PLASMA 1,25(OH)$_2$D$_3$ AND iPTH IN TRANSPLANTED ADULTS WITH PERSISTING HYPOPHOSPHATAEMIA

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Summary

Hypophosphataemia is a common finding among kidney transplanted patients [1,2]. In a previous study in kidney transplanted children with plasma creatinine below 1.1mg/dl, we demonstrated [3] a negative correlation between plasma phosphorus and 1α,25-dihydroxyvitamin D$_3$ (1,25(OH)$_2$D$_3$), the renal hormonal form of vitamin D. No such correlation was apparent in children with minimal increase in plasma creatinine. The aim of the present investigation carried out in hypophosphataemic transplanted adults was two-fold: 1) to determine whether hypophosphataemia results from persisting hyperparathyroidism or from a renal phosphorus leak, or both, and 2) to study the relation between plasma phosphorus, iPTH and 1,25(OH)$_2$D$_3$ in these patients.

Patients and Methods

At least 6 months after kidney transplantation, 12 adults (aged from 28 to 50 years) were investigated because of persisting hypophosphataemia. In some of them additional symptoms such as transient increased plasma calcium, hypercalciuria, muscle or bone pain, or radiological findings consistent with hyperparathyroidism were observed. All but one received prednisone (15 to 20mg/day) and azathioprine (100 to 200mg/day), and no other medication such as diuretics, phosphorus or vitamin D metabolites (one patient was on azathioprine alone). At the time of investigation plasma creatinine was below 1.2mg/dl. The patients were first put on a normal phosphorus (NP) diet (1g phosphorus, 1g calcium and 5 to 6g NaCl daily) for three days. They were then put on a low-phosphorus (LP) diet (450mg phosphorus, 1g calcium and 5 to 6g NaCl daily) to which was added 3g Al(OH)$_3$ daily, for 4 and in some patients 6 days. The urines of the 3rd day on NP-diet and of the 2nd, 4th and 6th days on LP-diet were collected. Fasting plasma samples were obtained at 8 a.m. on the same days. The results in NP and LP-diets were compared with those obtained in 8 normal subjects and in 3 patients with primary hyperparathyroidism (surgically proven parathyroid
adenoma) while on the same diet. The same study was performed in an additional transplanted adult with post-surgical hypoparathyroidism requiring calcium and vitamin D supplements.

**Results**

**NP-diet**

Results are summarised in Table I. Plasma phosphorus was $3.0 \pm 0.5$ mg/dl (SEM) a value significantly lower than that in control subjects on the same diet ($p < 0.001$, unpaired t test). Similarly, TRP (24-hour determination) was $0.72 \pm 0.03$ (SEM) versus $0.88 \pm 0.005$ in control subjects ($p < 0.001$). Plasma iPTH was above normal values in all patients in whom it was measured and ranged between 11 and 75 ng prot/ml. No correlation was demonstrated between plasma iPTH and plasma phosphorus or TRP. Plasma $1,25(\text{OH})_2\text{D}_3$ ranged between 11 and 383 pg/ml. In 5 patients plasma $1,25(\text{OH})_2\text{D}_3$ was within the normal range, whereas in the remaining 7, it was elevated, above 250 pg/ml in 3 of them. There

**TABLE I.** Plasma and urine chemistries ($\pm$ SEM) in 12 hypophosphataemic transplanted adults and 8 control subjects while on a normal-phosphorus diet*

<table>
<thead>
<tr>
<th></th>
<th>Transplanted patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.5 $\pm$ 0.2</td>
<td>9.3 $\pm$ 0.2</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>3.0 $\pm$ 0.5†</td>
<td>3.9 $\pm$ 0.3</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.03 $\pm$ 0.05</td>
<td>0.95 $\pm$ 0.05</td>
</tr>
<tr>
<td>$1,25(\text{OH})_2\text{D}_3$ (ng/ml)</td>
<td>10.6 $\pm$ 4.1*</td>
<td>–</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium/creatinine* (mg/mg)</td>
<td>0.21 $\pm$ 0.04</td>
<td>0.12 $\pm$ 0.02</td>
</tr>
<tr>
<td>TRP*</td>
<td>0.72 $\pm$ 0.03†</td>
<td>0.88 $\pm$ 0.005</td>
</tr>
<tr>
<td>Creatinine clearance* (ml/min)</td>
<td>80.7 $\pm$ 5.2†</td>
<td>100.6 $\pm$ 3.1</td>
</tr>
</tbody>
</table>

* 1g phosphorus, 1g calcium and 6g NaCl daily
† $p < 0.001$, vs controls, unpaired t-test
* Measured in 6 patients (normal value $\pm$ SD: 20.0 $\pm$ 7.4 ng/ml)
* 24hr determination

was no correlation between plasma $1,25(\text{OH})_2\text{D}_3$ and plasma or urine calcium, plasma phosphorus or TRP. No correlation was demonstrable between plasma $1,25(\text{OH})_2\text{D}_3$ and iPTH. However (Figure 1) the highest plasma $1,25(\text{OH})_2\text{D}_3$ concentrations were observed in two patients with the highest plasma iPTH values. In the transplanted patient with hypoparathyroidism, plasma phosphorus was 4.3 mg/dl, iPTH 1.9 ng prot./ml and $1,25(\text{OH})_2\text{D}_3$ 30 pg/ml.
Figure 1. Plasma 1,25(OH)$_2$D$_3$ and iPTH in hypophosphataemic transplanted adults during the normal phosphorus diet

