

## Parathyroid function in long-term renal transplant patients: importance of pre-transplant PTH concentrations

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**Abstract** Lack of resolution of hyperparathyroidism after long-term renal transplantation is common. The relative roles of the graft function attained and the degree of pre-transplant hyperparathyroidism have not been established. Intact parathyroid hormone (iPTH) and several clinical parameters were studied before and  $68.6 \pm 26.8$  months (range: 30–124) after renal transplantation in 62 patients (20 females/42 males) with good renal function (creatinine  $< 2$  mg/dl). iPTH decreased from  $214 \pm 229$  pre-transplantation to  $116 \pm 70$  pg/ml post-transplantation ( $P < 0.01$ ). However, only 22.6% of patients had PTH concentrations in the normal range, and values greater than twice the upper normal limit were not uncommon (27.4%). Of the many variables analysed, creatinine ( $r = 0.43$ ;  $P = 0.001$ ) and pre-transplant PTH ( $r = 0.31$ ;  $P = 0.02$ ) significantly correlated with post-transplant PTH. After selecting patients with serum creatinine  $< 1.5$  mg/dl ( $n = 46$ ), pre-transplant PTH emerged as the more important predictor of post-transplant PTH ( $r = 0.58$ ;  $P < 0.0001$ ). After controlling for creatinine, the partial correlation was  $r = 0.53$ ,  $P < 0.0001$ . We concluded that spontaneous resolution of hyperparathyroidism after renal transplantation is uncommon. In addition, the magnitude of pre-transplant hyperparathyroidism and the renal function determine the long-term post-transplant parathyroid function.

**Key words:** bone; parathyroid hormone; persistent hyperparathyroidism; renal transplantation

### Introduction

Renal transplantation represents the treatment of choice for most uraemic patients. Despite the attainment of a normal metabolic environment which is expected to resolve bone and mineral alterations, this

is not always the case. Transplanted patients are at risk of developing several conditions such as persistent hyperparathyroidism, osteopenia and aseptic necrosis [1]. As a consequence of the restoration of renal function and the normalization of calcium, phosphorus and calcitriol [2,3], serum parathyroid hormone (PTH) progressively decreases during the first 3–6 months after grafting [4–9]. However, 1 year after transplantation more than half of the patients show incomplete resolution of hyperparathyroidism [6,8–11]. This may be due to incomplete normalization of renal function [1,7,12] and/or to an incomplete resolution of the pre-transplant parathyroid hyperplasia [1,12].

More than 2 years after renal transplantation, the degree of resolution of hyperparathyroidism in patients maintaining a good renal function has been reported only rarely [13,14]. Lobo *et al.* [13] observed that 55% of such patients have PTH concentrations greater than normal. However, the factors involved in this lack of resolution of hyperparathyroidism after long-term renal transplantation are not well established.

The aim of the present study was to examine the long-term ( $> 2.5$  years) parathyroid status of renal transplant patients immunosuppressed with cyclosporin and with a well functioning graft ( $< 2$  mg/dl of creatinine). The factors responsible for the persistence of hyperparathyroidism, including pre-transplant PTH, were analysed.

### Materials and methods

#### Patients

The 62 patients from our transplant clinic that fulfilled the following criteria were studied: (i) age  $> 18$  years at transplantation; (ii) cyclosporin (CsA)-based immunosuppression; (iii) more than 2.5 years after transplantation; (iv) good and stable graft function ascertained by creatinine  $< 2$  mg/dl; and (v) availability of pre-transplant intact PTH (iPTH) measurements in the month preceding transplantation. No patient had had a rejection episode in the last 6 months, and none had received calcium, phosphorus or vitamin D supplements after transplantation. None of them were

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receiving oestrogen or anti-epileptics or had been parathyroidectomized.

Patient age was  $44.9 \pm 11.3$  years (range: 24–68), 42 were males and 20 females. Only three patients were diabetics. Mean dialysis duration before transplantation was  $31.1 \pm 31$  months (range: 1–150), 42 were on chronic haemodialysis and 20 on CAPD. Mean follow-up after transplantation was  $68.6 \pm 26.8$  months (range: 30–124).

