to be a key pathogenic factor because it decreases calcitriol production and interferes with the calcemic effect of PTH [2–5]. In addition, recent work demonstrates that high extracellular phosphate directly stimulates PTH secretion and gene transcription independently of the calcitriol and calcium levels [6]. The importance of phosphate retention as a cause of secondary hyperparathyroidism is illustrated by the fact that in animals and humans with renal insufficiency, dietary phosphorus restriction prevents the development of secondary hyperparathyroidism [7–12]. Furthermore, in dialysis patients in whom secondary parathyroid hyperplasia is already established, calcitriol administration fails to decrease PTH levels when the serum phosphate concentration is not controlled [13].

Almaden et al showed that, *in vitro*, a high extracellular phosphate concentration prevented the inhibition of PTH secretion by a high calcium concentration in the incubation medium [14]. Other authors have obtained similar results in *in vitro* experiments [15, 16]. Whether these findings are reproducible *in vivo* in uremic patients is unknown. This is an important question to be addressed since situations of high serum phosphate concentrations associated with hyperparathyroidism are usually present in end-stage renal disease patients.

During hemodialysis, there is a decrease in serum PTH levels caused by the influx of calcium from the dialysate to the blood. At the same time, during the first one to two hours of hemodialysis there is a decrease in serum phosphate that potentially could directly affect PTH secretion. The aim of the present study was to investigate the effect of changes in serum phosphate concentration on the dynamics of calcium regulated PTH secretion (PTH-calcium curve). To accomplish this goal, the PTH-calcium curve was determined in uremic patients during hemodialysis with and without a concomitant decrease in serum phosphate. Serum phosphate was changed by manipulating the concentration of phosphate in the dialysate.

Key words: phosphorus, PTH, hemodialysis, calcium, secondary hyperparathyroidism.

Received for publication December 5, 1997
and in revised form July 15, 1998
Accepted for publication July 16, 1998

METHODS

The study was performed in 10 stable hemodialysis patients: seven females and three males. The mean age (mean ± SE) was 62.7 ± 12 years (range 37 to 81 years), and their average length of time on dialysis was 52 months (range 5 to 120 months). All patients had serum PTH levels greater than 300 pg/ml. The serum aluminum levels were less than 50 μg/liter in nine patients and 86 μg/liter in one. Vitamin D treatment was discontinued two months before the study. Diabetic patients were excluded. To control serum phosphate, the patients received calcium carbonate or calcium acetate. Patients were on a four-hour three times per week hemodialysis schedule. The research protocol and the consent form was approved by the Hospital Ethics Committee; each patient was informed about the study and a signed consent form was obtained before entering the study.

In eight patients, the PTH-calcium curve was obtained twice: during the conventional hemodialysis using the phosphate-free dialysate (P-free) and during hemodialysis using a dialysate containing high phosphate (high-P). Thus, each patient was dialyzed in four consecutive hemodialysis sessions using the following dialysate concentrations: (*a*) low calcium (1.5 mEq/liter), high-P (1.9 to 2.6 mM); (*b*) low calcium (1.5 mEq/liter), P-free; (*c*) high calcium (3.5 mEq/liter), high-P (1.9 to 2.6 mM); and (*d*) high calcium (3.5 mEq/liter), P-free. The high phosphate dialysate was obtained by adding sodium phosphate buffer to attain the desired dialysate phosphate concentration, which was between 1.9 and 2.6 mM (values measured after dilution). Two additional patients underwent the two high calcium hemodialyses and the low calcium hemodialysis was not performed. Patients underwent the two low Ca hemodialysis first (the high-P and P-free) and three weeks later the other two high Ca hemodialysis sessions. The time period allowed between the two high or low Ca hemodialysis sessions was one week. In four patients, the P-free hemodialysis was performed first in both high and low calcium hemodialysis regimens; in the other six patients the order was reversed. The magnesium concentration in the dialysate was 1 mEq/liter.

Serum ionized calcium, phosphate, magnesium and intact PTH were determined every 30 minutes throughout the 240 minutes of the hemodialysis study. After completion of the high-P dialysis, the patients were immediately changed to a phosphate free dialysate for one additional hour. Using this maneuver, the patients completed the hemodialysis session with a phosphate level below 1.45 mM. To avoid PTH adsorption to hydrophobic membranes, cuprophan membranes were used in all cases [17].

