PATHOGENESIS OF HYPOPHOSPHATAEMIA IN KIDNEY NECROGRAFT RECIPIENTS: A CONTROLLED TRIAL

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Introduction

Disordered mineral metabolism in renal transplant patients has attracted increasing attention in recent years. Improved analytical methods for determination of parathyroid hormone (PTH) and development of assays for various vitamin D metabolites have greatly improved the possibility of studying the pathogenesis of hypophosphataemia in kidney transplanted patients.

A high incidence of hypophosphataemia has been reported in long-term survivors after renal transplantation [1, 2]. This condition has mostly been attributed to a renal phosphate leak and/or to altered tubular sensitivity to PTH [2, 3].

Numerous factors can affect the renal handling of phosphate, but it has been shown [4] that the level of circulating PTH has a key role in this respect. Vitamin D may modify the renal handling of phosphate, but the net effect of the vitamin has been a matter of controversy. An increasing effect of various vitamin D metabolites on the tubular reabsorption of phosphate has been proposed [5], while others have failed to demonstrate a PTH-independent tubular effect of vitamin D [6].

Direct measurement of the biologically active vitamin D, 1,25-dihydroxyvitamin D$_3$ (1,25(OH)$_2$D$_3$) has shown that most uraemic patients after a successful renal transplantation achieve an increase and in many cases almost normalisation of the previously severely reduced levels of 1,25(OH)$_2$D$_3$. Therefore it should be considered whether hypophosphataemia after kidney transplantation could be attributed to the persistence of reduced levels of 1,25(OH)$_2$D$_3$.

In the present study, designed as a controlled trial, biochemical and clinical features were examined in normo- and hypophosphataemic kidney transplanted patients in order to elucidate the pathogenesis of hypophosphataemia after transplantation.
Material and Methods

Twenty long-term survivors after kidney transplantation were investigated. Ten patients had persistent hypophosphataemia (serum phosphate below 0.78 mmol/L) and ten patients were normophosphataemic (serum phosphate 0.78–1.48 mmol/L). The two groups were comparable as regards age, sex, duration of their previous uraemic state, time after grafting, glomerular filtration rate and immunosuppressive treatment (Table I).

<table>
<thead>
<tr>
<th>Nephrograft recipients</th>
<th>Serum-P mmol/l</th>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Mo. post tranpl.</th>
<th>Y. of uraemia</th>
<th>GFR ml/min</th>
<th>Prednisone mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphataemia</td>
<td>0.61 (0.48–0.75)</td>
<td>10</td>
<td>3F,7M</td>
<td>41</td>
<td>21 (21–56)</td>
<td>4 (2–118)</td>
<td>62 (35–89)</td>
<td>21 (0–30)</td>
</tr>
<tr>
<td>Normophosphataemia</td>
<td>0.97 (0.80–1.17)</td>
<td>10</td>
<td>4F,6M</td>
<td>42</td>
<td>27 (27–54)</td>
<td>4 (5–120)</td>
<td>64 (40–91)</td>
<td>16 (0–27.5)</td>
</tr>
</tbody>
</table>

Blood samples were drawn after an overnight fast. The following parameters were measured: serum total and ionised (Ca++) calcium, phosphate, magnesium, alkaline phosphatase, standard bicarbonate, immunoreactive PTH (i-PTH), 25-hydroxy-vitamin D₃ (25(OH)D₃) and 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃). Finally the daily urinary excretion of calcium and phosphate was measured and the cold and warm ischaemia times of the grafts determined. Ca++ was measured with the Orion SS-20 [7]; i-PTH by a radioimmunoassay primarily detecting the carboxy-terminal part of the PTH molecule [8]; 25(OH)D₃ by a competitive protein-binding assay [9] and 1,25(OH)₂D₃ was measured by a competitive protein-binding method using rachitic chick intestinal cytosol binding protein [10]. The renal handling of phosphate was expressed as the ratio between the maximal tubular reabsorption of phosphate and the glomerular filtration rate. This TmP/GFR index was calculated according to the method of Walton and Bijvoet [11].

Results

Due to the selection of the patients serum phosphate was significantly lower in the hypophosphataemic than in the normophosphataemic patients. Furthermore the TmP/GFR was significantly reduced in the hypophosphataemic patients (Table II). The i-PTH concentrations were significantly higher in the hypophosphataemic than in the normophosphataemic patients, while no significant differences were found between the two groups as regards Ca++, 25(OH)D₃, 1,25(OH)₂D₃ or any of the other measured parameters. In particular no differ-
TABLE II. Main Results in the Hypo- and Normophosphataemic Kidney Transplanted Patients. Mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>S-P mmol/l</th>
<th>U-P mmol/day</th>
<th>Tmp/GFR μmol/ml</th>
<th>Ca++ mmol/l</th>
<th>i-PTH pmol Eqv/l</th>
<th>25(OH)D3 ng/ml</th>
<th>1,25(OH)2D3 pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphataemia</td>
<td>0.61</td>
<td>21.6</td>
<td>0.34</td>
<td>1.10</td>
<td>430</td>
<td>24.1</td>
<td>24.2</td>
</tr>
<tr>
<td></td>
<td>±0.08</td>
<td>± 7.6</td>
<td>±0.08</td>
<td>±0.08</td>
<td>±196</td>
<td>± 8.0</td>
<td>±18.4</td>
</tr>
<tr>
<td>Normophosphataemia</td>
<td>0.97</td>
<td>21.7</td>
<td>0.72</td>
<td>1.14</td>
<td>247</td>
<td>33.1</td>
<td>27.7</td>
</tr>
<tr>
<td></td>
<td>±0.13</td>
<td>± 6.6</td>
<td>±0.09</td>
<td>±0.05</td>
<td>± 56</td>
<td>±12.6</td>
<td>±17.9</td>
</tr>
<tr>
<td>**</td>
<td>n.s.</td>
<td>**</td>
<td>n.s.</td>
<td>*</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
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</table>

* p < 0.05; ** p < 0.001; n.s. not significant

ence in the warm and cold ischaemia times of the grafts existed between the two groups.

