Elevation of Serum Phosphate Affects Parathyroid Hormone Levels in Only 50% of Hemodialysis Patients, Which Is Unrelated to Changes in Serum Calcium\textsuperscript{1,2}

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ABSTRACT

Hyperphosphatemia is said to cause hyperparathyroidism either by depressing the plasma levels of ionized calcium and/or by affecting serum 1,25(OH)\textsubscript{2} vitamin D\textsubscript{3} levels. Direct evidence that hyperphosphatemia contributes to hyperparathyroidism in hemodialysis patients is unclear because previous published data are with older parathyroid hormone (PTH) assays. Phosphate was added to the dialysate of 15 patients for 12 wk whose predialysis serum phosphates were between 1.5 and 1.9 mM (4.7 to 5.9 mg/dL) in order to further increase their serum phosphate by 0.75 mM (2.4 mg/dL) without adjustments in other medications. No patient was on vitamin D therapy. In half of the patients, PTH levels remained unchanged (nonresponders; 214 ± 64 versus 219 ± 60 ng/L), whereas in the other patients, PTH rose from 204 ± 53 to 338 ± 60 ng/L (P < 0.05; responders). The degree of induced hyperphosphatemia was virtually identical in both groups, 1.7 mM increasing to 2.4 mM. Ionized calcium was unchanged in both groups after phosphate. Plasma 1,25(OH)\textsubscript{2} vitamin D\textsubscript{3} levels were low to start with and remained low throughout. Nonresponders had been on dialysis twice as long as responders and had consumed over seven times more aluminum salts. Nonresponders had higher postdeferoxamine increments in plasma aluminum (3,588 ± 1,466 versus 603 ± 390; P < 0.05), although neither these amounts nor plasma levels were in the toxic range. In conclusion, (1) phosphate affects PTH in only 50% of hemodialysis patients; (2) these effects are independent of changes in plasma levels of ionized Ca\textsuperscript{2+} and 1,25(OH)\textsubscript{2} vitamin D\textsubscript{3}; (3) the mechanism for PTH changes after this hyperphosphatemia must reside therefore in either bone or PTH glands themselves; (4) resistance to the effects of hyperphosphatemia may be related to aluminum accumulation and occurs in 50% of patients.

Key Words: Hyperphosphatemia, hyperparathyroidism, 1,25(OH)\textsubscript{2} D\textsubscript{3}

For decades, nephrologists have attempted to rigidly control the serum phosphate in dialysis patients in the belief that renal bone disease, specifically hyperparathyroidism, will be ameliorated. However, direct evidence for this beneficial effect is lacking.

All descriptions and reviews of the subject ascribe a pivotal role for the hyperphosphatemia-induced reductions in serum ionized calcium (by precipitation) in stimulating parathyroid hormone (PTH) production (i.e., the "trade-off hypothesis") (1–4). The evidence for this phenomenon was based on early studies in which calcium phosphate deposition in tissues was widespread (5). However, this occurred in the early days of dialysis in which phosphate was poorly dialyzed, as verified by the fact that 40% of those patients had very high serum phosphates (i.e., above 2.9 mM [mg/dL]) (5). Serum phosphates in more recent studies are usually 1.7 to 2.3 mM (5.2 to 7 mg/dL), and clinical tissue calcification is now seldom, if ever, mentioned (3,4,6–8). In contrast to the trade-off hypothesis, increasing phosphate concentration in serum, \textit{in vitro}, within the usual range found in dialysis patients, does not reduce the ionized calcium concentration (9). Indeed in normal subjects, \textit{in vivo}, a very large increase in serum phosphate (2.2 mM) is needed to reduce total serum calcium by 0.18 mM (10).

If, then, calcium phosphate precipitation is not a mechanism for phosphate-induced hyperparathyroidism, how does phosphate restriction work? There is no doubt that in early/moderate chronic renal failure, phosphate restriction reduces PTH activity; however, this is independent of changes in serum phosphate (11) and is considered to be due to phosphate-induced increases in 1,25(OH)\textsubscript{2} D\textsubscript{3} production, leading to PTH suppression (12). However, this mech-
anism is most unlikely to be effective in dialysis patients in whom blood levels of 1,25 \( \text{OH}_2 \) D$_3$ are invariably low (7) and, on account of renal destruction, are unlikely to be able to be stimulated.

