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Reduced parathyroid functional mass after successful kidney transplantation

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Reduced parathyroid functional mass after successful kidney transplantation.

Background. Chronic uremia is responsible for secondary hyperparathyroidism (HPT II). Parathyroid secretion usually tends to normalize after kidney transplantation (KT), but the parameters of the reversibility of HPT II remain poorly defined, particularly the intrinsic mechanisms underlying the improvement of parathyroid function.

Methods. The kinetic functional parameters of the ionized calcium (iCa)/parathormone (PTH) relationship curve were studied in 11 patients with mild to moderate HPT II one and six months after successful KT. Hypercalcemia and hypocalcemia were induced, respectively, by $CaCl_2$ and Na_2-ethylenediaminetetraacetic acid (Na_2-EDTA) infusions.

Results. The mean glomerular filtration rate remained stable during follow-up. Basal PTH decreased from 195 ± 54 pg/ml before KT to 70 ± 12 pg/ml six months later ($P < 0.005$). During the tests, mean PTH levels decreased significantly between the two measured times for all iCa levels, indicating an improved parathyroid function. An analysis of the kinetic parameters of the curves showed significant decreases of the mean maximal and minimal PTH levels, respectively, from 340 ± 91 to 220 ± 30 pg/ml ($P = 0.03$) and from 25 ± 6 to 15 ± 5 pg/ml ($P = 0.005$). On the other hand, no change was noted in the parathyroid-cell calcium-sensitivity parameters (slope, set point) assessed using two different approaches, either the entire curve or the limited calcium-mediated suppression curve.

Conclusion. Improvement of the parathyroid function between the first and sixth months post-KT seems mainly attributable to a reduction of the parathyroid functional mass.

Metabolic abnormalities induced by long-standing renal failure lead to renal osteodystrophy for which secondary hyperparathyroidism (HPT II) is one of the major features. Successful kidney transplantation (KT) corrects the endocrine and metabolic imbalances and the main abnormalities responsible for HPT II through the first months [1, 2]. Normalization of renal function corrects phosphorus retention and increases renal production of calcitriol [2]. Nevertheless, these early favorable events are not followed by the rapid normalization of parathormone (PTH) secretion. Detailed studies of the early changes after KT show a progressive decrease of the mean basal PTH levels, but without complete normalization [1, 2]. Biochemical HPT II can persist for several years after successful KT [1, 3, 4], even when the glomerular filtration rate (GFR) is almost normal [4, 5]. After more than one year, many patients still have absolute or relative HPT II with inappropriate PTH levels [6].

However, the extent of parathyroid function recovery and the intrinsic mechanisms underlying the lowering of PTH secretion after KT remain incompletely defined. It has been established that post-KT HPT II is not a reflection of autonomous function, as the parathyroid glands remain sensitive to acute changes in ionized calcium (iCa) and particularly to the suppressive effect of induced hypercalcemia [7, 8]. Furthermore, it has been shown that parathyroid function in renal transplant recipients is characterized by a sigmoidal relationship curve between iCa and PTH [7], as in normal subjects [9]. But information is scarce about the natural course of kidney recipients' parathyroid function, and it has not been determined whether the lowered PTH secretion is due to a reduced parathyroid functional mass or a change in the regulation of the PTH release by the parathyroid cell. This prospective study was undertaken to investigate changes in the PTH secretion parameters of the iCa/PTH relationship curve during the first six months post-KT in order to define the conditions underlying the reversibility of HPT II in an homogeneous group of patients with mild or moderate biochemical HPT II.

Key words: secondary hyperparathyroidism, parathyroid mass, calcium sensitivity, PTH secretion, parathyroid function, renal graft.

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METHODS

Patients

Eleven patients were included in the study after they had received a functioning renal allograft from cadaveric

Table 1. Characteristics of the patients ($N = 11$) before transplantation

Sex (M/F)	8/3
Age *years*[a]	44.3 ± 2.3 (27–51)
Nephropathy *N*	
Interstitial	2
Glomerular	7
Polycystic	2
Dialysis	
Mode (HD/CAPD)	9/2
Duration *months*	26 ± 19 (1–60)
Basal PTH *pg/ml*[a]	195 ± 54 (41–665)
Ionized Ca *mmol/liter*[a]	1.21 ± 0.02 (1.13–1.25)
Alpha-calcidiol therapy *N*	2
Phosphate binders therapy ($CaCO_3$) *N*	10

[a] Data are: mean ± SEM (range)

donors. All patients gave their informed consent to participate in the study. Characteristics of the patients before KT are summarized in Table 1. Three patients had a basal PTH of less than 100 pg/ml. Seven had levels between 100 and 500 pg/ml, and one patient had a basal PTH level of 665 pg/ml. None of them had hyperphosphoremia of more than 2.2 mmol/liter.

