Original Article

Effects of oral phosphorus supplementation on mineral metabolism of renal transplant recipients

Francisco Caravaca, María A. Fernández, Rosa Ruiz-Calero, Juan Cubero, Angel Aparicio, Francisca Jimenez, María C. García

S. Nefrología, Hospital Universitario Infanta Cristina, Badajoz, Spain

Abstract

Background. Persistent hyperparathyroidism (HPT) is frequently observed in kidney transplant recipients. Hypophosphataemia is a common biochemical consequence of HPT. Theoretically, oral phosphorus administration may induce negative effects on the control of HPT, though this point has never been demonstrated in kidney-transplant recipients. This study was designed to evaluate the effects of oral phosphorus supplementation on the mineral metabolism of successful kidney transplant recipients.

Methods. Thirty-two kidney transplant recipients with serum creatinine <2 mg/dl and serum phosphate levels <3.5 mg/dl were included in the study. After a washout period in which oral phosphorus supplementation was discontinued, the following parameters were determined (F0 period): serum calcium, phosphate, alkaline phosphatase, uric acid, bicarbonate, PTH, 1,25-dihydroxyvitamin D3 (1,25(OH)2D) and 25-hydroxyvitamin D3 (25OHD). Creatinine clearance, calcium, and phosphate excretion were determined from a 24-h urine sample. The same determinations were repeated (F1 period) after all patients received 1.5 g of oral phosphorus for 15 days. For data analysis, patients were divided into two subgroups (optimal and suboptimal) according to allograft function (Ccr > or < 70 ml/min/1.73 m2).

Results. In the F0 period, only nine of 32 patients had PTH levels within the normal range (<65 pg/ml). The mean concentrations of PTH, 1,25(OH)2D and 25OHD were 132 ± 97 pg/ml, 40.5 ± 16 pg/ml and 12.5 ± 8.2 ng/ml respectively. Phosphorus supplementation led to significant reductions in serum calcium and 1,25(OH)2D concentrations, as well as in urinary calcium excretion in the whole group. On the contrary, serum phosphate, PTH, and urinary phosphate excretion increased significantly. The percentage increase in PTH concentrations after phosphorus supplementation were similar in patients with optimal and suboptimal allograft function (33 vs 36%). The reduction of 1,25(OH)2D concentrations after phosphorus supplementation was observed mainly in the subgroup with optimal allograft function (21% reduction with respect to baseline values), while the mean 1,25(OH)2D concentrations in patients with suboptimal allograft function scarcely changed (1.4% increase). Changes in 1,25(OH)2D concentrations after phosphorus supplementation, expressed as a percentage of the initial concentrations, correlated positively with the percentage changes in PTH concentrations for the whole group, as well as for each subgroup. The best determinants for the percentage and the absolute increase in PTH concentration after phosphorus supplementation was the final serum phosphate concentration (F = 4.84, r = 0.37, P = 0.035) and the increase in serum phosphate (F = 7.69, r = 0.45, P = 0.009) respectively.

Conclusions. Oral phosphorus supplementation led to a significant increase in the PTH concentration of kidney transplant recipients. The mean 1,25(OH)2D concentration decreased mainly in recipients with optimal allograft function. The counterbalance effect of PTH on 1,25(OH)2D production may account for the relative preservation of 1,25(OH)2D levels in recipients with suboptimal allograft function.

Key words: kidney transplantation; phosphate; secondary hyperparathyroidism; vitamin D

Introduction

A large proportion of patients with successful kidney allografts have persistent hyperparathyroidism [1–3]. In addition to the negative effects on bone mineralization and bone-related complications after transplantation [4,5], persistent hyperparathyroidism is one of the main causes of the hypophosphataemia frequently observed in these patients. Oral phosphate supplementation is, therefore, a common practice in many transplant units.