The direct evidence that phosphate reduction in dialysis patients significantly improves hyperparathyroidism is tenuous. One early and widely quoted study, purporting to demonstrate the importance of phosphate reduction, showed that PTH levels fell from 35 to 28 times normal with a reduction in serum phosphate (13); it is hard to imagine that this confers therapeutic benefit. In another report, PTH levels did not change when the serum phosphate was brought into the normal range in dialysis patients (14). These and most other similar studies have been with older PTH assays, which often measure PTH fragments. There are no reports of the effects of phosphate on PTH values in dialysis patients with an immunoradiometric assay specific for intact hormone (which has been shown to be reliable and sensitive to changes in serum calcium concentration [15,16]).

Because most of our therapeutic effort and expense in trying to lower the serum phosphate in dialysis patients is centered around those in whom the serum phosphate is between 1.5 and 2.5 mM (5 and 8 mg/dL), we investigated whether a patient with chronic mild hyperphosphatemia would have worse hyperparathyroidism if the serum phosphate was further elevated (thereby justifying therapeutic intervention) and whether this effect was mediated by changes in serum calcium, we achieved this elevation of serum phosphate in dialysis patients with an immunoradiometric assay specific for intact hormone (which has been shown to be reliable and sensitive to changes in serum calcium concentration [15,16]).

Phosphate was added to the dialysate to increase the predialysis serum phosphate by approximately 0.75 mM (2.4 mg/dL). Predialysis serum phosphates were determined at each dialysis until the desired increment was produced, and was usually obtained within 3 wk. Weekly serum phosphates were then obtained over the next 10 to 12 wk, with minor adjustments in the amount of phosphate added to maintain steady blood levels. In almost all patients, no adjustments were needed over the last 7 wk of the study.

Within 6 wk from the end of this study period, prededeferoxamine (DFO) and post-DFO infusion serum aluminum levels were determined. DFO was infused at 40 mg/kg over 2 h at the end of a dialysis, with predialysis serum aluminum repeated at the next dialysis. Aluminum medications were discontinued during the test.

The results given in the text are from the following determinations: pre–serum phosphate is the mean of three weekly predialysis values obtained before phosphate was added to the dialysate, and post–phosphate addition phosphate is the mean of three predialysis phosphate values at weekly intervals during 10 to 12 wk of phosphate addition. PTH values are the mean of two values obtained 1 to 3 wk before phosphate addition and similarly at weeks 10 and 12 (postphosphate addition values). Ionized calcium values were taken at exactly the same time as the serum phosphates described above. Plasma 1,25 \( \text{OH}_2 \) D$_3$ and aluminum levels were taken 1 wk before phosphate addition and at the 12th week (one determination for each period).

Serum phosphate, creatinine, and alkaline phosphatase were determined by autoanalyzer, and ionized calcium was determined by ion-specific electrode (Ciba-Corning Co., Ontario, Canada). Intact PTH hormone and 1,25 \( \text{OH}_2 \) D$_3$ were measured by RIA (Nichols Institute, San Juan Capistrano, CA), and serum aluminum was measured by atomic absorption spectrophotometry. The normal values for Ca$^{2+}$, PTH, 1,25 \( \text{OH}_2 \) D$_3$, and aluminum levels are 1.17 to 1.32 mM, 15 to 66 ng/L, 15 to 45 pg/mL, and 0 to 222 mM, respectively. The lower limit of detection of 1,25 \( \text{OH}_2 \) D$_3$ is 7 pg/mL. All data are expressed as mean ± SE.

**STATISTICS**

Patients whose PTH values did not vary more than the coefficient of variation for the assay (8%) after serum phosphate elevation were classified as nonresponders. The rise in PTH in responders after phosphate was compared with baseline values by paired \( t \) test, as were the pre- and post–serum Ca$^{2+}$ and phosphate in both groups. For other data, responders and nonresponders are compared by use of a two-tailed two-sample \( t \) test, with the exception of 1,25 \( \text{OH}_2 \) D$_3$ levels. Because the vast majority of patients...
has 1,25(OH)_{2}D_{3} levels below normal, many of these being below the limits of accurate measurement, comparison of the proportion of patients below the normal range before and after serum phosphate elevation was made.