Exclusion criteria were previous parathyroid surgery, previous KT, or serum creatinine levels above 180 μmol/liter during the six months of follow-up. After transplantation, none of them received phosphate binders or vitamin D analogues. The triple-drug immunosuppressive regimen consisted of corticosteroid, azathioprine, and cyclosporine A. The dose of cyclosporine was adjusted to obtain a residual blood concentration between 100 and 200 ng/ml. Methylprednisolone was given intravenously during the first week at the dose of 120 mg/day and was then replaced by oral prednisone and progressively reduced over three months until a minimal dose of 4 mg/day was reached. The mean prednisone dose was 25.8 ± 2.7 mg/day at one month and 4.5 ± 0.5 mg/day at six months.

Biochemical follow-up

Blood samples were collected immediately before surgery and at 15 days and 1-, 3-, and 6-months post-KT. The following serum parameters were measured: creatinine, iCa, phosphorus, and intact PTH.

1-25$(OH)_2$ vitamin D_3 and osteocalcin [bone Gla protein (BGP)] were measured before KT and at one-, three-, and six-months post-KT. Phosphorus and creatinine determinations were performed using a Technicon Autoanalyzer. iCa was determined with a Corning analyzer. Intact PTH was measured using a two-site chemiluminometric immunoassay for human PTH 1-84 (Magic Lite; Ciba Corning Diagnostics Corp., Medfield, MA, USA). BGP was determined by radioimmunoassay (PR; Cis Biointernational, Gif-sur-Yvette, France). Serum 1,25$(OH)_2$-vitamin D_3 was assessed with a radioreceptor assay (^{3}H RRA Kit; Incstar, Stillwater, MN, USA) after extraction through C_{18}OH cartridges. The GFR was evaluated at the same time as the dynamic parathyroid function tests, one and six months after KT, by means of an isotopic method based on the urinary clearance of ^{51}CrEDTA [10].

Evaluation of parathyroid function

For every patient, parathyroid function was evaluated one- and six-months post-KT. We used the previously described protocol [11] of a PTH secretion-stimulation test during which hypocalcemia is progressively induced, followed two days later by a PTH secretion-suppressibility test, which consists of progressively inducing hypercalcemia.

Parathormone secretion-stimulation test. A total amount of 50 mg/kg of body weight of disodium ethylenediaminetetraacetate (Na_2-EDTA; Pharmy II, St-Germain-en-Laye, France) was infused intravenously over a three-hour period. During that time, 500 ml of 5% glucose were infused via the same catheter to dilute Na_2-EDTA. Blood samples were withdrawn from the contralateral arm at 0, 30, 60, 90, 120, 150, and 180 minutes for simultaneous measurements of iCa and PTH.

Parathormone secretion-suppressibility test. Calcium chloride ($CaCl_2$, 100 mg/ml; Brown Medical SA, Boulogne, France) was infused intravenously over a three-hour period at a constant rate of 3 mg of elemental calcium/kg body wt/hr. During that time, 300 ml of 5% glucose were infused via the same catheter to dilute calcium. Blood samples were withdrawn from the contralateral arm at 0, 10, 20, 30, 60, 120, and 180 minutes for simultaneous measurements of iCa and PTH.

From these data, the individual iCa/PTH curves plotted for each patient enable the calculation of the usual secretory parameters of parathyroid function according to Felsenfeld and Llach [12]: basal PTH, minimal PTH, maximal PTH, and the basal/maximal PTH ratio when PTH levels are expressed in absolute values; slope (calculated from the more linear part of the curve), and set point of Ca (as iCa concentration corresponding to 50% maximal PTH) when PTH levels are expressed as percentages of maximal PTH.

In addition, as previously described [13], we also evaluated the slope and the set point derived from the limited calcium-mediated PTH-suppression curve, respectively, defined as partial slope and EC_{50}. For calculation of these two parameters, the curves derived from the PTH-suppressibility test results were expressed as percentages of basal PTH for each patient, and the data were linearized by plotting the natural logarithm (Ln) of the percentage of basal PTH versus the iCa concentration at each time point. Linear regression analysis generated the regression equation: Ln(% basal PTH) = a + b[iCa]. Partial slope, defined as *b*, represents the sensitivity of the para-

thyroid cell to the iCa increment. EC_{50}, defined as the iCa concentration at 50% of the maximal PTH suppression, is thought to have the same meaning of the set point [13]: [(100% + ending PTH% suppression)/2].

