PREDICTIVE FACTORS FOR PERSISTENT HYPERPARATHYROIDISM AFTER KIDNEY TRANSPLANTATION


Background: A successful kidney transplantation (KT) corrects the main metabolic abnormalities responsible for secondary hyperparathyroidism (HPT). Nonetheless, after several months, many patients keep abnormally high parathyroid hormone (PTH) levels and/or become hypercalcemic with persistent HPT.

Objective: In the present survey, the frequency of high PTH levels and the influence of certain important factors on its evolution among patients with successful KT were investigated within three months posttransplantation.

Methods: A total of 126 patients, who had successful KT, entered the study between 2000 and 2002. On the day of operation and three months later, demographic data and serum calcium, phosphorus, albumin, creatinine, and immunoreactive PTH (iPTH) (by IRMA) were checked. Hypercalcemic patients, at third month, were followed up for one year after transplantation. With respect to the post-KT iPTH level, patients were divided into two groups; those with iPTH above and below 60 pg/mL. The importance of several factors on the evolution of hyperparathyroidism was determined. Sequential changes in serum calcium were also assessed in hypercalcemic patients up to one year after transplantation.

Results: Twenty-one (16.6%) out of 126 patients had a post-KT serum calcium of >10.8 mg/mL. Post-KT iPTH value of > 60 pg/mL was found in 9 (7.1%) out of the 126 cases. There was a statistically significant relationship between the age of patients and duration of dialysis and a post-KT high PTH level (P < 0.001). Other risk factors did not seem to have a significant correlation with the post-KT high PTH level. In all hypercalcemic patients, PTH levels normalized but hypercalcemia persisted in 14 (88%) out of 16 patients up to 1 year after transplantation.

Conclusion: Increased age of the patient as well as the duration of dialysis had significant influences on development of persistent HPT, three months posttransplantation. We believe that it is better to transplant the patients as soon as possible, in order to prevent the devastating complication of persistent HPT and hypercalcemia.

Keywords: Kidney transplantation • renal osteodystrophy • secondary hyperparathyroidism

Introduction

Since 1970, it has been known that secondary hyperparathyroidism (HPT) may persist months or even years after a successful kidney transplantation (KT).\textsuperscript{1 - 4} Since then, various reports with comparable results in adult patients have been published.

Chronic renal failure (CRE) and prolonged dialysis could cause hyperplasia or adenomatous transformation of parathyroid cells, which may maintain the altered response of parathyroid cells to the suppressive effect of calcium.\textsuperscript{5, 6}

Several factors including age,\textsuperscript{7, 8} sex,\textsuperscript{6} underlying renal disease,\textsuperscript{8} duration of dialysis,\textsuperscript{10} and severity of preexisting HPT\textsuperscript{7, 10} may contribute to
persistence or worsening of HPT.

The aim of the present study was to evaluate the factors influencing the evolution of secondary HPT after KT, as well as the sequential changes of serum calcium and phosphorus in hypercalcemic patients up to one year posttransplantation.

**Materials and Methods**

From September 2000 through September 2002 about 200 patients with chronic renal failure underwent kidney transplantation (KT). After overnight fasting, their serum calcium, phosphorus, albumin, blood urea nitrogen (BUN), creatinine, and immunoreactive parathyroid hormone (iPTH) were measured before and three months after transplantation. The patients were visited regularly by nephrologists and had a special chart containing their medication, dosage, drug side effects, BUN, and creatinine. Each patient had a computer file in the Research Laboratory of Kidney Transplant Ward, containing all these data. As a consequence, we had two sources for their follow-up. One hundred twenty-six patients completed the work-ups. Two had expired, six had rejection within the first three months post-KT, and three had not enough blood samples for checking iPTH, calcium, phosphorus, creatinine, and albumin. Others were visited at inappropriate time intervals for the second sampling. All the patients received prednisolone (cumulative dose with a three-month posttransplant dose of 1000 mg during the first year [2,500 mg]) and cyclosporine A (dose was adjusted with the whole blood drug concentration between 120 – 180 ng/mL). In addition, 95 patients received azathioprine (between 50 and 150 mg), and 35 received mycophenolate. None of the patients received vitamin D, calcium, or phosphate supplementation or other drugs known to interfere with calcium or phosphate metabolism except corticosteroid that was prescribed during posttransplantation period.

Twenty-one out of the 126 patients with hypercalcemia, during a period of three months, were prospectively followed up and investigated throughout the first year posttransplantation. Sixteen hypercalcemic patients completed the follow-up (one was expired, two had rejection, and two were lost to follow-up).

Serum creatinine, calcium, phosphorus, and albumin were measured by a standard technique. The albumin corrected calcium was calculated according to the method of Payne et al. All iPTH values were controlled with the immunoradiometric assay (IRMA) (intact PTH SP; Diasorin Inc. Stillwater, Minnesota, USA). The normal range should be between 13 and 54 pg/mL. The statistical methods used included the independent Student’s *t*-test, paired *t*-test, and the McNemar’s test.