RESULTS

Serum phosphate was raised by a mean of 0.71 ± 0.12 mM. In 8 of the 15 patients, serum PTH did not change (nonresponders), whereas in the remaining 7 patients, PTH rose by 58% (Figure 1). The smallest percent rise in PTH in this group was 38%. The baseline (prephosphate elevation) level of PTH was virtually identical in both nonresponders and responders (214 ± 64 versus 204 pm 53 ng/L, respectively). The baseline serum phosphates and their further elevations were virtually identical in both groups (Table 1).

No change in serum Ca\textsuperscript{2+} occurred in either group after the elevation of serum phosphate, and there was no difference in serum Ca\textsuperscript{2+} values at baseline and postphosphate addition (Table 1).

In an attempt to identify possible differences that could be associated with responder versus nonresponder status, various data were obtained and compared. There were no differences between age, hemoglobin, alkaline phosphatase, and predialysis serum creatinines (Table 2). There was a marked difference in the duration of hemodialysis between the groups, nonresponders having been on dialysis more than twice as long as responders (35 ± 5.4 versus 16 ± 4 months; \( P < 0.01 \)). Not surprisingly, therefore, the total intake of oral aluminum was considerably higher in the nonresponders group (Table 2). However, the eightfold higher aluminum dosage was much higher than expected from the twofold increased duration of dialysis. It should be pointed out that, although these data represent a retrospective search of pharmacy records, in our unit, all drugs are issued by our own pharmacy free of charge to all of our patients and a careful record of all refills were kept so that these numbers are reasonably accurate. Serum aluminum levels tended towards higher levels in the nonresponders, but this

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<th>TABLE 1. The effects on serum Ca\textsuperscript{2+} and phosphate of the addition of phosphate to the dialysate</th>
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| \begin{tabular}{lcc}
| Phosphate (mM) (Pre) | 1.66 ± 0.1 | 1.7 ± 0.1 \\
| Phosphate (mM) (Post) | 2.38 ± 0.07\textsuperscript{a} | 2.39 ± 0.15\textsuperscript{a} \\
| Ca\textsuperscript{2+} (mM) (Pre) | 1.14 ± 0.02 | 1.16 ± 0.01 \\
| Ca\textsuperscript{2+} (mM) (Post) | 1.11 ± 0.02 | 1.16 ± 0.02 |
\end{tabular} |

\textsuperscript{a} \( P < 0.01 \) pre versus post.

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<th>TABLE 2. Demographics and serum values in responders and nonresponders</th>
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| \begin{tabular}{lcc}
| Creatinine (mM) | 860 ± 51 | 738 ± 60 \\
| Aluminum (mM) | 1,226 ± 356 | 615 ± 230 \\
| Total Dose of Aluminum (g) (Post-Pre) | 671 ± 220 | 86 ± 45\textsuperscript{a} \\
| DFO Aluminum (nM) \textsuperscript{b} | 3,588 ± 1,466 | 603 ± 390\textsuperscript{c} \\
| Alkaline Phosphatase (U/L) | 146 ± 21 | 111 ± 15 \\
| Hemoglobin (g/L) | 89 ± 0.8 | 92 ± 0.7 \\
| Duration of dialysis (months) | 35 ± 5.4 | 16 ± 4\textsuperscript{a} \\
| Age (yr) | 70 ± 3.5 | 68 ± 3 \\
| HCO\textsubscript{3\textsuperscript{-}} (mM) | 26 ± 0.8 | 20 ± 1.9\textsuperscript{b} |
\end{tabular} |

\textsuperscript{a} \( P < 0.01 \), nonresponders versus responders. 
\textsuperscript{b} (Post-Pre), before and after the addition of phosphates. 
\textsuperscript{c} \( P < 0.05 \), nonresponders versus responders.

of charge to all of our patients and a careful record of all refills were kept so that these numbers are reasonably accurate. Serum aluminum levels tended towards higher levels in the nonresponders, but this

Figure 1. The effects of elevating the serum phosphate on serum PTH. Individual and mean values are given before and after (Pre and Post) the addition of phosphate.
was not statistically significant (Table 2). The rise in serum aluminum post-DFO was significantly higher in the nonresponders (3.588 ± 1.466 versus 605 ± 390 nM; *P* < 0.05).