Statistical analysis

All the results are expressed as means ± SEM. For comparison of basal data between different time periods or for comparison of PTH concentrations during dynamic tests between one- and six-months post-KT, we used Wilcoxon's matched-pairs signed-rank test. For comparison of different basal data at the same time, we used Spearman's correlation test. The software used was Stata 4.0 (Stata Corp., College Station, TX, USA). Statistical significance was defined as $P < 0.05$.

RESULTS

Baseline and post-kidney transplant evolution of bone-metabolism parameters and renal function

All patients had a functioning renal graft, as assessed by the onset of diuresis and the decrease of serum creatinine, within the first postoperative days, except for one patient, who presented transiently delayed graft function during the first week after KT. Renal function, assessed by serum creatinine and isotopic clearance of ^{51}CrEDTA, remained stable in all patients throughout the entire duration of the study. Mean serum creatinine was 124 ± 12 μmol/liter at one-month and 122 ± 10 μmol/liter at six-months post-KT (P = NS), and the mean GFR was 48 ± 5 ml/min at one-month and 57 ± 8 ml/min at six months post-KT (P = NS). The evolution of the bone metabolism parameters during the study is shown in Figure 1.

Serum iCa (Fig. 1A), which was at the lower limit of the normal range before KT, increased significantly, from 1.21 ± 0.02 to 1.35 ± 0.03 mmol/liter at the third month ($P < 0.03$) and then remained stable. Between three and six months, 64% (7/11) of the patients presented hypercalcemia (iCa > 1.3 mmol/liter). During that period, iCa was positively correlated with PTH levels (at three months, $P < 0.02$; at six months, $P < 0.03$).

Serum phosphorus (Fig. 1B) dramatically decreased during the first month from 1.68 ± 0.1 to 0.76 ± 0.1 mmol/liter ($P < 0.003$), increased slightly after one month to reach the normal range, and then remained unchanged during follow-up. Seven of the 11 patients developed transient hypophosphoremia during the study.

At the time of KT, the mean basal serum PTH concentration was 195 ± 54 pg/ml, and this decreased rapidly during the first 15 days after KT ($P < 0.05$). Between one and six months, a significant decrease until 70 ± 12 pg/ml ($P < 0.02$) was also observed (Fig. 1C).

Serum calcitriol progressively increased over the first six months, with the mean level attaining the normal range as early as the first month (Fig. 1D).

Serum BGP rapidly declined during the first month and then gradually increased to threefold the upper limit of the normal range, where it remained constant (Fig. 1E).

Ionized calcium and parathormone changes during $CaCl_2$ infusion

As shown in Figure 2A, infusion of $CaCl_2$ induced a progressive and significant increase of serum iCa levels. It should be noted that the mean iCa levels at the end of the tests were not different at one and six months (1.73 ± 0.05 vs. 1.79 ± 0.02 mmol/liter, P = NS). There was also no difference between the two times concerning either the magnitude of the iCa increase (0.43 ± 0.04 vs. 0.46 ± 0.02 mmol/liter, P = NS) or the rate of increase assessed by the slope of the regression line of serum iCa against time (0.0023 vs. 0.0022 mmol/liter/min, P = NS). These results enabled us to compare the mean PTH concentrations between one- and six-months post-KT at each time point of the tests. At both times, serum PTH levels decreased in a curvilinear manner (Fig. 2B). The comparison revealed that the mean PTH concentrations were lower at six months than at one month at each time point. This difference was always significant ($P < 0.05$), except at 180 minutes, thus suggesting improvement of parathyroid function between the two times.

Concerning the kinetic parameters of the iCa/PTH curves (Table 2), a minimal PTH-secretion plateau defining minimal PTH could be obtained for all patients at one and six months. Between one and six months, the mean minimal PTH decreased significantly from 25 ± 6 to 15 ± 5 pg/ml (P = 0.005). On the other hand, when the curves were plotted as the percentage of basal PTH against iCa (Fig. 3), no change of either EC_{50} or the partial slope was observed during this period.

