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Effects of Parathyroidectomy on Renal Allograft Survival

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Key Words

Transplantation, renal · Kidney · Parathyroidectomy · Allograft survival, kidney · Graft survival · Mortality · Hyperparathyroidism · Calcium · Parathyroid hormone

Abstract

Background: Hyperparathyroidism is a common problem secondary to renal insufficiency and is often not entirely resolved after renal transplantation (TX). ***Methods:*** In this retrospective analysis, the effects of parathyroidectomy (PTX) on allograft function were evaluated and the risk factors involved in allograft deterioration in patients after PTX will be discussed. ***Results:*** The rise in creatinine was steeper 1 year after PTX compared to 2 years before PTX in the majority (13 of 22) of patients. Compared to a cohort without PTX, graft survival was significantly decreased by 60% in 6 years ($p < 0.0001$). After multivariate adjustment, risk factors attributed to graft function included baseline creatinine ($p = 0.02$), baseline systolic blood pressure ($p = 0.04$) and time between TX and PTX, but not PTX itself. The peri-PTX drop in serum calcium was significantly more accentuated in patients exhibiting a worsening of graft function after PTX ($p = 0.04$). ***Conclusions:*** In patients requiring PTX, graft function is in danger of worsening. Since many factors contribute to this negative correlation and no association with parathyroid hormone (PTH) levels before PTX has been observed, we do not recommend prophylactic PTX on the basis of PTH levels only. However, appropriate management of peri-PTX risk factors is highly important. If the clinical situation, e.g. progressive renal osteodystrophy, requires removal of parathyroid glands, the procedure should be performed, if possible, in the presence of stable graft function.

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Introduction

Hyperparathyroidism (HPT) is a common problem secondary to renal insufficiency attributed to the loss of phosphate clearance and deficient synthesis of active vitamin D ($1,2\text{-}(OH)_2D_3$) [1]. The resulting symptoms and consequences of HPT and hypercalcemia can include renal osteodystrophy, vascular calcification, mood changes, lithiasis, pancreatitis, or musculoskeletal problems [2].

Although successful renal transplantation (TX) is often viewed as a cure to HPT and the consequential hypercalcemia [2, 3], the appropriate management of patients with HPT remains controversial with no consensus on indica-

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tions for treatment [2, 4, 5]. While the prevalence of operative treatment (parathyroidectomy, PTX) after TX ranges widely from 1.3 to 20% [4, 5], the commonly accepted indications for PTX are acute hypercalcemia (>3.1 mmol/l) in the period early after TX, persisting hypercalcemia of >3.0 mmol/l >1 year after TX, as well as symptomatic hypercalcemia [5].

It has been argued that hypercalcemia and HPT in patients after TX must be treated more aggressively due to increased osteopathy [6] and bone turnover rates [7]. However, the effects of PTX on allograft function and hence discussion about the appropriate timing of PTX (before or after TX) has been sparse and fragmentary. The reported literature on the effects of PTX following transplantation mostly focused on the clinical course of HPT after PTX [5, 8]. However, Schmid et al. [4] did mention that a third of their patients had a rejection crisis following PTX, and thus recommended early PTX in cases of advanced HPT. Similarly, Uchida et al. [8] suggested that hypercalcemia due to HPT may aggravate allograft dysfunction, and recommend PTX prior to TX in patients with severe HPT. So the question remains: does PTX negatively impact on allograft function? If so, what are the risk factors, and should prophylactic PTX in patients known to be at risk be recommended prior to kidney transplantation to prevent deterioration of allograft function after PTX?

In this article, the effect of PTX on renal allografts was determined by (i) comparing function before and after PTX, (ii) comparing survival with a control population without PTX, and (iii) evaluating the risk factors involved in patients with deterioration in allograft function after PTX.