**Results**

Our study group was composed of 40 (31.7%) female and 86 (68.3%) male patients, with a mean ± SD age of 35.5 ± 12.5 years (range: 6 – 65). The mean ± SD duration of hemodialysis was 17.4 ± 14.6 months before transplantation (range: 1 – 96). The underlying renal disease was unknown in nine patients, focal segmental glomerulosclerosis (FSGS) in ten, diabetes mellitus (DM) in 99, hypertension (HTN) in 29, and other diseases (Alport disease, membranoproliferative glomerulonephritis [MPGN], chronic pyelonephritis [CPN], gout, congenital anomaly, systemic lupus erythematosus [SLE], and autosomal dominant polycystic kidney disease [ADPKD]) in 29 patients.

The mean ± SD of initial iPTH was 153.21 ± 131.63 pg/mL (range: 44.6 – 730.1). Three months posttransplantation, it was 43.24 ± 13.23 pg/mL (range: 14 – 711.9 pg/mL), which was significantly different (*P* < 0.001). No significant difference was noted between the male and female patients. There was a highly significant rise in the serum calcium level during these three months from a mean ± SD of 6.76 ± 0.67 to 9.7 ± 1.36 mg/dL (*P* < 0.001). In addition, there was a significant decline in the mean ± SD serum phosphorus level from 9.29 ± 1.87 to 2.76 ± 0.82 mg/dL (*P* < 0.001). There were no significant differences between male and female patients, regarding the serum calcium or phosphorus levels.

The mean ± SD serum creatinine on the third month was 0.6 ± 0.2 mg/dL which was significantly different from the creatinine level before KT (*P* < 0.001).

After KT, nine (7.1%) patients had an iPTH of > 60 pg/mL (mean ± SD: 212.28 ± 210.9), with a male to female ratio of 2:1. Twenty one (16.6%) patients had a calcium level of > 10.8 mg/dL, with a male to female ratio of 4:3.

In patients with an iPTH of > 60 pg/mL, all had a calcium level of > 10.8 mg/dL. The reverse was
not true, and only nine (42.8%) patients with calcium of >10.8 mg/dL, had an iPTH of >60 pg/mL.

The mean ± SD age of patients with a post-KT iPTH of \( \leq 60 \) was 34.7 ± 12 years; for those with a post-KT iPTH of > 60 pg/mL, the mean ± SD was 50.5 ± 7.0 years (\( P < 0.001 \)). Furthermore, the mean ± SD duration of dialysis for the two groups was 14.26 ± 8.34 and 54 ± 18.68 months (\( P < 0.001 \)), respectively. There was no significant difference between the male and female patients (Table 1).

The mean ± SD serum calcium level in patients with a normal PTH (9.4 ± 1.07 mg/dL) was significantly (\( P < 0.001 \)) lower than that in those with high PTH levels (12.81 ± 0.75 mg/dL). No significant change was noted between these two groups in terms of serum phosphorus level (2.77 ± 0.82 vs. 2.67 ± 0.90 mg/dL). The mean serum creatinine for these two groups was also not different (Table 2).

The first and second common causes of chronic renal failure in all patients were DM (39.8%) and HTN (23.6%), followed by chronic glomerulonephritis (CGN, 22.2%) and CPN (4.9%). In patients with a post-KT iPTH of > 60 pg/mL, the most common cause was again DM (44.4%) followed by CGN (22.2%) and CPN (11.1%). In patients with a post-KT iPTH of \( \leq 60 \) pg/mL, the most common cause was DM (39.6%) followed by HTN (25.2%), CGN (6.3%), and CPN (4.5%).

Three months after transplantations, 21 (16.8%) patients (mean ± SD age of 34.5 ± 11.2 years) were identified as being hypercalcemic, with a mean ± SD serum calcium level of 11.7 ± 0.9 mg/dL. Sixteen hypercalcemic patients (nine males and seven females) were followed for one year after transplantation. The mean serum calcium, phosphorus, albumin, and creatinine levels one year post-transplantation were compared with those obtained three months after transplantation. There was a significant fall in the serum PTH and calcium concentration, as well as an increased level of albumin and phosphorus, up to one year after transplantation (Table 3).

Although the mean concentration of calcium declined up to one year posttransplantation, hypercalcemia was resolved in only two patients; 14 (87.5%) patients continued to suffer from hypercalcemia.

In addition to determining persistent hypercalcemia, sequential parathyroid assessment indicated a normalization of PTH in all the hypercalcemic patients.

Those patients with PTH levels of > 60 pg/mL before transplantation, also had a significantly higher PTH concentrations three months after transplantation (\( P < 0.001 \)).