Ionized calcium and parathormone changes during Na_2-EDTA infusion

Infusion of Na_2-EDTA induced a progressive decline in serum iCa (Fig. 4A). The mean iCa levels at the end of the tests were not statistically different at one and six months (1.03 ± 0.03 vs. 1.08 ± 0.03 mmol/liter, P = NS). Concerning iCa changes, there were no differences in the magnitude of the decrease (0.27 ± 0.01 vs. 0.25 ± 0.02 mmol/liter, P = NS) or in the slope of the regression line of serum iCa against time (−0.0014 mmol/liter/min). These results enabled PTH concentrations to be compared between one- and six-months post-KT at the different time points. During the tests, serum PTH levels progressively increased (Fig. 4B). A comparison revealed that PTH levels were significantly lower at six months than at one month at each time point, suggesting a marked improvement of parathyroid function between the two times post-KT.

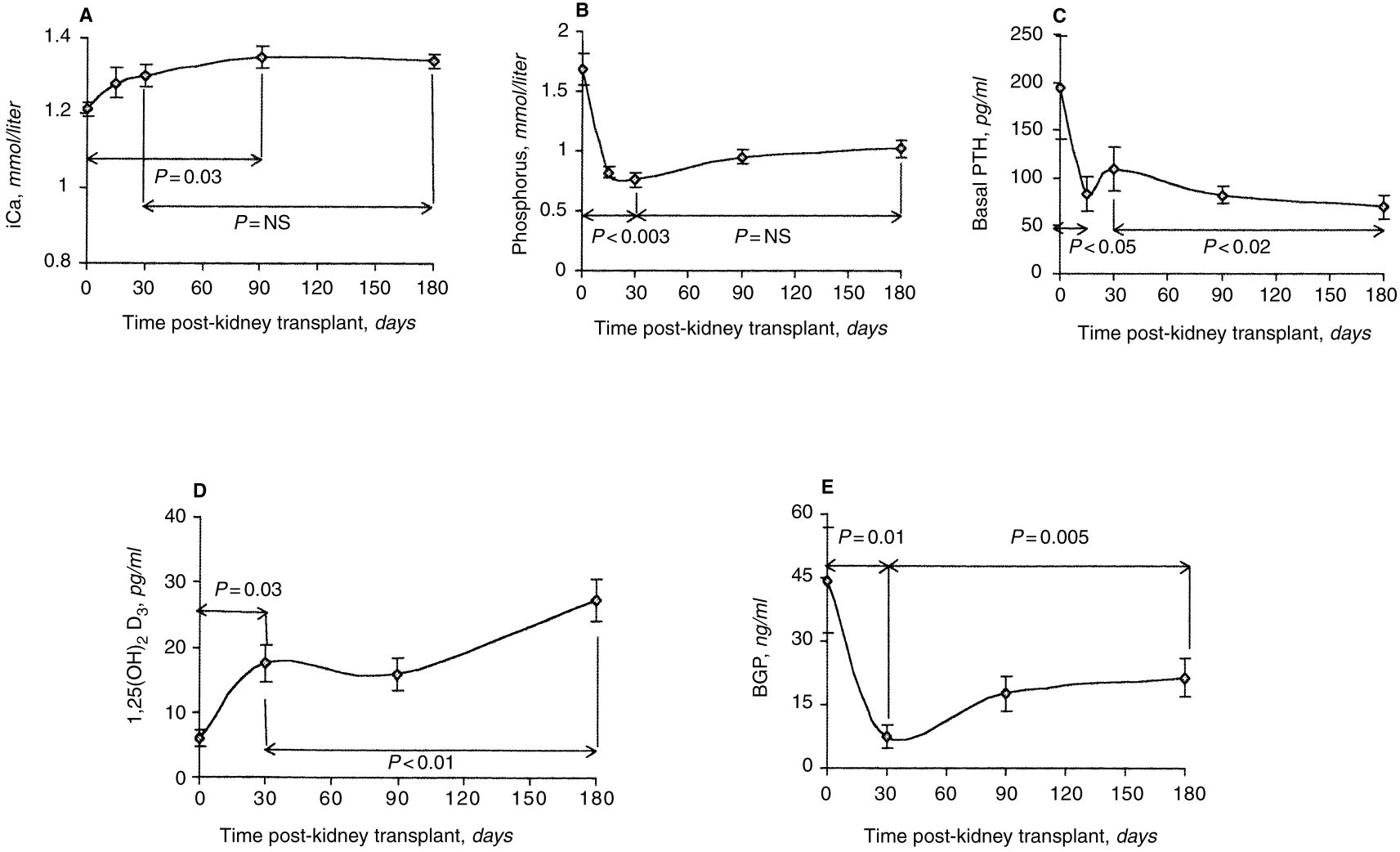

Fig. 1. Changes in the main bone metabolism parameters in the serum during the first six months following kidney transplantation (KT). Values are expressed as means ± SEM for the 11 patients. (*A*) Ionized calcium (iCa; normal range, 1.2 to 1.3 mmol/liter). (*B*) Phosphorus (normal range, 0.8 to 1.2 mmol/liter). (*C*) Intact parathormone (PTH; normal range, 10 to 60 pg/ml). (*D*) Calcitriol (normal range, 12 to 32 pg/ml). (*E*) Bone Gla protein (BGP; normal range, 3.7 to 6.9 ng/ml).