Phosphorus plays a key role in mineral metabolism. Phosphorus restriction and hypophosphataemia stimulate renal 1-alpha-hydroxylase [6–9]. On the contrary,
a large oral intake of phosphorus can reduce intestinal calcium absorption and 1,25-dihydroxyvitamin D3 production \((1,25(OH)_2D)\) \([6–10]\). Hyperphosphataemia may also be a major stimulus for PTH synthesis and secretion \([11–14]\). PTH \([15–17]\) and renal function \([17–20]\) are also involved in the regulation of \(1,25(OH)_2D\) production. Thus the multiple interactions among these elements obscure their respective roles in the pathogenesis of secondary hyperparathyroidism.

Although the potential negative effect of phosphorus supplementation on renal transplant recipients has long been suggested \([21]\), as far as we know it has never been demonstrated. This study was designed to investigate the effects of phosphorus supplementation on mineral metabolism in a group of patients with successful kidney allografts.

### Subjects and methods

The study group consisted of 32 patients (mean age 50 ± 12 years, 15 females). The mean elapsed time since transplantation was 4 ± 8 months (range 7–74 months). Criteria for inclusion in the study were: stable allograft function with a serum creatinine concentration consistently < 2 mg/dl and a serum phosphate concentration equal or < 3.5 mg/dl at the time of the study.

None of the patients had acute or chronic inflammatory, infectious, tumoral, or liver diseases, diabetes, or proteinuria greater than 1 g/24 h. All of them were on triple immunosuppressive therapy, maintaining plasma cyclosporin levels within the normal therapeutic ranges. Prednisone was prescribed to all patients at the maintenance dosage of 10 mg/day. None of them received allopurinol, anticonvulsants, vitamin D supplements, antacids, or other drugs known to affect mineral metabolism. Only three patients received diuretics (furosemide 40 mg/day).

The design of the study was prospective. Baseline (F0 period) determinations were taken after a wash-out period in which phosphorus supplements were withdrawn for 1 month in those patients who were on this treatment. Patients received 1 g per day of oral neutral phosphate (Phosphorus Sandoz® 750 mg tablets, b.i.d) after the two main meals for 15 days. They were advised to continue with their habitual diets during these 15 days. After this period, the same determinations were repeated in each patient (F1 period).

The following parameters were determined in blood samples: creatinine, uric acid, total calcium corrected to albumin, phosphate, alkaline phosphatase (Hitachi autoanalyser, Boehringer, Germany), serum bicarbonate, PTH (7–84 molecule IRMA, Incstar Co. Stillwater, USA), 25 hydroxycholecalciferol and 1,25 dihydroxycholecalciferol (RIA Incstar, Boehringer, Germany), serum bicarbonate, PTH (7–84 molecule IRMA, Incstar Co. Stillwater, USA), 25 hydroxycholecalciferol and 1,25 dihydroxycholecalciferol (RIA Incstar Co.). The inter- and intra-assay variabilities for 1,25 dihydroxycholecalciferol (1,25(OH)_2D) at a concentration of 12 pg/ml were 15.1 and 12.5% respectively, and at a concentration of 45–50 pg/ml were 13.6 and 9.5% respectively. The intra-assay variabilities for PTH and 25OHD were < 6% and 8% respectively.

The PTH concentrations obtained immediately before kidney transplantation were available in all patients. In a 24-h urine sample, creatinine, calcium, and phosphate excretions were also determined. All blood samples were taken in the morning after a fasting period of at least 8 h. Renal function was assessed by creatinine clearance corrected for a body-surface area of 1.73 m². Although all patients had serum creatinine concentrations less than 2 mg/dl, creatinine clearances varied widely, and in order to define optimal and suboptimal allograft function, a creatinine clearance of 70 ml/min/1.73 m² was considered as the cut-off point. The study was performed during January and February 1997.

### Statistical analysis

Differences between the means of the biochemical parameters before and after phosphorus supplementation were evaluated by paired-sample t test, and independent samples t test was utilized for comparisons of parameters between subgroups. The correlation between continuous variables was measured with Spearman’s rank correlation coefficient (r) and found to be statistically significant.

