PATHOGENIC APPROACH TO THE HYPOPHOSPHATAEMIA OF RENAL TRANSPLANTATION

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Summary

Soon after kidney grafting, 69% of the patients who return to normal renal function develop hypophosphataemia.

Increased phosphaturia through a partially or totally PTH-independent mechanism is common to all of them.

Because the phosphate leak disappears late in the post-transplant period, reversible tubular damage seems to be the most likely mechanism.

Introduction

Hypophosphataemia after kidney grafting is quite common, varying according to different authors between 15—50% of the patients who resume normal renal function [1—3].

During the first few months after transplantation, a decrease in serum phosphate concentration, usually unnoticed clinically, can be reasonably attributed to secondary hyperparathyroidism due to incomplete involution of the hyperplastic glands [1,4].

However, a high incidence of hypophosphataemia has been reported in long-term survivors, the majority of them with normal serum PTH levels, in whom parathyroid hyperfunction can not be invoked. This condition has been attributed to a renal PTH-independent phosphate leak, and/or heightened tubular sensitivity to the hormone [3—5].

In the present study, in an attempt to analyse the relative importance of these factors, we evaluated several phosphate biochemical parameters early and late in the post-transplant period.

Subjects and methods

We evaluated 23 out of 47 adult transplanted patients, recipients of either living related or cadaver donor organs, who were assumed to have normal renal function
(serum creatinine < 1.5mg%). The subjects ages ranged from 19 to 51 years (mean 30) and the length of the previous haemodialysis period was 5 to 53 months. The total daily intake of phosphorus and calcium was not standardised.

The warm and cold ischaemia times of the graft varied, but were never over 10 minutes or 26 hours respectively. Immunosuppressive treatment included azathioprine (1.5—3mg/kg/day) and prednisone (0.5—0.7mg/kg/day at the end of the third month), and none of them were ingesting phosphate binders. Serum phosphate values prior to transplantation were normal or high in all patients.

The investigation period started as soon as renal function had stabilised, between the 20th and 40th day after kidney grafting, and continued during the ten following months. Blood samples and urine were collected from all the patients after an overnight fast to determine calcium, phosphorus, magnesium, creatinine and alkaline phosphatase, and the tubular reabsorption of phosphate (TRP) was calculated and the renal threshold for phosphate (TmP/GFR) determined by the nomogram of Walton and Bijvoet [6]. In those patients with serum phosphorus below 2.5mg/dl (16 cases) a calcium infusion test was performed according to the protocol of Nordin and Fraser [7]; 15mg/kg of calcium gluconate was infused during a four hour period in order to obtain a serum calcium concentration over 11.5mg/dl at the end of infusion. Before and 12 hours after hypercalcaemia, serum phosphorus, TRP, TmP/GFR, PTH and PEI (phosphate excretion index) were calculated. iPTH and serum phosphorus were also checked immediately after infusion. PEI expresses the relationship between C_p and C_Cr according to the serum phosphate concentration and can be predicted from the formula C_p/C_Cr = 0.055 x P-0.07 + 0.09.

iPTH in serum was measured by radioimmunoassay using two different c-terminal antisera, both cross-reacting with the human and bovine molecules: one antiserum was raised in guinea pig (GP 500 MA) against porcine PTH (pPTH 1—84), provided through the kindness of Dr Arnaud (upper normal limit 825pg/ml of bPTH 1—84). The other was a chicken antiserum supplied by Immuno Chemical Corp (upper normal limit, 212pg/ml of H-PTH 1—84). Because of these two different methods, iPTH values were expressed as a percentage of the upper normal limit.

Serum calcium was measured by atomic absorption spectrophotometry, serum phosphate by the method of Fiske and Subbarow and creatinine values by acid picrate Jaffé. Student’s ‘t’ test was used to assess differences between groups of patients.

Results

Sixteen out of 23 transplanted patients with assumed normal renal function (serum creatinine < 1.5mg%), had fasting serum phosphate concentrations less than 2.5mg/dl whereas the other seven had normal values. The concentration of serum phosphate in the hypophosphataemic patients (Hypo), was 1.99 ± 0.1mg/dl, significantly lower than 3.4 ± 0.22mg/dl of the normophosphataemic group (Normo) (p < 0.0005).