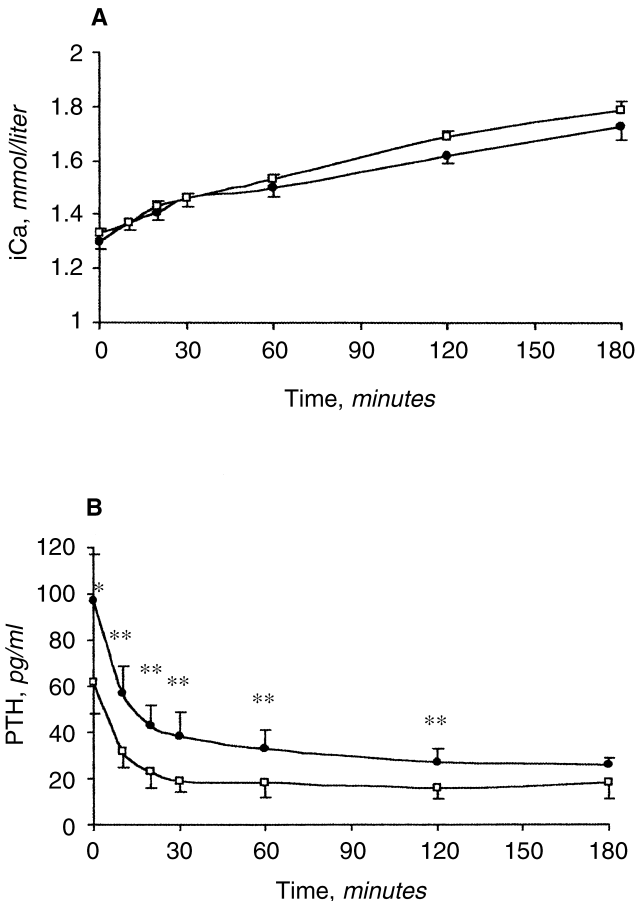

Fig. 2. (*A*) Serum intact calcium (iCa) concentrations during a three-hour infusion of calcium ($CaCl_2$) one month (●) and six months (□) after kidney transplantation (KT). Values are expressed as means ± SEM for the 11 patients. The magnitude, rate of iCa increase, and the end iCa levels were comparable at the two times. (*B*) Parathormone (PTH) levels during a three-hour infusion of calcium at one month (●) and six months (□) after KT. Values are expressed as the means ± SEM of the 11 patients. $*P < 0.05$; $**P < 0.01$ indicate differences between PTH values at one- and six-months post-KT at the designated time points.

Maximal PTH was defined as the highest PTH-secretion plateau reached by the patients during Na_2-EDTA infusion. In this respect, we excluded four patients for whom such a plateau could not be obtained at the two tests: Two patients did not reach a maximal secretion plateau at one month. Another did not attain it at six months, and the last one had no maximal secretion plateau at one and six months. In the seven patients for whom the comparison was possible, the mean maximal PTH concentration decreased from 340 ± 91 at one month to 220 ± 30 pg/ml at six months ($P = 0.03$; Table 2). Plotting the results of both hypocalcemia and hypercalcemia tests together for these seven patients generated the well-known sigmoidal curve of the iCa/PTH relationship. A comparison of the composite iCa/PTH curves for the

Table 2. Evolution of the kinetic parameters of the iCa/PTH curves between 1 and 6 months after KT ($N = 11$)

Parameter	1 month	6 months	*P*
Minimal PTH *pg/ml*	25 ± 6	15 ± 5	0.005
EC_{50} *mmol/liter*	1.37 ± 0.03	1.38 ± 0.01	NS
Partial slope	−6.6 ± 1.2	−9.4 ± 2.4	NS
Maximal PTH[a] *pg/ml*	340 ± 91	220 ± 30	0.03
Slope[a] *%/mmol·l⁻¹*	−369 ± 60	−365 ± 36	NS
Set point[a] *mmol/liter*	1.25 ± 0.03	1.27 ± 0.03	NS
Basal/max PTH[a] %	33 ± 3	27 ± 2	NS