From the data obtained during hemodialysis-induced hypocalcemia and hypercalcemia, two individual PTH-calcium curves, with and without phosphate in the dialysate, were constructed for each patient. For analysis of the PTH-Ca curves the following terms were defined [18]: (*1*) basal PTH was the predialysis PTH level; (*2*) maximal PTH was the highest PTH level observed in response to hypocalcemia with no further increase of PTH produced by an additional reduction of serum calcium. (*3*) Minimal PTH was the lowest PTH level during suppression by hypercalcemia with no further decrease of PTH produced by an additional increase of serum calcium. (*4*) The ratio of basal to maximal PTH was the basal PTH divided by the maximal PTH, and this fraction was multiplied by 100 to provide a percentage. This ratio should indicate the relative degree of PTH stimulation in the basal state, and in normal volunteers this ratio is 20 to 25% [19]. (*5*) The set point of calcium was defined as we have done in prior studies [13, 18, 20], as the serum calcium concentration at which maximal PTH secretion was reduced by 50%. (6) Basal serum calcium was the serum calcium concentration at the basal (predialysis) PTH. (*7*) The serum calcium at maximal PTH (Ca_{max}) was the serum calcium concentration at which the PTH level was first observed to be maximal or within 10% of the maximal PTH. This definition was used because the PTH-calcium curve is sigmoidal, and as the PTH value approaches the asymptotic portion of the curve a considerable variation in serum calcium can be observed during small changes in PTH. For the same reason, (*8*) the serum calcium at minimal PTH (Ca_{min}) was defined as the serum calcium concentration at which the PTH level was first observed to be minimal or within 10% of the minimal PTH.

Intact PTH was measured with an immunoradiometric assay for parathyroid hormone (Allegro; Nichols Institute, San Juan Capistrano, CA, USA). Normal values are 10 to 65 pg/ml and the range of the standard curve is 0 to 1400 pg/ml. During the low and high calcium studies, serum ionized calcium was measured at the bedside with a selective ionized calcium electrode (Ciba-Corning SA, Madrid, Spain); the normal range for ionized calcium using this method is 1.19 to 1.28. The serum phosphate, alkaline phosphatase, albumin and bicarbonate were measured by standard laboratory techniques.

Statistical analysis

The nonparametric Wilcoxon test was used to compare paired data. Differences between more than two means were evaluated by analysis of variance for repeated measures. The data are expressed as the mean ± SE.

RESULTS

Biochemical and demographical data for the patients included in the study are presented in Table 1.

Changes in serum phosphate concentration during the P-free and high-P hemodialyses are shown in Figure 1. During the regular, P-free hemodialysis, the serum phosphate decreased progressively from 2.93 ± 0.23 to 1.02 ± 0.06 mM ($P < 0.001$). At 90 minutes, the serum phosphate concentration was 1.23 ± 0.10 mM and, therefore, the

Table 1. Biochemical and demographical data

Name	Sex	Age *years*	Dialysis *months*	Etiology of ESRD	i-PTH *pg/ml*	Ca *mM*	P *mM*	Alb *g/dl*	Bicarbonate *mEq/liter*
MG	F	67	82	Renal Tumor	478	2.6	2.8	4.1	21.5
MMV	F	37	5	GN	762	2.4	1.5	4.4	20.1
BM	F	73	48	Vasculitis	712	2.4	2.0	4.5	20.5
EP	M	70	28	Vasculitis	380	2.2	2.3	4.2	21.2
ESM	F	69	108	GN	972	2.6	1.8	4.1	20.3
AZ	M	60	10	Nephroagioesclerosis	330	2.1	2.5	3.8	20.7
CQ	F	50	72	GN	780	2.5	2.6	4.0	19.8
FP	F	81	120	Unknown	1084	2.4	2.3	4.0	26.3
FM	M	55	21	GN	636	2.5	2.4	4.1	23.4
RC	F	65	32	Polycystic	314	2.5	2.2	4.2	22.1

Abbreviations are: ESRD, end-stage renal disease; i-PTH, intact parathyroid hormone; GN, glomerulonephritis; Ca, calcium; P, phosphate; Alb, albumin.