Methods

Surgery

PTX was performed when serum calcium levels remained higher than 3.0 mmol/l during the first year or 2.8 mmol/l after the first year after TX, and/or symptoms of hyperfunctioning parathyroid-like renal osteodystrophy, myopathy, mood changes or calciphylaxis occurred. The serum parathyroid hormone (PTH) concentration was elevated at least 3-fold in all cases.

Cervical exploration with identification of all four parathyroid glands was performed in all patients. All glands were biopsied intraoperatively and the diagnosis of HPT was confirmed by histopathological evaluation of frozen sections. A residuum of the smallest gland was marked by a clip and left in situ, and was approximately half the size of a normal gland (2 × 2 × 2 mm). Since all glands were routinely explored during surgery, we did not use routine intraoperative PTH monitoring. Autotransplantation of remnant glands was not performed.

Patients and Follow-Up

By reviewing the clinical records, all TX patients with PTX (n = 22) who were operated between 1995 and 2002 at Benjamin Franklin University Hospital (Berlin, Germany) were analyzed. Directly prior to PTX, the patients were not treated with calcitriol or oral calcium tablets, but received both active vitamin D and calcium during the course of HPT. Follow-up was done both by cross-section retrieval of data in June 2002 from attending nephrologists and dialysis facilities, and a scheduled follow-up at the outpatient transplant clinic. Measures of serum creatinine (normal 62–106 μmol/l), serum calcium (normal 2.24–2.78 mmol/l), phosphate (normal 16–87 pg/ml), serum PTH (normal 0.87–1.45 mmol/l) and proteinuria (normal 0–150 mg/day) levels were determined at least once every 3 months. For baseline measures, either the 1-year creatinine or the earliest available stable creatinine after TX was retrieved. Graft survival was retrieved in a prospective fashion by transplant coordinators.

Immunosuppression was performed by a triple regimen consisting of low-dose steroids, cyclosporine A and azathioprine or mycophenolate mofetil. Antihypertensive therapy was started with calcium antagonists. β- or α-blockers were added if blood pressure was not normalized. Angiotensin-converting enzyme inhibitors or angiotensin-receptor antagonists were allowed in the absence of TX artery stenosis. HLA match was assessed by an arbitrary score of mismatch points: HLA-A = 1 mismatch point; HLA-B = 3 mismatch points, and HLA-DR = 5 mismatch points.