Results are expressed as means ± SEM.
[a] $N = 7$

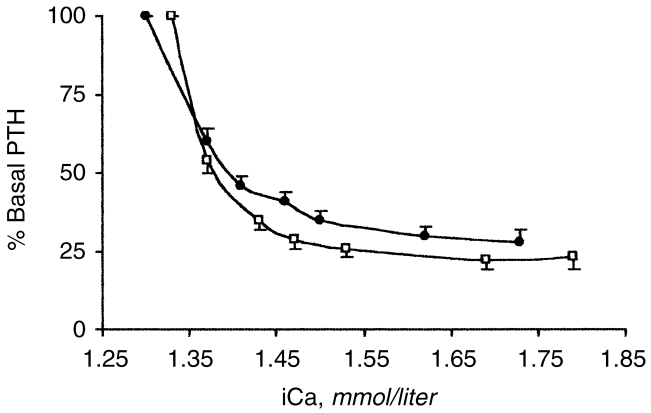

Fig. 3. Ionized calcium (iCa)/parathormone (PTH) curves based on the hypercalcemia tests of the 11 patients with PTH levels expressed as the percentage of basal PTH (means ± SEM) at one (●) and six months (□) after transplantation. EC_{50} and partial slope were not significantly different for the two times.

two test times showed lower absolute PTH levels six months after KT when the entire range of iCa concentrations was considered, with a significant difference on the iCa intervals ranging from 0.95 to 1.05 and 1.41 to 1.75 mmol/liter (Fig. 5A). However, when the curves were plotted with PTH levels expressed as percentages of maximal PTH, neither the set point of calcium nor the slope of the entire curve varied significantly (Table 2 and Fig. 5B) between one- and six-months post-KT. The basal/maximal PTH ratio did not vary significantly during this period, indicating no change of the basal operational status of the glands between the two periods.

DISCUSSION

This study was designed to determine the changes in parathyroid function after KT. Using both static and dynamic tests in patients with mild or moderate biochemical HPT II, we observed between one- and six-months post-KT significantly decreased mean PTH concentrations over a wide range of iCa levels, indicating improved parathyroid function. The evolution of the kinetic parameters of the iCa/PTH relationship curve suggests that

this improvement is mainly due to a reduction of the parathyroid functional mass. One month after KT, the mean maximal PTH and minimal PTH levels, both indicators of functional mass [12], were approximately threefold higher than those reported in normal subjects [9]. Five months later, a significant decrease of these parameters, by more than 35%, was observed. To the best of our knowledge, such a sequential study post-KT has never been conducted in humans. A previous comparison of the mean iCa/PTH curve of transplant recipients with that of a normal control group [7, 14] led the authors to conclude that the very high PTH levels, which were measured at all iCa levels in the transplant-recipients group, likely reflected increased gland mass rather than altered sensitivity of the parathyroid cell, because there was no difference between the slopes of the curves for the two groups. More recently, using a model of experimental HPT II in 5/6 nephrectomized rats, parathyroid function was studied before and after isogenic KT [15]. As in our patients, HPT II was rapidly reversed with normalization of both maximal and minimal PTH values shortly after transplantation, but the slope and set point were not evaluated in this study [15]. In our current study, we did not observe any significant change in these parameters assessed by the entire curve (set point, slope) or the limited PTH-suppression portion of the curve (EC_{50}, partial slope). These data suggest that the correction in the regulation of PTH release by iCa does not account for the lowering of PTH secretion after KT. However, the real physiopathological meaning of the set point must be interpreted with caution, as some authors consider that it might not necessarily reflect a specific intrinsic property of the parathyroid gland *in vivo* and could be directly modified by sustained changes in the existing serum iCa [16, 17].

It has long been known that parathyroid enlargement is a major determinant of PTH hypersecretion [18], thus explaining the success of surgical parathyroid mass reduction. A few studies [13, 14] have established a relationship between functional mass parameters and the parathyroid size evaluated by ultrasonography [13] or measured at the time of parathyroidectomy in transplant patients [14]. Therefore, our findings could be compatible with a reduction of the gland's size due to regression of parathyroid cell hypertrophy or hyperplasia, although in this study, the anatomical parathyroid mass was not evaluated. However, experimental studies tend to demonstrate that cellular hypertrophy is much more easily reversible than hyperplasia after removal of stimuli (abstract; Chin et al, *J Bone Miner Res* 11(Suppl 1):S121, 1996) [19–21].