Mean TRP (52.8 ± 2.9%) and TmP/GFR (1.15 ± 0.10mg/dl) in the Hypo group were lower than in the Normo patients (p < 0.0005), whereas the PEI was increased
TABLE I. Biochemical data on the hypo- and normophosphataemic early kidney transplanted patients

<table>
<thead>
<tr>
<th></th>
<th>Serum P (mg%)</th>
<th>TRP (%)</th>
<th>TmP/GFR (mg%)</th>
<th>PEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphataemic</td>
<td>1.99±0.10</td>
<td>52.8±2.92</td>
<td>1.15±0.10</td>
<td>0.255±0</td>
</tr>
<tr>
<td>Normophosphataemic</td>
<td>3.42±0.22</td>
<td>73.28±4.2</td>
<td>2.35±0.17</td>
<td>0.08±0</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.0005</td>
<td>&lt; 0.0005</td>
<td>&lt; 0.0005</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Results are the mean ± SEM

TABLE II. Biochemical data on the hypophosphataemic early kidney transplanted patients before and after induced hypercalcaemia

<table>
<thead>
<tr>
<th></th>
<th>% of iPTH upper normal limit (pg/ml)</th>
<th>Serum phosphate (mg/dl)</th>
<th>TRP %</th>
<th>TmP/GFR (mg%)</th>
<th>PEI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Total group</td>
<td>16</td>
<td></td>
<td></td>
<td>1.99±0.10</td>
<td>2.44±0.12</td>
</tr>
<tr>
<td>Increased iPTH</td>
<td>9</td>
<td>179±18</td>
<td>97±21</td>
<td>2.1±0.17</td>
<td>2.25±0.14</td>
</tr>
<tr>
<td>Normal iPTH</td>
<td>5</td>
<td>66±12</td>
<td></td>
<td>2.27±0.1</td>
<td>2.6±0.3</td>
</tr>
<tr>
<td>iPTH not measured</td>
<td>2</td>
<td></td>
<td></td>
<td>1.95±0.1</td>
<td>2.85±0.1</td>
</tr>
</tbody>
</table>

Results are the mean ± SEM  
B = before induced hypercalcaemia  
A = after induced hypercalcaemia
(0.255; p < 0.01) in the former group indicating that hypophosphataemia was due to decreased renal phosphate reabsorption (Table I).

All 23 patients were normocalcaemic, and there was no difference between them with regard to sex, age, time after grafting, months of uraemia or the source of the kidney graft.

**Calcium infusion in hypophosphataemic patients (Table II)**

**Early post-transplant period (range 0.8–1.3 months)** In the whole group, 12 hours after the calcium infusion test, serum phosphate, TRP and TmP/GFR increased (p < 0.0025), and PEI decreased (p < 0.01) although they did not return to normal in any of the cases, probably indicating incomplete parathyroid gland suppressibility, or a partial PTH-independent mechanism of phosphaturia.

Dividing the patients into two groups with high (nine cases) and normal (five cases) PTH serum levels, we could see that before the test, TRP and TmP/GFR were lower in the high PTH patients (p < 0.005), whereas PEI was increased and similar in both groups.

During hypercalcaemia (total calcium > 11.5mg%), serum PTH levels exhibited an immediate post-infusion mean decrease of 49.3 ± 20.9% (p < 0.01) below the basal value, although TmP/GFR was not modified probably because of inadequate design of the test), and PEI, although decreased (p < 0.025), did not reach a normal level.

In the high PTH group of patients, we could identify three particular cases who, although exhibiting a decrease of PTH after hypercalcaemia (minimal in one case), did not modify either TRP, TmP/GFR or PEI at all, supporting the idea of a totally independent mechanism of phosphaturia. If we disregarded these three patients, the high PTH group normalised their PEI after hypercalcaemia from 0.25 ± 0.17 to 0.08 ± 0.14 (p < 0.01), clearly showing in this group two different kinds of patients; one in whom the PEI was diminished (partially PTH-dependent phosphaturia), and the other in whom phosphaturia was invariable during the calcium test (PTH-independent phosphaturia).

One out of the five patients in the normal PTH group, and another of the two

**Table III. Effects of calcium infusion on renal phosphate handling by hypophosphataemic early PTH ‘independent’ transplanted patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>% iPTH upper normal limit</th>
<th>P</th>
<th>TRP</th>
<th>TmP/GFR</th>
<th>PEI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pg/ml</td>
<td>mg/dl</td>
<td>%</td>
<td>mg/dl</td>
<td></td>
</tr>
<tr>
<td>JLP</td>
<td>67/85</td>
<td>2.2/2.3</td>
<td>77/76</td>
<td>1.70/1.75</td>
<td>0.139/0.149</td>
</tr>
<tr>
<td>TLP</td>
<td>263/120</td>
<td>1.8/1.6</td>
<td>39.5/40</td>
<td>0.6 /0.6</td>
<td>0.476/0.475</td>
</tr>
<tr>
<td>CSV</td>
<td>224/212</td>
<td>2.3/2.6</td>
<td>47/38</td>
<td>1.0 /1.0</td>
<td>0.208/0.239</td>
</tr>
<tr>
<td>SZA</td>
<td>245/90</td>
<td>2.5/2.4</td>
<td>58/54</td>
<td>1.5 /1.3</td>
<td>0.199/0.258</td>
</tr>
<tr>
<td>CSF</td>
<td>–/–</td>
<td>2.0/2.9</td>
<td>56/49</td>
<td>1.1 /1.4</td>
<td>0.256/0.281</td>
</tr>
</tbody>
</table>

% values before and after hypercalcaemia
with unmeasured serum PTH, showed similar results, indicating a similar hormone-independent mechanism (Table III).