### Results

#### Biochemical characteristics at baseline

The biochemical characteristics of patients at baseline are summarized in Table 1. In the F0 period, nine patients had PTH levels within the normal range (<65 pg/ml). The mean 1,25(OH)_2D and 25OHD levels were 40.5 ± 16 pg/ml and 12.5 ± 8.2 ng/ml respectively. Although the mean 25OHD concentrations were within the normal range for the season in which the study was performed, several determinations fell below the lower normal limit. However, 1,25(OH)_2D and 25OHD did not correlate significantly (r = 0.18, P = 0.30).

In the F0 period, PTH concentrations correlated with pre-transplant PTH concentrations according to the equation: PTH post-Tx = 55.7 + 0.1438 PTH prep-Tx, (r = 0.67, P < 0.0001). PTH concentrations did not correlate with the time elapsed since transplantation (r = 0.082).

Table 1. Biochemical characteristics for the whole group at baseline (F0) and after phosphorus supplementation (F1)

<table>
<thead>
<tr>
<th></th>
<th>F0</th>
<th>F1</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.23 ± 0.34</td>
<td>1.23 ± 0.34</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>79 ± 21</td>
<td>82 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>10.53 ± 0.90</td>
<td>10.23 ± 0.70</td>
<td>0.0003</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>2.62 ± 0.58</td>
<td>3.37 ± 0.80</td>
<td>0.0001</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>199 ± 88</td>
<td>187 ± 77</td>
<td>NS</td>
</tr>
<tr>
<td>(mU/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum uric acid (mg/dl)</td>
<td>6.5 ± 1.3</td>
<td>6.3 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/l)</td>
<td>24.6 ± 1.5</td>
<td>23.8 ± 1.7</td>
<td>0.0025</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>132 ± 97</td>
<td>172 ± 138</td>
<td>0.0001</td>
</tr>
<tr>
<td>1,25(OH)_2D (pg/ml)</td>
<td>40.5 ± 15.9</td>
<td>33.8 ± 12.8</td>
<td>0.0006</td>
</tr>
<tr>
<td>25OHD (ng/ml)</td>
<td>12.4 ± 8.2</td>
<td>12.1 ± 7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary calcium (mg/24 h)</td>
<td>189 ± 10.6</td>
<td>122 ± 7.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Urinary phosphorus (mg/24 h)</td>
<td>824 ± 332</td>
<td>1668 ± 478</td>
<td>0.0001</td>
</tr>
<tr>
<td>TPR/GFR (%)</td>
<td>70.5 ± 11.6</td>
<td>52 ± 13.7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Twenty-two patients had a creatinine clearances/1.73 m² > 70 ml/min (optimal allograft function) and 11 patients had a creatinine clearance ranging between 46 and 69 ml/min/1.73 m² (mean 58 ± 7 ml/min) (suboptimal allograft function).

Patients with optimal allograft function had significantly lower PTH and higher 1,25(OH)₂D concentrations than patients with suboptimal allograft function (Table 2). However, the mean 1,25(OH)₂D/GFR (Ccr) ratios, as an expression of 1,25(OH)₂D concentrations factored for the functional renal mass, were identical in both subgroups, suggesting a similar degree of stimulation for 1,25(OH)₂D production.

There were no significant differences in the serum concentrations of calcium, phosphate or 25OHD. The urinary excretion of calcium and phosphate did not differ significantly between the subgroups. The mean tubular reabsorption of phosphate (TRP/GFR) was significantly less in patients with suboptimal allograft function, in accordance with their higher PTH levels (correlation between PTH and TRP/GFR: r = −0.51, P = 0.0028).