The improvement of the parathyroid function may be due to changes in calcemia, phosphoremia, and calcitriol levels observed after KT. Prolonged hypocalcemia has been implicated in parathyroid gland growth, hypertrophy [22], or hyperplasia [23]. The significant rise of iCa observed in our patients during the first three months led to a reduction of basal PTH, and furthermore, hypercalcemia observed after the third month (mean iCa level > 1.30 mmol/liter) likely contributed to improve the parathyroid function. Moreover, these changes in iCa could be the consequence of the progressive recovery of the normal calcemic activity of PTH. Many factors involved in the resistance to this PTH activity during uremia, including hyperphosphatemia, low calcitriol level, and uremia itself, tended to normalize after KT in our patients. Subsequently, after the third-month post-KT, we, like other researchers, found a positive correlation between PTH and iCa [6, 24].

The second factor potentially able to explain the improved parathyroid function is the recovery of normal

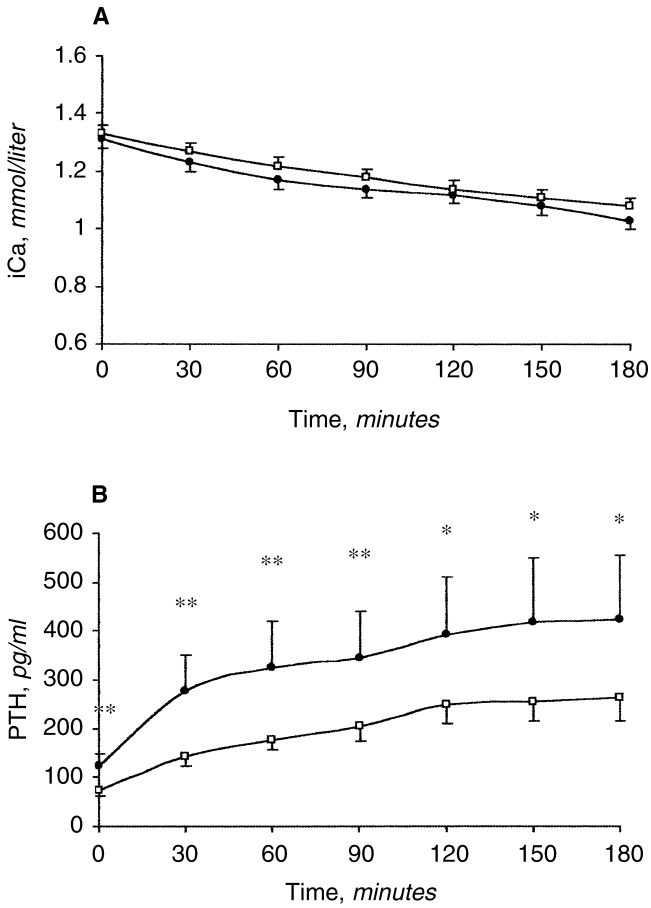

Fig. 4. (*A*) Serum ionized calcium (iCa) concentrations during a three-hour infusion of Na_2-EDTA at one (●) and six months (□) after kidney transplantation (KT). Values are expressed as means ± SEM of the 11 patients. The magnitude, rate of iCa decrement, and the end iCa level were comparable at the two times. (*B*) PTH levels during a three-hour infusion of Na_2-EDTA at one month (●) and six months (□) after KT. Values are expressed as means ± SEM of the 11 patients. $^*P < 0.03$ and $^{**}P < 0.01$ denote differences between PTH values at one and six months post-KT at the designated time points.