Immunosuppression consisted of anti-lymphoblastic globulin (Merieux, Lyon, France) for induction, and prednisone, Cs and azathioprine for maintenance [6,15]. Recipients older than 50 years did not receive azathioprine. The dose of prednisone was 0.3 mg/kg body weight/day during the first 3 months, and then was reduced gradually to 10 mg/day by 1 year. Episodes of acute rejection were treated initially with three boluses of 500 mg of i.v. methylprednisolone. Resistant episodes were treated with a 10-day course of OKT3 (5 mg/day) (Ortho Pharmaceutical, NJ).

### Determinations

Total serum calcium corrected for albumin, phosphorus and creatinine were measured using a computerized autoanalyser [6]. Serum concentrations of iPTH were determined by an immunoradiometric assay (IRMA) (Nichols Institute, San Juan Capistrano, CA). Creatinine clearance from a 24 h urinary specimen was also calculated.

### Statistical analysis

Students 't' test was used to compare two group means. Linear regression analysis was used to compare two quantitative variables. In order to correct for co-linearity with other quantitative variables, partial correlation analysis was used.  $\chi^2$  with Yates correction, or Fisher's exact test, as appropriate, were used to compare proportions. A *P* value <0.05 was considered to be significant. Results are expressed as mean  $\pm$  SD. All computations were obtained using the SPSS 6.1.3 software for Windows® (Chicago, IL).

## Results

Table 1 summarizes clinical and biochemical parameters. At long-term, PTH after transplantation decreased significantly with respect to pre-transplant

**Table 1.** Clinical and biochemical data of 62 long-term renal transplant patients with good renal function (serum creatinine <2 mg/dl)

Follow-up (months)	$68.6 \pm 26.8$
No. of acute rejections per patient	$0.46 \pm 0.67$
Patients with acute rejections (%)	36%
Cumulative methylprednisolone (mg)	$886.5 \pm 1205$
Patients under loop diuretics (%)	10%
CsA concentrations (ng/ml)	$174 \pm 40$
Serum creatinine (mg/dl)	$1.3 \pm 0.3$
Creatinine clearance (ml/min/1.73 m <sup>2</sup> )	$75.4 \pm 30$
Serum calcium (mg/dl)	$10.3 \pm 0.5$
Serum phosphorus (mg/dl)	$3.4 \pm 0.6$
Pre-transplant serum PTH (pg/ml)	$213.6 \pm 229$
Post-transplant serum PTH (pg/ml)	$116.4 \pm 70^a$

CsA: cyclosporin A (monoclonal FPIA).

<sup>a</sup>*P*<0.01 vs pre-transplant PTH.

levels. However, only 22.6% of patients showed PTH concentrations in the normal range. On the other hand, PTH values greater than twice the upper normal limit (>130 pg/ml) were not uncommon (27.4%).

A direct and significant correlation between both plasma creatinine and creatinine clearance with post-transplant PTH was found ( $r=0.43$ ;  $P<0.01$ , and  $r=0.44$ ;  $P=0.001$ , respectively). Although a direct and significant correlation between pre- and post-transplant PTH was also observed ( $r=0.31$ ;  $P=0.02$ ), after controlling for serum creatinine the significance was lost ( $r=0.2$ ;  $P=0.1$ ). No significant correlation between post-transplant PTH and age, dialysis duration, time after transplantation, number of acute rejections, cumulative methylprednisolone and CsA concentrations was found.

A separate analysis of patients with a serum creatinine <1.5 mg/dl was performed ( $n=46$ ; creatinine clearance:  $80 \pm 29$  ml/min/1.73 m<sup>2</sup>). In these patients with excellent renal function, a significant correlation between post-transplant PTH and serum creatinine was still present ( $r=0.31$ ;  $P=0.04$ ). However, pre-transplant PTH showed a better correlation with post-transplant PTH ( $r=0.58$ ;  $P<0.0001$ ) (Figure 1). After controlling for serum creatinine, the correlation persisted ( $r=0.53$ ;  $P<0.0001$ ). The four patients receiving loop diuretics showed plasma PTH levels similar to the rest ( $102.5 \pm 35$  vs  $100.5 \pm 56$  pg/ml, respectively).