Figure 2. Effect of a low-phosphorus diet on hypophosphataemic transplanted adults (closed circles), patients with primary hyperparathyroidism (triangles) and control subjects (open circles). TRP: tubular reabsorption of phosphate (24-hr determination). PS: plasma phosphorus
LP-diet

As shown in Figure 2, a significant increase in TRP was noted in transplanted patients during the LP-diet. However TRP remained significantly lower than in control subjects on the LP-diet. In addition, on the fourth day on LP-diet, TRP in three patients with primary hyperparathyroidism was higher than that in transplanted patients but lower than in control subjects. A significant fall in plasma phosphorus (p < 0.01, paired t-test) was noted in transplanted patients between the third day on NP-diet and the second day on LP-diet, a finding that did not occur in control subjects. An increase in plasma phosphorus was noted in two out of three hyperparathyroid patients between the third day on NP-diet and the second day on LP-diet. Meanwhile, no consistent change in iPTH in transplanted patients was noted. Between the third day on NP-diet and the fourth day on LP-diet, plasma 1,25(OH)₂D₃ decreased in five patients and remained unchanged in the three others in whom it was measured. On the fourth day on LP-diet, again no correlation was demonstrable between plasma 1,25(OH)₂D₃ and plasma phosphorus or TRP. In the hypoparathyroid transplanted patient, TRP rose from 0.85 on the NP-diet to 0.89 and 0.96 on the LP-diet.

Effect of subtotal parathyroidectomy (Sub-PTX)

Sub-PTX was performed in one patient because of threatening hypercalcaemia and in another because of mild hypercalcaemia together with radiological osteitis fibrosa. After sub-PTX, plasma phosphorus increased from 1.0 to 1.3 mmol/L in the first patient and from 1.1 to 1.3 mmol/L in the second patient. TRP rose in both patients (0.78 and 0.82 on the third day on NP-diet) but remained well below the value observed in normal subjects. Plasma 1,25(OH)₂D₃ decreased from 275 ± 29 pg/ml in one patient and from 75 to 42 pg/ml in the other.

Discussion

This study provides data concerning plasma 1,25(OH)₂D₃ and iPTH in hypophosphataemic transplanted adults. Hypophosphataemia in these patients could result from persisting hyperparathyroidism or from a renal tubular leak of phosphate, or from both [2,5–7]. Our results are consistent with the participation of both factors. In our previous report in transplanted children [3] a correlation was found between plasma 1,25(OH)₂D₃ and phosphorus only in children with normal GFR. In our adults with normal plasma creatinine no such correlation was found. The finding of a decreased creatinine clearance despite normal plasma creatinine could explain this absence of correlation since in children with decreased creatinine clearance there was no correlation between plasma phosphorus and 1,25(OH)₂D₃. The discrepancy between plasma creatinine and creatinine clearance (24-hr determination) stresses the need for accurate GFR determination in patients with transplanted kidneys. In some of our patients, persisting hyperparathyroidism probably played an important role in increased plasma 1,25(OH)₂D₃.
Finally, there was no correlation between plasma 1,25(OH)$_2$D$_3$ and either plasma or urinary calcium in these adults. That suggests an impairment of the intestinal action of 1,25(OH)$_2$D$_3$ that is perhaps the consequence of corticosteroid therapy.

References

1. Bricker NS, Slatopolsky E, Reiss E, Avioli LV. Arch Int Med 1969; 123: 543
5. Christensen MS, Nielsen HE. Clin Nephrol 1977; 8: 472

Open Discussion

ALJAMA (Cordoba) We are very concerned because our patients develop very early severe hypophosphataemia and would you like to comment on the long term effect of the hypophosphataemia on transplants? Secondly, what do you think is the best therapeutic approach in these patients?

ULMANN I will answer first of all the second part of your question. We don’t know as yet which is the best therapeutic attitude to these patients. Possibly the administration of 1 alpha hydroxy vitamin D could improve plasma phosphorus. We have no experience in our patients with this treatment. In our patients no absolute deficiency in plasma 1,25 was observed. However, we think that maybe if we compare with the children which we previously reported, they could have relative insufficiency.

ZAZGORNIK (Vienna) Two years ago we investigated the behaviour of iPTh in hypophosphataemic transplant recipients. Hypophosphataemia was observed in 56 of our patients but their iPTh level was normal. Only 3 patients had elevated iPTh levels. In these patients the serum creatinine was increased. Have you seen any progression in the bone changes in your patients? How long was your observation time?

ULMANN I have no answer to this question.

LINDQUIST (Umeå) Patients with phosphate diabetes have distinct complaints. Have you found any complaints in your patients with hypophosphataemia?

ULMANN Complaints – No. This was usually asymptomatic hypophosphataemia.

LINDQUIST Why do you think that these patients have no complaints?

ULMANN I can’t comment on this.
KOKOT (Katowice) Could you tell us something about the method you used for iPTh estimation, because your units are unfamiliar as compared to those from the literature? And the second question is, how often did you encounter an elevated level of iPTh in transplanted patients in your centre?

ULMANN We used the C-terminal antibody assay and the unit is in fact comparable with that for iPTh. The normal is 428. As for elevated plasma iPTh in transplanted patients, I cannot give you any answer at the moment, because all the patients were studied because of hypophosphataemia or other symptoms and in more than 90% of the cases we found elevated iPTh, but I cannot answer for transplanted patients who have not been studied. This is a study which we are now performing to try to have an idea of the frequency of elevated plasma iPTh levels in these patients.