Relationship between serum phosphate and 1,25(OH)₂D concentrations at baseline

Serum phosphate correlated negatively with 1,25(OH)₂D concentration in the whole group (r = −0.39; P = 0.024). This correlation was at the limit of statistical significance when the separate data from the subgroup with optimal allograft function were examined (r = −0.43; P = 0.05). However, the correlation was not statistically significant in recipients with suboptimal allograft function (r = −0.17).

Changes in biochemical parameters of the whole group after phosphate supplementation

Serum calcium, 1,25(OH)₂D concentration, and urinary calcium excretion significantly decreased after phosphorus supplementation in the whole group (Table 1). Conversely, serum phosphate, PTH and urinary phosphate excretion increased significantly. Only five patients had fasting serum phosphate concentrations over 4.4 mg/dl after phosphorus supplementation, though none of them reached concentrations above 4.7 mg/dl. Serum uric acid, creatinine, creatinine clearance, and 25OHD D concentrations did not change.

Mean serum bicarbonate levels decreased significantly after phosphorus supplementation. The changes in serum bicarbonate correlate with the percentage increase in PTH concentrations in the optimal allograft function subgroup (r = −0.39, P = 0.077), but not in the suboptimal subgroup.

Determinants of 1,25(OH)₂D levels after phosphate supplementation

The reduction in the mean 1,25(OH)₂D concentration was observed only in the optimal allograft function subgroup, while the mean 1,25(OH)₂D concentration scarcely changed in patients with suboptimal allograft function (Table 2). Changes in 1,25(OH)₂D concentration after phosphorus supplementation, expressed as the percentage of the initial concentration, correlated positively with the percentage changes in PTH concentrations for the whole group, as well as for each subgroup (Figure 1). However, the absolute changes in PTH concentrations did not correlate with the changes in 1,25(OH)₂D levels after phosphate supplementation. Moreover, when patients were divided into three subgroups according to the severity of the hyperparathyroidism at baseline, a similar percentage or absolute increase in the PTH levels of each subgroup resulted in a more attenuated decrease in the mean 1,25(OH)₂D in patients with suboptimal than with optimal allograft function (Table 3).

The percentage changes in 1,25(OH)₂D after phosphorus supplementation did not correlate with the absolute increase in serum phosphate (serum phosphate F1 minus serum phosphate F0; r = 0.11) for the

| Table 2. Biochemical differences at baseline (F0) and after phosphorus supplementation (F1) between patients with optimal and suboptimal allograft function |
|---------------------------------|----------------|----------------|----------------|
| Serum creatinine (mg/dl)        | 1.07 ± 0.22    | 1.54 ± 0.32*   | 1.02 ± 0.19    | 1.48 ± 0.29*   |
| Creatinine clearance (ml/min/1.73 m²) | 91 ± 17       | 58 ± 8*        | 93 ± 19        | 61 ± 10*       |
| Serum calcium (mg/dl)           | 107.6 ± 0.96   | 104.5 ± 0.86   | 104.7 ± 0.64   | 101 ± 0.72     |
| n patients Ca > 10.5 mg/dl      | 7/21           | 7/11           | 5/21           | 5/11           |
| Serum phosphorus (mg/dl)        | 2.56 ± 0.63    | 2.74 ± 0.48    | 3.20 ± 0.64    | 3.70 ± 0.64    |
| Alkaline phosphatease (μU/ml)   | 199 ± 78       | 197 ± 109      | 190 ± 62       | 180 ± 100      |
| Serum uric acid (mg/dl)         | 5.9 ± 1.2      | 7.0 ± 1.4      | 6.2 ± 1.1      | 7.1 ± 1.4***   |
| Serum bicarbonate (mEq/l)       | 24.6 ± 1.7     | 24.5 ± 1.1     | 24.1 ± 2.0     | 23.9 ± 1.0     |
| PTH (pg/ml)                     | 106 ± 88       | 180 ± 97***    | 135 ± 124      | 242 ± 144***   |
| 1,25(OH)₂D (pg/ml)              | 45.5 ± 15.8    | 30.9 ± 11.4*** | 35.4 ± 13.1    | 30.8 ± 12.1    |
| 25OHD (ng/ml)                   | 12.8 ± 8.0     | 11.6 ± 8.7     | 12.5 ± 7.6     | 11.4 ± 8.3     |
| Urinary calcium (mg/24 h)       | 206 ± 120      | 155 ± 64       | 134 ± 70       | 100 ± 73       |
| Urinary phosphorus (mg/24 h)    | 822 ± 371      | 828 ± 259      | 1676 ± 546     | 1653 ± 332     |
| TPR/GFR (%)                     | 74.2 ± 10.5    | 63.4 ± 10.5**  | 55.7 ± 13.1    | 45.3 ± 12.6*** |
| ΔPTH (% baseline PTH)          | 33.3 ± 51.3    | 35.7 ± 28.4    | 20.9 ± 16.2    | 1.3 ± 27.9     |