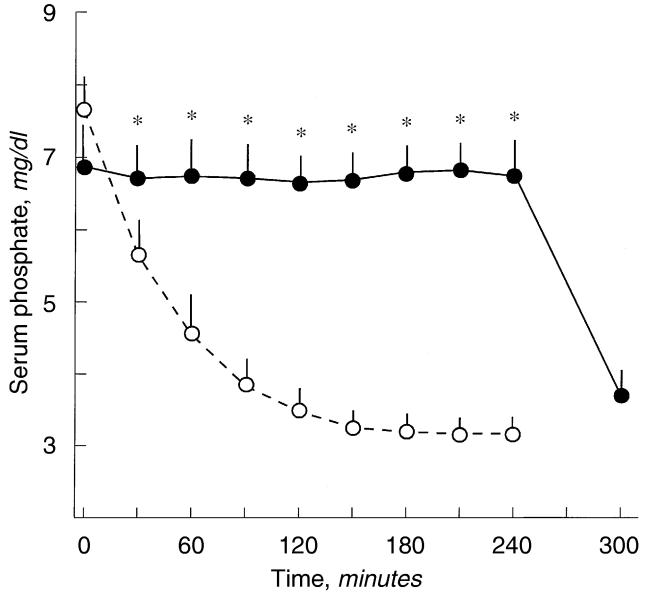

Fig. 1. Changes in serum phosphate concentration during the high phosphate hemodialysis (high-P hemodialysis; ●) and the phosphate-free hemodialysis (P-free hemodialysis; ○). Values are the mean ± SE, $N = 10$. *$P < 0.05$ versus P-free hemodialysis.

largest decrease in serum phosphate occurred during the first 90 minutes of hemodialysis. During the rest of the session the serum phosphate remained within normal levels. By contrast, during the high-P hemodialysis the serum phosphate concentration did not change significantly; the values were 2.21 ± 0.21 mM and 2.17 ± 0.18 mM before and after 240 minutes, respectively. During the last additional hour in which a P-free dialysate was used, the serum phosphate decreased to a normal level of 1.14 ± 0.22 mM ($P < 0.001$ vs. 240 min).

The parameters of the PTH-calcium curve obtained with both the high-P and the P-free hemodialysis are presented in Table 2. While the basal and maximal PTH were similar, the minimal PTH was greater during the high-P hemodialysis than the regular P-free hemodialysis 413 ± 79 versus 318 ± 76 pg/ml, $P < 0.003$. Since the maximal PTH was

Table 2. Parameters of the PTH-calcium curve

	High-P	P-free	*P*
Basal PTH *pg/ml*	617 ± 89	631 ± 86	NS
Maximal PTH *pg/ml*	1037 ± 166	991 ± 146	NS
Minimal PTH *pg/ml*	413 ± 79	318 ± 76	0.003
$PTH_{basal/max}$ %	65 ± 5	66 ± 4	NS
$PTH_{min/max}$ %	38 ± 4	30 ± 5	0.03
Set point *mM*	1.19 ± 0.03	1.17 ± 0.03	NS
Basal Ca *mM*	1.17 ± 0.04	1.15 ± 0.05	NS
Max Ca *mM*	1.06 ± 0.03	1.03 ± 0.04	NS
Min Ca *mM*	1.24 ± 0.03	1.25 ± 0.03	NS

Data are mean ± SE; ($N = 8$).

similar during both procedures, the minimal/maximal PTH ratio was greater during the high-P than P-free hemodialysis. The calcium concentration required to produce the minimal PTH (Ca_{max}) was similar with high P and P-free hemodialysis. The basal calcium, set point and Ca_{min} were also similar during both procedures. The rate of decline in serum ionized calcium was similar in both high-P and P-free hemodialysis; however, the Ca_{max} was reached after 51 ± 15 minutes in high-P hemodialysis and after 56 ± 16 minutes in the P-free hemodialysis. The rate of increase in serum ionized calcium was greater during the P-free rather than high-P hemodialysis. Thus, the Ca_{min} was reached after 81 ± 24 and 102 ± 26 minutes ($P = 0.08$) of P-free and high-P hemodialysis, respectively. According to previous experiments by others, this difference in the rate ionized calcium increased does not affect the PTH response in humans [19].