## Discussion

The prevalence of persistent hyperparathyroidism after renal transplantation has been generally appreciated using hypercalcaemia as an index [1]. Recent studies have measured iPTH in unselected patients during the first post-transplant year, and a high prevalence of values greater than the normal range has been reported [6,8–11]. However, studies reporting long-term PTH values are scarce, especially in normocalcaemic patients [13,14]. Again, the reported frequency of greater than normal PTH at this time is high (>50%) [13,14]. The factors involved in this lack of resolution of hyperparathyroidism after long-term renal transplantation are not well established. To our knowledge, the relative roles of the graft function attained and the degree of pre-transplant hyperparathyroidism have not yet been established.

The present study demonstrates that after a mean follow-up of 69 months, only 23% of patients have PTH concentrations in the normal range, and that 27% show a value more than twice the upper normal limit. It is important to note that the majority of the study patients were normocalcaemic (75%). This finding suggests that there is no trend towards spontaneous resolution of hyperparathyroidism in long-term renal transplant patients with an acceptable renal function (serum creatinine <2 mg/dl).

In long-term transplant patients with serum creatinine <2 mg/dl, the degree of renal function was the more important determinant of plasma PTH. However,

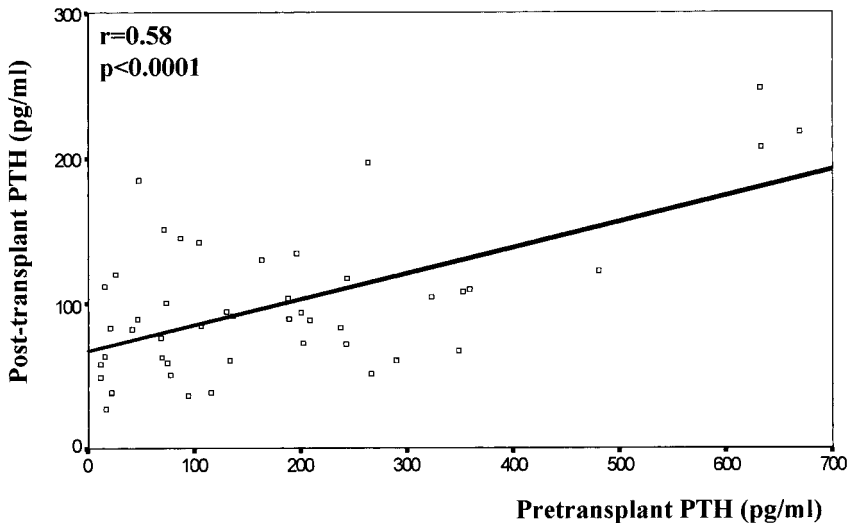


Fig. 1. Correlation between pre-transplant and post-transplant PTH levels 71.4 ± 28 months after transplantation in 46 patients with serum creatinine < 1.5 mg/dl.

pre-transplant PTH emerged as the more important predictor when those patients with an excellent renal function (serum creatinine < 1.5 mg/dl) were analysed separately (Figure 1). This finding suggests that when other confounding variables such as mild to moderate renal failure are controlled, the degree of parathyroid hyperplasia at the time of transplantation emerges as an important factor determining the parathyroid function in the long-term. As suggested by Parfitt *et al.* [16,17], the long lifespan of parathyroids cells (~36 years) contributes to the very slow involution of the gland after transplantation. Additional factors such as suboptimal levels of calcitriol [13], a relative decrease of parathyroid vitamin D receptors [18] and steroid-induced increase in PTH gene expression [19] may play an additional role in maintaining parathyroid cell hyperplasia after successful renal transplantation in spite of attaining an excellent long-term renal function.

In conclusion, spontaneous resolution of hyperparathyroidism after renal transplantation is uncommon. The degree of renal function and the magnitude of hyperparathyroidism during chronic dialysis are the major determinants of long-term parathyroid function. Thus, in order to prevent significant persistent hyperparathyroidism after renal transplantation, efforts should be made to control secondary hyperparathyroidism effectively during dialysis, and to establish strategies to minimize chronic transplant nephropathy.

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