Optimal vs suboptimal *P < 0.0001; **P < 0.01; ***P < 0.05.
whole group. However, while the percentage changes in $1,25(\text{OH})_2\text{D}$ and serum phosphate correlated positively in the optimal allograft function subgroup ($r = 0.46$, $P = 0.05$), this correlation was negative, though not statistically significant, in the suboptimal allograft function subgroup ($r = -0.52$, $P = 0.10$).

The rate of urinary phosphorus excretion or the changes in phosphorus excretion did not correlate with the changes in $1,25(\text{OH})_2\text{D}$ concentrations. Total serum calcium corrected for albumin did not correlate with $1,25(\text{OH})_2\text{D}$ levels at baseline ($r = 0.24$) or after phosphorus supplementation ($r = 0.12$). There were no differences in the $1,25(\text{OH})_2\text{D}$ levels between patients with hyper- or normocalcaemia, before ($45.1 \pm 17.8 \text{ vs } 36.9 \pm 14.4 \text{ pg/ml}$, $P = 0.14$) or after ($32.1 \pm 15.4 \text{ vs } 34.6 \pm 11.7 \text{ pg/ml}$) phosphorus supplementation.

The changes in serum bicarbonate did not correlate with either $1,25(\text{OH})_2\text{D}$ concentrations or $1,25(\text{OH})_2\text{D}$ changes.

**Determinants of PTH changes after phosphate supplementation**

The percentage increase in PTH concentrations after phosphate supplementation were similar in both subgroups (33 vs 35.7%). Only five of 32 patients remained with PTH concentrations less than 65 pg/ml after phosphorus supplementation.

The best determinants of the percentage and absolute increase in PTH concentrations after phosphorus supplementation were the final serum phosphate concentration ($F_1 \text{ period}$) ($F = 4.84$, $r = 0.37$, $P = 0.035$) and the absolute increase in serum phosphate ($F = 7.69$, $r = 0.45$, $P = 0.009$) respectively. This is according to a stepwise multiple linear regression model in which the following independent variables were introduced: final serum phosphate, changes in serum and urinary phosphate, final serum calcium and changes in serum calcium, final serum bicarbonate concentrations and changes in serum bicarbonate.

**Discussion**

The results from the present study can be summarized as follow: (i) persistent hyperparathyroidism was highly prevalent among patients with successful kidney transplants. The severity of the persistent hyperparathyroidism correlated with the severity of the hyperparathyroidism before transplant. (ii) Recipients with optimal allograft function had lower PTH and higher $1,25(\text{OH})_2\text{D}$ concentrations than patients with suboptimal allograft function (moderate renal insufficiency). (iii) Phosphorus supplementation led to a significant increase in PTH concentrations in both groups. However, other aspects of mineral metabolism differed between patients with optimal and suboptimal allograft function.