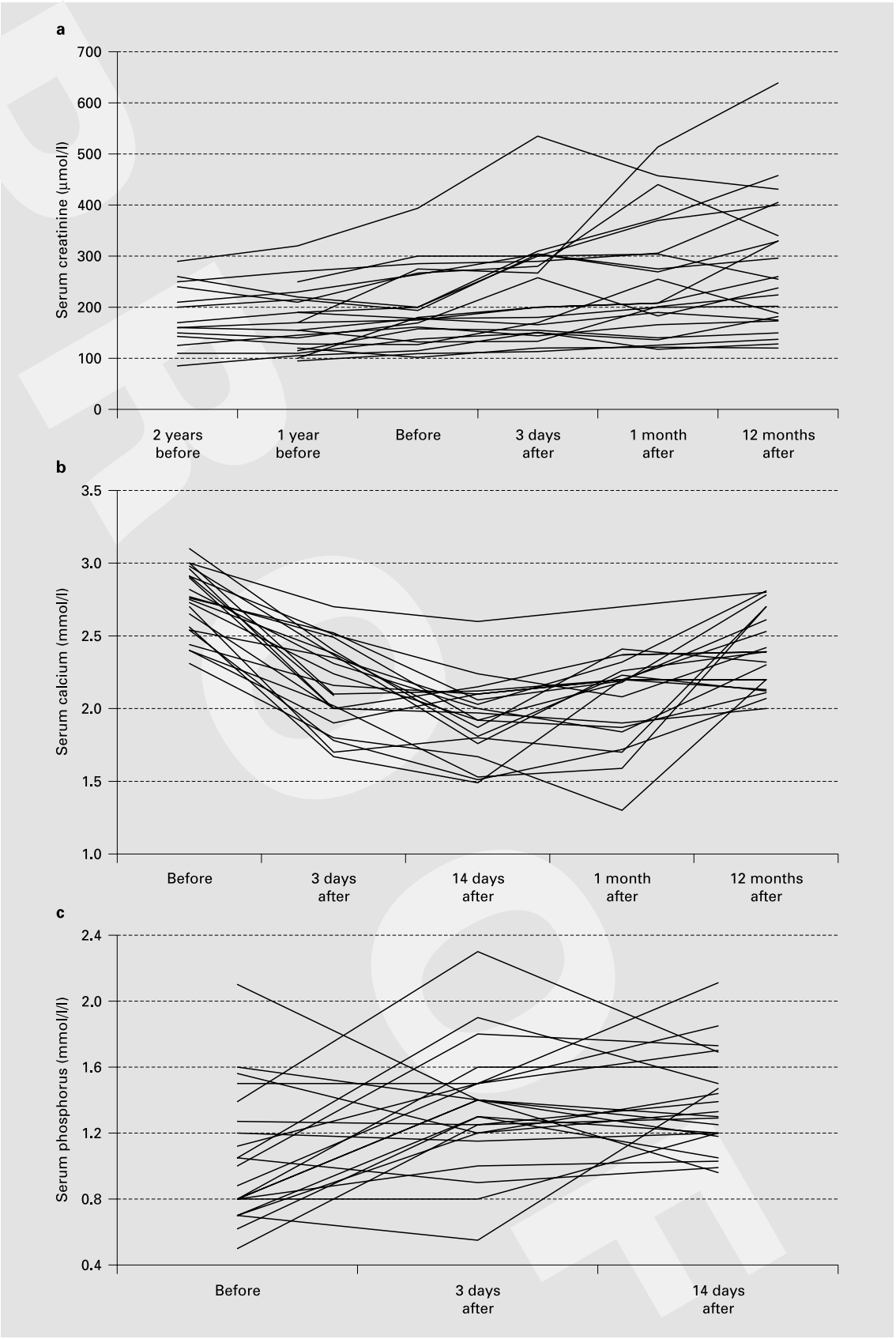
Controls and Biometrics

A 'virtual PTX' date was set at January 1, 1998, and was assigned to 131 TX patients as controls with no real PTX. These patients were transplanted between 1983 and 1997, and their baseline TX and graft function data were available. This approach was chosen to enable computation of time-dependent studies with 'survival after virtual PTX' in no-PTX patients.

Allograft survival after PTX was compared between PTX and no-PTX patients using Kaplan-Meier survival curves and Cox multivariate regression analysis. Graft function in PTX patients was analyzed by comparing the creatinine slope before and after surgery. For comparison of proportions, χ^2 statistics and contingency tables were used.

Results

The data before PTX and before and after TX and anthropometrical data are given in table 1. Patients treated by PTX had increased blood pressure at TX baseline (p = 0.009 for diastolic blood pressure) compared to no-PTX patients. Allograft function was frequently altered by the surgical procedure: 13/22 PTX patients experienced a steeper creatinine slope course during the 1-year follow-up compared to 4/22 patients with improved and 5/22 with non-changed transplant function (fig. 1a). Inferior graft function was significantly associated with a perioperative drop in serum calcium of >0.5 mmol/l (calcium drop > 0.5 mmol/l in 9/13 patients with a steeper creatinine course; calcium drop <0.5 mmol/l in 4/13


a
Serum creatinine (µmol/l)
700
600
500
400
300
200
100
0
2 years before
1 year before
Before
3 days after
1 month after
12 months after
b
Serum calcium (mmol/l)
3.5
3.0
2.5
2.0
1.5
1.0
Before
3 days after
14 days after
1 month after
12 months after
c
Serum phosphorus (mmol/l/l)
2.4
2.0
1.6
1.2
0.8
0.4
Before
3 days after
14 days after