**Late post-transplant period**

We were able to follow up nine out of the 14 reported hypophosphataemic patients for between 4 and 12 months (mean 7.87) including two assumed to have PTH-independent mechanisms of phosphaturia.

All of them had normal serum phosphate values (3.07 ± 0.14) and PEI (0.049 ± 0.02) and had significantly improved their TRP (72.7 ± 2.5) and TmP/GFR (2.23 ± 0.10). Serum PTH levels became normal in four of the five patients in whom it was measured, the only exception being one of the subjects with presumed totally PTH-independent phosphaturia.

After hypercalcaemia TRP (82 ± 2.92) and TmP/GFR (2.81 ± 0.26) became normal and PEI, previously normal (0.049 ± 0) decreased below the normal range in the same way as normal subjects (−0.041 ± 0).

**Comments**

In our patients, renal phosphate leak seems to be the most important factor in the genesis of hypophosphataemia (low TRP and TmP/GFR, high PEI) although other causes not evaluated in the study, like a relative defect in vitamin D synthesis [2] or inhibition of intestinal phosphorus absorption [8] could contribute to the final result.

Hypophosphataemia soon after transplantation in five patients with normal serum PTH levels, and the nine patients with high levels of phosphate excretion which did not return to normal with PTH suppression after hypercalcaemia, suggest that the same mechanism can be invoked for the long-term hypophosphataemic transplanted patients, that is, partial PTH independence and/or incomplete suppressibility of the hyperplastic glands in the high PTH group, and heightened tubular sensitivity to the hormone in the group with normal values. Actually both groups (high and normal PTH) had a decrease in phosphaturia although not to normal after hypercalcaemia indicating some hormonal dependence.

However it seems reasonable to suggest a totally PTH-independent phosphaturia in those five patients who, irrespective of their serum PTH levels, did not modify phosphate excretion at all during hypercalcaemia. The reversibility of this finding in the long-term post-transplant period indicates that whatever the cause of total PTH-independent phosphaturia it is temporal and reversible, and ischaemic tubular post-transplant damage seems to be the most likely mechanism.

**Acknowledgment**

We are indebted to Dr Pedro Esbrit who performed PTH radioimmunoassay.
References

1 Hampers L, Katz Al. Arch Intern Med 1969; 124: 282
4 Bernheim J et al. Nephron 1976; 16: 381
5 Moorhead JF et al. Lancet 1974; i: 694
6 Walton RJ, Bijvoet OLM. Lancet 1975; ii: 309
7 Nordin BEC, Fraser R. Clin Sci 1954; 13: 477
8 Walker GS et al. Nephron 1980; 26: 225

Open Discussion

KOKOT (Katowice) Do you have data on plasma active vitamin D metabolites in your patients?

PLAZA No.

PARSONS (London) This is a very interesting study, especially the patients who did not have a parathyroid hormone suppression response to your calcium infusion test. Is there any difference in the steroid dosage between the groups, is it identical, or were those receiving higher steroids in the low phosphate group?

PLAZA They are identical groups. Immunosuppressive treatment included azathioprine 1.5 to 3mg/kg/day and prednisone 0.5 to 0.7mg/kg/day. So the two groups are similar.

PARSONS You kept the steroids going when you did your tests? The steroids were continued throughout your testing period?

PLAZA Yes.

PARSONS Do you know what your calcium infusion does to patients who have no parathyroid glands? In other words, if you give a calcium infusion test to a patient who has had four glands removed, and there are several of these patients about, what does your test do to the phosphate excretion indices? The mere infusion of calcium may alter the transport of phosphate in the absence of parathyroid hormone.

PLAZA We did not actually check that, but we assume in general that phosphaturia is mainly managed via the parathyroid hormone.

PARSONS Did you see any aminoaciduria in your three resistant patients?

PLAZA We checked glycosuria and aminoaciduria and they did not have it.
PARSONS Finally, bicarbonate handling: was the bicarbonate different in those three patients?

PLAZA The plasma bicarbonate was in the normal range, but we did not use any kind of acidification test.