Although significant reductions in PTH concentrations are usually seen in most transplant recipients, complete involution of the hyperplastic parathyroid glands appears to be less common [1–3]. It is not clear that normalization of renal function and in turn, the reversion of the metabolic abnormalities related to

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**Table 3. $1,25(\text{OH})_2\text{D}$ concentrations and PTH changes according to the severity of the hyperparathyroidism at baseline**

<table>
<thead>
<tr>
<th>Baseline PTH (pg/ml) in allograft function subgroups</th>
<th>&lt;100</th>
<th>100–250</th>
<th>&gt;250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal</td>
<td>3</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>$1,25(\text{OH})_2\text{D}$ at baseline (pg/ml)</td>
<td>21.2 ± 9.8</td>
<td>43.1 ± 15.9*</td>
<td>37.6 ± 12.6</td>
</tr>
<tr>
<td>(pg/ml per 100 ml)</td>
<td>56.3 ± 27.0</td>
<td>40.1 ± 59.0</td>
<td>14.8 ± 15.1</td>
</tr>
<tr>
<td>$%\Delta$PTH (% baseline concentrations)</td>
<td>30.3 ± 34.5</td>
<td>-21.0 ± 18.3*</td>
<td>-6.21 ± 16.7</td>
</tr>
<tr>
<td>$%\Delta$1,25(\text{OH})_2\text{D} (% baseline concentrations)</td>
<td>56.3 ± 27.0</td>
<td>40.1 ± 59.0</td>
<td>14.8 ± 15.1</td>
</tr>
</tbody>
</table>

*P<0.05, Mann–Whitney test.
uraemia are able to completely reduce the increased number of parathyroid cells [22,23]. Thus the final PTH concentrations may depend on the severity of the pre-transplant hyperparathyroidism and on the maintenance of the best conditions that favour the control of PTH synthesis and secretion per cell. The results from the present study are in agreement with this hypothesis. Patients with more severe hyperparathyroidism before transplantation had higher PTH levels irrespective of the time elapsed since transplantation. Moreover, those with optimal renal function after transplantation, hypophosphataemia, hypercalcaemia and higher 1,25(OH)₂D levels, had lower PTH concentrations.

In this study, a short-term course of phosphorus supplementation increased PTH concentrations significantly, irrespective of allograft function. The magnitude of the reduction in serum calcium and the increase in serum phosphate were similar in patients with optimal or suboptimal allograft function. However, while the mean 1,25(OH)₂D reduction was approximately 21% in patients with optimal allograft function, it scarcely changed in those with suboptimal allograft function.

Although mean fasting serum phosphate levels at baseline were equal or below the lower normal limit in all patients, it is not unreasonable to speculate that patients with suboptimal renal function may have a greater total burden and retention of phosphate irrespective of serum phosphate levels. Although both subgroups had similar 1,25(OH)₂D/GFR ratios, suggesting a similar degree of stimulation of 1,25(OH)₂D production factored for renal function, hypophosphataemia appeared to be a more sensitive stimulus of 1,25(OH)₂D production in patients with optimal allograft function than in patients with moderate allograft dysfunction. Consequently, phosphate supplementation, by blunting this stimulus, may account for the decrease in the mean 1,25(OH)₂D concentrations of the optimal allograft function subgroup. On the contrary, 1,25(OH)₂D production in the suboptimal allograft function subgroup seemed to be less sensitive to the phosphate load, or alternatively this subgroup may possess a more efficient mechanism in order to counterbalance the potential negative effect of phosphate on 1,25(OH)₂D production.

The positive correlation between the percent changes in PTH and 1,25(OH)₂D concentrations suggest that PTH modified 1,25(OH)₂D concentrations. This may explain the preservation of the 1,25(OH)₂D levels in the suboptimal allograft function subgroup. However, the key question from this observation is: why does a similar percentage increase in the mean PTH concentration apparently counterbalance the decrease in 1,25(OH)₂D after phosphorus supplementation in patients with suboptimal allograft function but not in the subgroup with optimal function? It may be due to the greater absolute values of PTH at baseline in the subgroup with suboptimal allograft function compared with the optimal one. At any given percentage change of PTH, the magnitude of the absolute changes would be greater in those with greater baseline PTH concentrations.