All of the above data (Table 2) are from the pre-phosphate addition period with the exception of DFO infusion data, which were obtained 2 to 6 wk after the study was completed. There were no changes in mean serum bicarbonate or aluminum levels during the course of the study.

With regard to 1,25 (OH)₂ D₃ levels, all but one patient had baseline levels below normal, the level in that patient being low normal (17 pg/mL). In the nonresponders, six of the seven samples (the samples from one patient were spoiled), were below normal (and three of these were below 7, which is the lower limit of accurate assay) before the addition of phosphate. After the phosphate addition, six of the seven samples were below normal (four of these were below seven). The corresponding figures in the responder group were seven of seven below normal (four with levels below seven) before phosphate addition and seven of seven below normal (four with levels below seven) after phosphate. In other words, 1,25 (OH)₂ D₃ levels were far below normal and remained so throughout the study (Figure 2).

PTH data were available in five of seven responders 8 to 12 wk after the end of the study (one patient having been transplanted, another having been transferred to another center). The PTH value fell to 231 ± 52 ng/L, a value no different than the control value (204 ± 53). Similarly, PTH values remained unchanged in the nonresponders at that time (228 ± 49 ng/L).

**DISCUSSION**

These results demonstrate that raising the serum phosphate in chronic hemodialysis patients has a variable effect of PTH levels, with half of the patients showing no response. Furthermore, regardless of PTH response, phosphate elevation does not reduce the serum ionized calcium. Because serum 1,25 (OH)₂ D₃ levels did not change with phosphate elevation and the levels were the same in both responders and nonresponders, then the effects of phosphate on PTH in dialysis patients are not mediated via renal production of 1,25 (OH)₂ D₃. Our results are similar to recent findings in the dog with advanced renal failure (18).

We did not measure postdialysis serum values because these are unlikely to be contributory for the following reasons: at the dialysate concentration of calcium used (1.55 mM), minimal net calcium transfer occurs so that ionized calcium levels change minimally with small PTH changes (19); the latter is expected to be transient because of the very short (i.e., minutes) half-life of PTH.

The role of phosphate elevation in the hyperparathyroidism in renal failure is unclear. The classical trade-off hypothesis (1,2) assumed that ionized calcium levels fall after phosphate elevation, giving rise to the stimulation of PTH production. There is, however, considerable evidence against this hypothesis. Adding phosphate *in vitro* has little effect on ionized calcium (9). In early renal failure, before serum phosphate rises, phosphate restriction reduces PTH production without changes in serum calcium or phosphate (11).

![Figure 2](image_url) Plasma 1,25 (OH)₂ D₃ before and after phosphate addition to the dialysate. N, lower limit of normal; L.L.D., lower limit of detection. Note that datum points below the L.L.D. are shown for descriptive purposes but do not represent numerical values.
The mechanism for the reduced PTH production after phosphate restriction in early renal failure is now considered to be due to increased 1,25 (OH)₂ D₃ production (12). Renal cortical cells change from 24,25 (OH)₂ D₃ to 1,25 (OH)₂ D₃ production when phosphate concentration falls (20). 1,25 (OH)₂ D₃ has a significant suppressant effect on PTH production at the level of gene transcription (21). However, recent evidence in humans contradicts the above and suggests that 1,25 (OH)₂ D₃ production is unchanged by phosphate restriction in early renal failure (22). Furthermore, in more advanced renal failure, it is unlikely that the grossly reduced renal mass could significantly increase its production of 1,25 (OH)₂ D₃ after phosphate restriction. Indeed, this has been shown in (predialysis) humans (23) and in the rat (24) with severe uremia, where 1,25 (OH)₂ D₃ levels remain unchanged after phosphate restriction. Our results confirm for the first time in dialysis patients the lack of a role of 1,25 (OH)₂ D₃ in mediating phosphate-induced changes in PTH; these levels remained low after phosphate addition without any difference in levels between those in whom PTH responded to phosphate addition and those in whom there was no such response.