The PTH-calcium curves during high-P and P-free hemodialysis are shown in Figure 2. When the serum ionized calcium concentration was greater than 1.15 mM, the inhibition of PTH secretion was less during the high-P than the P-free hemodialysis. The individual values of minimal PTH during the high-P and the P-free hemodialysis are shown in Figure 3. Although the interindividual variation was considerable, in all cases the high-P hemodialysis produced an increase in the minimal PTH. The percent increase in the minimal PTH post-high-P hemodialysis relative to the

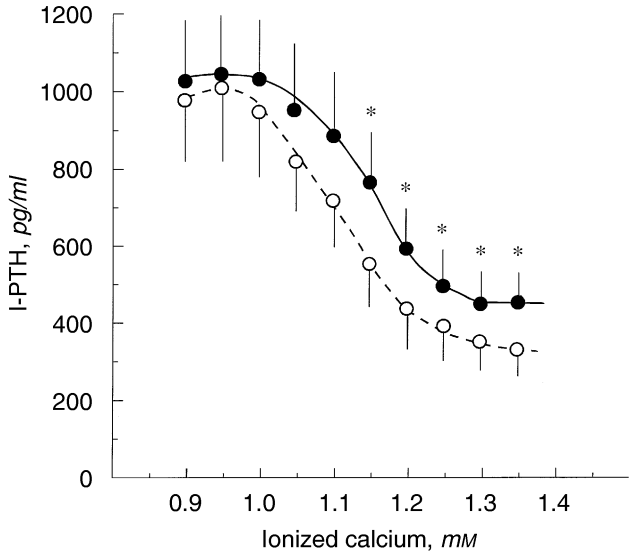

Fig. 2. The PTH-calcium curve during the high phosphate hemodialysis (high-P hemodialysis; ●) and the phosphate-free hemodialysis (P-free hemodialysis; ○). The PTH values at each calcium concentration are the means obtained from the individual PTH-calcium curves obtained in the eight patients studied. *$P < 0.05$ versus P-free HD. The mean ± SE PTH value at 1.15 mM calcium is 767 ± 131 and 554 ± 115 pg/ml for high-P and P-free hemodialysis, respectively ($P < 0.05$). Note that these values are not identical to the mean basal PTH values presented in Table 2. In Table 2 the mean basal PTH value was obtained from basal PTH values corresponding to each individual basal calcium, which varies from patient to patient. The change from each individual basal calcium concentration to a calcium of 1.15 induces a change in PTH. This explains that the mean PTH at 1.15 mM calcium is not the same as the mean basal PTH presented in Table 2.

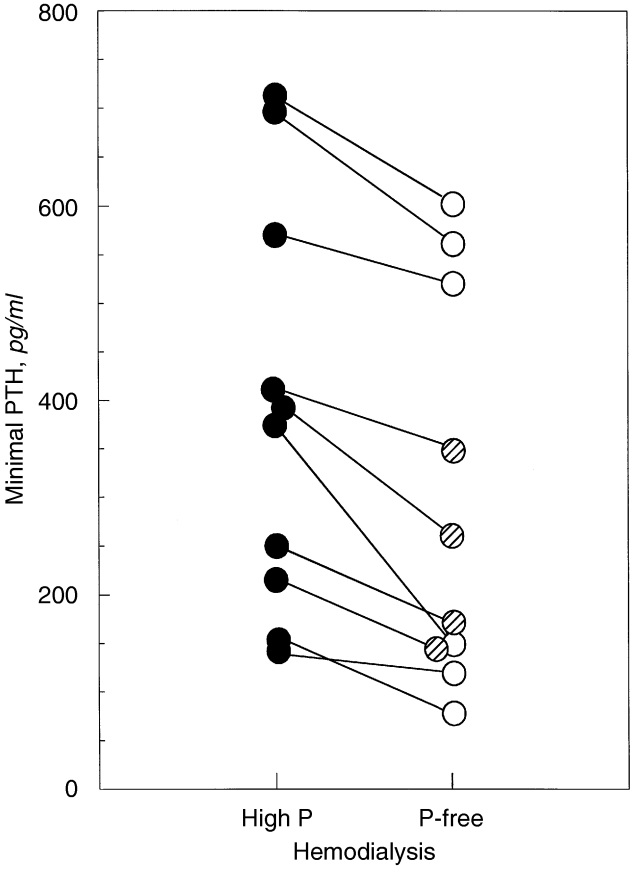

Fig. 3. Individual values of maximal inhibition of PTH secretion (minimal PTH) with hypercalcemia during the high phosphate hemodialysis (high-P hemodialysis) and the phosphate-free hemodialysis (P-free hemodialysis). Dashed circles indicates that P-free hemodialysis was performed first. In all patients the values of minimal PTH were greater during the high-P hemodialysis than the P-free hemodialysis.

minimal PTH post P-free hemodialysis was significantly correlated with the difference between serum phosphate post-high-P hemodialysis and post-P-free hemodialysis ($r = 0.666$, $P = 0.035$). None of the parameters of the PTH calcium curve showed a significant correlation with the percent increase in minimal PTH after the high-P hemodialysis.