### Discussion

There are many reports showing that successful KT corrects, as of the first months, the main metabolic abnormalities responsible for secondary HPT (e.g., phosphorus retention). After several months, however, a significant number of patients with secondary HPT remain hypercalcemic and/or hypophosphatemic.12–14 Despite a better control of HPT during dialysis, the incidence of hypercalcemia after kidney transplantation remains considerably high. It varies between 8.5% and 53% in transplanted patients, among whom 1.6% to 17% underwent parathyroidectomy.15, 16 The natural course of hypercalcemia after a successful transplantation, in most cases, tends to follow a pattern of initial resolution within the first postoperative months, followed by a rebound with persistent or recurrent hypercalcemia.

### Table 1. Demographic data in patients with normal and high iPTh levels during a period of three months after transplantation.

<table>
<thead>
<tr>
<th>Factor (post-KT)</th>
<th>Post-KT iPTh (pg/mL)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &gt;60 )</td>
<td>( \leq 60 )</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.55 ± 7.05</td>
<td>34.73 ± 12</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/3</td>
<td>78/36</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>57 ± 18.68</td>
<td>14.26 ± 8.34</td>
</tr>
</tbody>
</table>

*NS = not significant.

### Table 2. Biochemical data in patients with normal and high iPTh levels during a period of three months after transplantation.

<table>
<thead>
<tr>
<th>Factor (post-KT)</th>
<th>Post-KT iPTh (pg/mL)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>12.81 ± 0.75</td>
<td>9.44 ± 1.07</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.67 ± 0.90</td>
<td>2.77 ± 0.82</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.60 ± 0.22</td>
<td>0.60 ± 0.20</td>
</tr>
</tbody>
</table>

*NS = not significant.
cases, is spontaneous resolution. In our patients, the incidence of hypercalcemia three months after transplantation was 16.6%.

Our data indicate that the age of patients has a significant influence on the outcome of secondary HPT, following a successful KT. This means that elderly patients have a greater chance of developing high PTH levels, although we could not find any specific age from which this chance significantly increases. It may depend on the duration of CRF before transplantation. Therefore, if possible, it seems better to determine the duration of azotemia; but it is very difficult to find it out precisely.

Also, the duration of dialysis had an important role in our study, with respect to the evolution of HPT. In fact, it was found that a longer duration of dialysis would result in a higher incidence of elevated PTH level three months after transplantation. Here again, if we had the duration of CRF in our patients, we would have found out whether the duration of dialysis is an independent risk factor for developing high PTH levels. Thereby, early transplantation is justified as planned by regular dialysis.

There was no sex difference between those with a normal PTH and those with high PTH after KT. Although, other researchers have found it as a risk factor for persistent HPT.6, 9

There was a significant difference in serum calcium level in patients with a high serum PTH, as compared to those with a normal iPTH. No significant difference in serum phosphorus was noted between the two groups of patients. This is most probably attributed to factors other than phosphaturic effect of PTH, which results in a low phosphate level immediately after transplantation. An initially low concentration of phosphate after transplantation is due to a decreased phosphate reabsorption from the renal tubule,17 – 19 and the phosphaturic effect of steroid, which gets better with tapering the steroid.20 We observed a gradual rise, from a low serum phosphate concentration up to one year after renal transplantation.

It was found that the most common cause of CRF in those patients with a high PTH level is the same as those with a normal PTH (i.e., DM). The interesting finding in patients with high PTH levels was that none had HTN as the cause of CRF, although the sequence of other causes was the same as that for patients with a normal PTH.

Twelve months after transplantation, a fall in PTH level was observed, as all hypercalcemic individuals had normal PTH levels. Only two (15%) out of the 16 hypercalcemic patients became normocalcemic. This discrepancy between the PTH level and calcium concentration is due to an excess PTH secretion23, 24 and a slow involution of the parathyroid gland.25

We have shown that the evolution of HPT after KT is significantly under the influence of age and the duration of dialysis but not the sex. Therefore, we conclude that conductance of an early transplantation, could reduce the chance of persistently high PTH levels after transplantation as well as its complications, which probably can lessen the need for future parathyroidectomy.

Hypercalcemia is a common phenomenon in the early period after KT and calcium constantly elevates in most hypercalcemic patients up to one year after transplantation. However, PTH becomes normal during this period. Such normal values of PTH are abnormal in the hypercalcemic state and show the presence of persistence HPT due to an excess of PTH secretion23, 24 and a slow involution of the parathyroid gland.

References


Table 3. Biochemical parameters of hypercalcemic patients after renal transplantation.

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>3 months after transplantation</th>
<th>1 year after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>11.7 ± 0.98</td>
<td>11.06 ± 0.49</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.3 ± 0.83</td>
<td>3.1 ± 0.89*</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.5 ± 0.7</td>
<td>4.6 ± 0.32</td>
</tr>
<tr>
<td>iPTH</td>
<td>114.6 ± 176</td>
<td>354 ± 14*</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 ± 0.20</td>
<td>0.8 ± 0.23</td>
</tr>
</tbody>
</table>

* P < 0.001 vs. values at 3 months after renal transplantation.