If, then, neither the ionized calcium nor the 1,25 (OH)₂ D₃ levels change, what is the mechanism for the effects of phosphate restriction on PTH production in dialysis patients, and as a corollary, what is the reason for the lack of response? Indeed, what is the evidence for phosphate-induced hyperparathyroidism in dialysis patients? Although considerable published data purport to show a beneficial effect of phosphate restriction for a variety of reasons, these data and their interpretation are open to question. In one early report (13) PTH values fell with phosphate restriction but to values still 28 times normal, conferring dubious therapeutic advantage. In addition, those data were based on "old" (i.e. 1971) PTH assays. Contrary evidence exists, showing no reduction in PTH levels after lowering of serum phosphate (14); the unexpected results in that study are surprising because of the additional observation that serum aluminum levels more than doubled as phosphate was lowered by aluminum salts, aluminum being a well-known suppressant of PTH production (25). In one study, widely quoted as evidence for an effect of phosphate on PTH production, the majority of the patients studied with advanced (predialysis) renal failure had normal serum PTH values before their serum phosphates were reduced; therefore, the relevance of a fall in PTH values in that series is unclear (23). Although there are considerable data comparing various phosphate-reducing agents and vitamin D therapy on PTH production (26), because the therapy itself (e.g., aluminum, vitamin D) could have independent effects on PTH, the role of phosphate reduction itself on PTH production has never been directly proven in dialysis patients. The above factors led to the design of our study, in which only the serum phosphate was varied and clearly only about one half of the patients showed a change in their PTH levels.

Skeletal resistance to the action of PTH is probably an etiologic factor for secondary hyperparathyroidism in chronic renal failure (27). Several postulated mechanisms for this include phosphate retention and changes in bone PTH receptors and bone aluminum content. With regard to the role of phosphate retention, it has been shown in the rat that an increase in the serum phosphate produces skeletal resistance to the calcemic action of PTH (24,28). However, in the dog, unlike the rat, PTH resistance is not restored by phosphate restriction (29). The ambient phosphate concentration in bone may be a factor in the amount of exchangeable calcium that can be mobilized by PTH, a higher phosphate leading to reduced calcium release. This has been shown in osteoclasts (30) and in the perfused rat tail preparation (31). Chronically raised PTH levels may induce down-regulation of bone receptors, leading to diminished calcemic response to PTH (32). Thus, thyroparathyroidectomy restores the calcemic effect of PTH (24,30). Our results suggest that a time factor for PTH responsiveness to hyperphosphatemia is important, but whether the above mechanisms play a role is unclear.

Whether our finding of a lower plasma bicarbonate in responders is relevant is unclear, but it has been shown that osteoclastic and osteoblastic activities are responsive to changes in pH (33). Of theoretical interest is the possibility that free serum aluminum concentration would be decreased by a lower plasma bicarbonate, thereby reducing aluminum-induced PTH suppression.

Although the described role of aluminum in renal osteodystrophy is usually focused on the direct damage to bone by deposition of aluminum, as well as an inhibitory effect on PTH production, evidence exists for a diminished calcemic response to PTH in uremic animals loaded with aluminum (34,35). In our patients, both the duration of dialysis and the total dosage of aluminum were increased in those patients in whom PTH did not respond to the phosphate increase. It is known that stainable aluminum increases with time on dialysis (36). Unfortunately, we do not have bone morphology for these patients. However, the much greater post-DFO infusion aluminum levels in nonresponders is good evidence for greater bone accumulation in these patients. It is noteworthy that the actual levels of baseline serum aluminum as well as post-DFO increment, although raised, are not at the levels usually assumed to represent severe body burden of aluminum (37). Our results, therefore, are strongly suggestive of a role for aluminum...
in lack of responsiveness, but further data are needed. The implications for these findings is significant; modest doses of aluminum may, after all, be reasonable therapy for the control of hyperparathyroidism.

The possibility remains that PTH responsiveness is due to subtle chronic changes within the parathyroid glands themselves that might be related to the duration of dialysis and/or to aluminum stores. Whether phosphate affects PTH itself is controversial; evidence exists for (38) and against (39) such an effect. Whatever the signal might be is conjectural; however, it is clearly neither the circulating blood levels of ionized calcium nor 1,25(OH)2D3.

ACKNOWLEDGMENTS

This work was supported by the St. Boniface Hospital Research Foundation, Winnipeg, Canada. 1,25(OH)2D3 levels were kindly measured by M. Gratton, Royal Victoria Hospital, Montreal.

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