Serum magnesium decreased during both high-P and P-free hemodialysis, and the change was similar, from 2.35 ± 0.16 mg/dl to 1.95 ± 0.14 mg/dl ($P = 0.06$) and from 2.52 ± 0.23 to 2.07 ± 0.11 ($P = 0.054$), respectively. During both the high-P and the P-free hemodialysis no statistical differences were observed at any of the sampling times.

DISCUSSION

The aim of the present study was to evaluate the effects of a high phosphate concentration on PTH secretion in hemodialysis patients. The results show that during hemodialysis, the maintenance of high serum phosphate levels by the addition of phosphate to the dialysate partially prevented the inhibition of PTH secretion by calcium. Thus, high serum phosphate was associated with an increase in the minimal PTH.

During regular hemodialysis, the high serum phosphate concentration decreases to normal levels as phosphate diffuses across the dialyzer; in our patients, the addition of phosphate to the dialysate prevented the decrease in serum phosphate. Thus, this experimental design appears to be valid to evaluate the effect of high versus normal serum phosphate concentration on PTH secretion. However, high extracellular phosphate concentration lowers the serum calcium concentration acutely; this is due to the fact that high phosphate decreases the efflux of calcium from bone [3, 21] and it may also induce precipitation of calcium in soft tissue [22]. Since low serum calcium is the main stimulus for PTH secretion, a direct effect of phosphate on PTH secretion cannot be demonstrated if the change in serum phosphate produces a concomitant change in serum calcium. In the present study, we overcame this potential methodological problem since each patient underwent a low and high calcium hemodialysis to produce progressive hypo and hypercalcemia respectively and this was repeated during both high-P and P-free hemodialysis. Therefore, the PTH secretion was evaluated at various levels of serum

calcium concentration in the presence of high and normal serum phosphate.

Our data showed that the degree of calcium induced PTH suppression was less during high-P than P-free hemodialysis. This relatively high PTH level despite hypercalcemia was attributed to the hyperphosphatemia. The fact that the increase in minimal PTH after high-P hemodialysis is proportional to the increase in phosphate contributes to demonstrate that the high phosphate is directly responsible for the increase in minimal PTH. It is known that the PLA2-arachidonic acid signaling pathway is involved in the inhibition of PTH secretion by high calcium [23]. We have shown that high phosphate inhibits arachidonic acid production [24]. These findings suggest that high phosphate affects PTH secretion in a situation of hypercalcemia.

Another potential variable that could have influenced PTH secretion was the decrease in serum magnesium concentration [25] usually observed during hemodialysis [26]. However, in our patients the decrease in magnesium was similar during the high-P and P-free hemodialysis. Thus, the high PTH levels during high-P hemodialysis were not due to differences in magnesium concentration.

Recent work has demonstrated a direct effect of phosphate on PTH secretion [14–16], gene expression [6, 27, 28] and parathyroid cell proliferation [15, 29–32]. A direct effect of extracellular phosphate in the regulation of parathyroid cell function seems reasonable based on these experimental studies; however, a direct effect of phosphate on PTH secretion in hemodialysis patients has not been previously reported. Although the long-term increase in serum phosphate increases PTH levels in only 50% of the patients [33], it is known that in predialysis patients a decrease in serum phosphate is followed by a reduction in PTH levels [34]. Furthermore, in hemodialysis patients with secondary hyperparathyroidism and hyperphosphatemia, the PTH levels fail to decrease in response to calcitriol therapy [13, 35]. This lack of response may be explained by the stimulatory effect of high phosphate on parathyroid cells.

In conclusion, during hemodialysis, the high serum phosphate level prevented the inhibition of PTH secretion by calcium, which strongly suggests that in dialysis patients the high serum phosphate contributes directly to the elevation of PTH levels despite normal or high serum calcium concentration.

ACKNOWLEDGMENTS

The work was supported in part by a grant from the government (PM95-0184) and the Extramural Grant Program from Baxter.

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