In a previous investigation [4] we found a significant inverse relationship between Tmp/GFR and i-PTH in normophosphataemic transplanted patients. This relationship was confirmed in the present investigation (Figure 1). However, in the hypophosphataemic patients no such relationship could be demonstrated. Despite higher PTH levels in the hypophosphataemic patients the serum Ca++ levels were similar in both groups and in no patient was hypercalcaemia present.

Discussion

Recent studies [12] have shown that the relationship between Tmp/GFR and i-PTH in fact conforms to the shape of a hyperbola when a wide spectrum of Tmp/GFR is included (Figure 1). A similar correlation was found in the normophosphataemic transplanted patients, but not in the hypophosphataemic patients, who showed that Tmp/GFR values did not correlate with i-PTH (Figure 1). This finding indicates that hypophosphataemic kidney transplanted patients exhibit a major defect in the PTH-mediated tubular reabsorption of phosphate.

The finding of identical levels of 25(OH)D3 and 1,25(OH)2D3 in the two groups of transplanted patients suggests that disturbed vitamin D metabolism after transplantation cannot account for the hypophosphataemia frequently found in such patients. These results are in accordance with those of Farrington et al [13]. However, since hypophosphataemia stimulates the renal 1-hydroxylation of vitamin D it should be expected that hypophosphataemic patients would exhibit higher levels of 1,25(OH)2D3. As such a difference was not observed in the present study, a relative defect in vitamin D synthesis may exist in the hypophosphataemic transplanted patients. It should therefore be considered whether these patients exhibit a reduced tubular response to vitamin D.

Finally, it should be emphasised that the demonstrated renal phosphate leak may not be the only factor contributing to hypophosphataemia after transplantation since it has recently also been shown [13] that intestinal phosphate absorption frequently remains inappropriately low after transplantation.
Figure 1. (a) Relationship between TmP/GFR and PTH in a wide spectrum of patients from a previous investigation [12]. Note the inverse linear correlation in the normophosphataemic transplanted patients. (b) The above shown hyperbola and the results of the present investigation in normo- and hypophosphataemic transplanted patients
References


Open Discussion

MALLUCHE (Los Angeles) First you gave us information on steroids and diuretics used, but you didn’t mention phosphate binders. I would like to know whether there were any differences as far as the intake of oral phosphate binders is concerned. Secondly, you showed 1,25-levels to be normal, but I have noticed some decreased values in individual patients on your slide and I can’t help wondering whether the picture you described here resembles what we are used to seeing in early renal failure. In early to moderate renal failure we do see normal to low, 1,25(OH)₂D₃ levels, and clinically there is a state of vitamin D resistance at the target organs. Would you care to comment on this?

MADSEN To your first question, we looked very carefully in our patient material and I can assure that there were no differences as regards phosphate binders in the two groups. Regarding your last question, we found a few patients who had slightly decreased values of 1,25, and I quite agree with your argument about the reason. They resemble very much patients with early renal failure. Still it was hard for us to explain why the hypophosphataemic patients showed values just as low as the other groups. One would expect that the hypophosphataemia had stimulated the renal hydroxylase, which it did not seem to do.

MALLUCHE The same lack of response to stimuli of 1-alpha-hydroxylase is seen in moderate renal failure for instance. Elevated PTH levels and hypocalcaemia fail to increase formation of 1,25(OH)₂D₃.

VINCENTI (San Francisco) Have you noticed a greater incidence of aseptic necrosis in your hypophosphataemic patients?

MADSEN We have seen patients with hypophosphataemia who had aseptic necrosis, but in our material it does not seem to be related to the hypophosphataemia.
KANIS (Oxford) I noticed that you used the expression "derived TmP/GFR" for renal handling of phosphate, which as you rightly say describes renal handling perhaps in the best way possible in normal subjects. In order to estimate TmP/GFR as you know, you need to know precisely the relationship between filtered load and renal excretion. I wonder are there any data available in patients with transplant and phosphate infusion to show that your expression of TmP/GFR is really the best thing to use.

MADSEN I showed a hyperbola of this on many patients which included kidney transplant patients, and those data were derived during phosphate infusion and not by calculating TmP/GFR from the nomogram. We have compared the other possible ways of expressing the mean handling of phosphate. In kidney transplant patients we found that the TmP/GFR still is the most consistent index.

VAN HOOFF (Leiden) Is there in your material a higher frequency of other tubular disturbances, for example hyperkalaemia or acidosis, etc?

MADSEN We didn't study that. In the original paper by Moorhead and co-workers I think they investigated this matter, and if I remember correctly they did not find any signs of other tubular disorders.