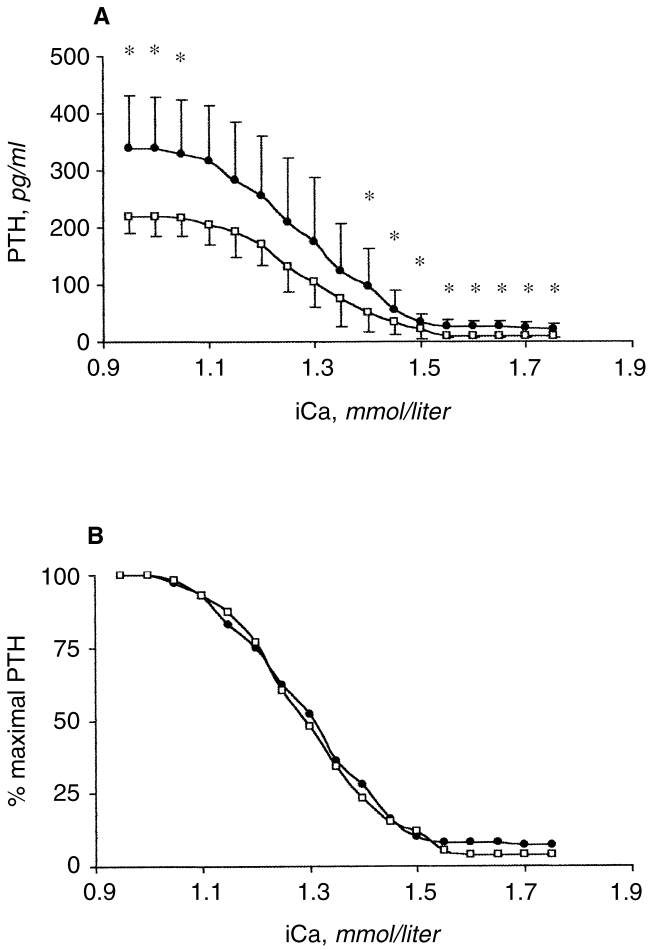

Fig. 5. Composite iCa/PTH curves from seven patients for whom a plateau of maximal secretion of parathormone (PTH) could be obtained one and six months post-KT. (*A*) PTH expressed as means ± SEM of the absolute values at one-month (●) and six months (□) after KT. $*P < 0.05$ denotes differences between PTH values at one and six months post-KT at the designated iCa level. (*B*) PTH, expressed as the percentage of maximal PTH at one (●) and six months (□) after KT, showed no change of either the set point or the slope of the curves at the two times.

circulating calcitriol levels observed during the first months after KT. The direct suppressive effect of calcitriol on the parathyroid gland has been well established, not only on PTH synthesis, but also on cellular proliferation [12, 23, 25, 26]. It should be noted that a regression of parathyroid enlargement, assessed by ultrasonography, and improvement of parathyroid functional mass parameters by more than 30% have been reported after calcitriol therapy in hemodialysis patients [27, 28]. Furthermore, the elimination of uremic toxins following KT probably improves the calcitriol–receptor interaction with its target gene [29].

The third major factor is the normalization of serum phosphorus. Like others [1, 2], during the first month post-KT we observed a rapid decrease of serum phosphorus in our patients who thereafter were all normophosphoremic or hypophosphoremic. Hyperphosphoremia is one of the major causes of HPT II [30, 31]. Indeed, a direct effect of phosphorus on PTH secretion has been established [11, 32–34], and it has been shown that phosphorus restriction could prevent parathyroid gland growth [34]. However, some authors failed to demonstrate a change in the size of the parathyroid glands in uremic rats with severe hyperparathyroidism fed with a low-phosphorus diet (abstract; Takahashi et al, *J Am Soc Nephrol* 8:580A, 1997).

However, in spite of all of these beneficial metabolic and endocrine changes, the normalization of parathyroid function is not complete six months after KT. The main features of this incomplete correction are the persistently high basal PTH, iCa, and BGP concentrations. In particular, BGP, after an initial transient decline because of the high corticosteroid dose [2, 35], remains more than threefold above the normal range at six-months post-KT, suggesting the persistence of abnormally high bone turnover. For some authors the persistent HPT II after KT does not show any spontaneous tendency to improve [3, 4]. A first explanation for this abnormality is the persistence of parathyroid hyperplasia, linked to its slow regression, because parathyroid tissue undergoes low cell turnover [19, 36].

The occurrence before KT of nodular parathyroid growths, known to be insensitive to calcitriol's inhibitory action [37] and unable to regress [38], seems unlikely in our patients.

On the other hand, although renal function can generally be considered optimal in our transplant recipients, with a mean GFR of about 50 ml/min, this rate is certainly insufficient to suppress all of the PTH stimulatory signals and insure the normalization of the parathyroid function, which probably is one of the main factors explaining this persistent HPT.

In conclusion, KT rapidly induces a partial reversibility of HPT II in patients with mild or moderate biochemical HPT II. Through a sequential determination of the iCa/PTH relationship curve, we found that the improved parathyroid function observed between the first month and the sixth month after KT seemed mainly to be caused by a reduction of the parathyroid functional mass. Maybe such an evolution in these patients was possible because they did not present with severe HPT II, and thus, there may have been no severe histological parathyroid changes such as nodular growth. It will be interesting to study the evolution of the parathyroid function after KT in patients with more severe HPT II, and determine the extent of the recovery and the time necessary under optimal transplantation conditions.

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