Accepting this hypothesis, however, we must assume that a minimal concentration of PTH is needed to stimulate 1,25(OH)₂D production up to a certain level. However, the present results do not support the idea that any concentration or absolute increase in PTH were the main determinants of 1,25(OH)₂D changes when the hypophosphataemic stimulus was removed. Furthermore, the better relationship between PTH and 1,25(OH)₂D changes when they were expressed in percentage rather than in their absolute values may suggest that the stimulating effect of PTH on 1,25(OH)₂D production may be the result of the interaction between the magnitude of the stimulus and the sensitivity to it. These results may point out the more sensitive role of phosphate in regulating 1,25(OH)₂D production when the allograft function is optimal and the more sensitive role of PTH in counterbalancing the potential diminishing effect of phosphate load on 1,25(OH)₂D production in recipients with suboptimal allograft function.

Long-term phosphorus administration to patients with primary hyperparathyroidism and normal renal function decreases 1,25(OH)₂D levels despite a significant increment in PTH concentration [24], further suggesting the dominance of phosphate over PTH in controlling 1,25(OH)₂D production in subjects with normal renal function. Moreover, though significant correlation between serum phosphate and 1,25(OH)₂D levels has been inconsistently found in kidney transplant recipients [25–27], a significant correlation between these two parameters has been demonstrated in recipients with optimal allograft function [28].

The decrease in serum bicarbonate levels after phosphorus supplementation was an unexpected finding. Chronic intravenous neutral phosphate administration to normal subjects with a replete sodium chloride state induces metabolic alkalosis, despite the significant increment in PTH levels [29]. The direct effect of PTH on inducing metabolic acidosis is controversial [29,30]. In the present study only a weak relationship between the changes in serum bicarbonate and the PTH increase was observed in patients with optimal allograft function. Alternatively, the bicarbonaturic effect of excess sodium intake in the form of phosphate salts when administered to a group of patients on a low-salt diet, may explain this slight reduction in the serum bicarbonate levels.

Calcium is the major regulator of parathyroid cell secretion and proliferation [20]. Therefore the reductions in serum calcium observed after phosphorus supplementation can explain the increase in PTH concentrations and obscure the potential role of serum phosphate and 1,25(OH)₂D changes in these patients. Fasting serum phosphate concentration was the best determinant of the percentage and absolute changes of PTH concentrations after phosphorus supplementation. Very few patients reached fasting serum phosphate concentrations over 4.4 mg/dl, though it is likely that postprandial serum phosphate concentrations or
phosphorus retention at the cellular level may have been higher. Thus, phosphorus supplementation might have been stimulating PTH synthesis and secretion by inducing postprandial hyperphosphataemic peak levels and increasing the total body burden of phosphate, or alternatively normalizing the previous depletion of phosphate. The role of phosphate depletion as a negative regulator of PTH synthesis, regardless of the changes in calcium and 1,25(OH)₂D concentrations, has already been suggested in animal studies [31].

It is difficult to extrapolate the results from the present study to what occurs in the early pathogenic stages of secondary hyperparathyroidism in renal failure patients. Transplantation is associated with other factors that can potentially affect bone and mineral metabolism (corticoids, cyclosporin, etc.). Perhaps these factors, and the time that patients are exposed to phosphorus supplementation, may help to explain the discrepancies between the results from the present study and those published by other investigators in renal failure patients [7]. Notwithstanding, the counterbalance effect of PTH over the potential inhibitory effect of phosphorus accumulation on calcitriol production in renal failure has already been demonstrated in other clinical [19] and experimental studies [32].

This observation suggests that phosphorus administration after kidney transplantation should be avoided as much as possible. In those cases in which hypophosphataemia is severe enough to require phosphorus supplementation, concomitant calcitriol administration may be of value to maintain calcitriol levels and to prevent the intestinal absorption of calcium and phosphorus.

References


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