1

Table 1. Peri-TX and PTX risk factors in cohorts with and without PTX (upper panel) and laboratory values (lower panel) pre PTX

	Dialysis before TX years	NTX to PTX years	Graft survival after PTX years	Recipient age, years	Donor age, years	Cold ischemic time, h	BP at TX baseline, mm Hg	Creatinine at TX baseline µmol/l
PTX (n = 22)	3.8 ± 2.6[a]	4.7 ± 5.5[b]	3.3 ± 1.6[c]	46.5 ± 11.9	44.4 ± 19.5	18.0 ± 9.7	152/96 ± 18/15[d,e]	158 ± 77
No-PTX (n = 131)	2.6 ± 2.7			44.6 ± 13.2	46.5 ± 11.8	19.1 ± 7.4	142/84 ± 18/11	158 ± 61

Before PTX levels of:	Creatinine µmol/l	Proteinuria g/day	PTH pg/ml	Calcium mmol/l
PTX (n = 22)	195 ± 74 (102–394)	0.3 ± 0.4 (0–1.6)	755 ± 644 (155–3130)	2.7 ± 0.23 (2.3–3.1)

[a] p = 0.07; [b] p = 0.001; [c] p < 0.0001; [d] p = 0.17; [e] p = 0.009.

Table 2. Results of multivariate Cox regression analysis exploring survival after PTX

Risk factors	Hazards ratio	95% CI	χ^2	p
Creatinine baseline	1.007	1.001–1.013	5.3	0.02
Systolic BP TX baseline	1.018	1.0–1.036	4.0	0.045
Time after TX	1.14	0.92–1.41	1.39	0.024
Donator age	1.008	0.98–1.036	0.29	0.98
PTX	1.23	0.33–4.63	0.09	0.76

BP = Blood pressure.
[a] p = 0.001.

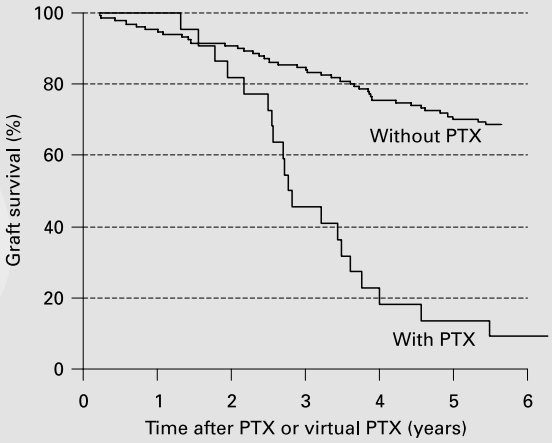


Fig. 2. Graft survival with and without PTX.

patients with a steeper course; p = 0.04), while the PTH levels before and after PTX were not significantly associated with transplant function. The course of creatinine, calcium and phosphate before and after PTX are displayed in figure 1. Overall transplant survival after PTX was 10% after 6 years. Compared to a cohort without PTX, this figure is significantly reduced (log rank p < 0.0001; fig. 2).

In a multivariate Cox analysis adjusting for the most important risk factors in this cohort (creatinine at TX baseline, blood pressure and donor age), the association between graft survival and PTX disappeared (table 2).

Fig. 1. Course of serum creatinine (**a**), serum calcium (**b**) and serum phosphate (**c**) after parathyroidectomy.

Discussion

The proper treatment of HPT remains a controversial issue, with treatments ranging from total or subtotal PTX, or conservative management [2, 4, 5]. Given the potentially severe consequences of uncontrolled HPT, PTX is often indicated in cases of acute, persisting, and symptomatic hypercalcemia. However, the data remain sparse on the effects of PTX on allograft function, and hence the appropriate timing of PTX (before or after TX).

In our retrospective study, allograft function was found to be significantly altered after PTX, as demonstrated by the accelerated rise in creatinine after PTX in the majority of patients. While we cannot directly differentiate the effects of surgery and anesthesia from the effects of removal of the parathyroid glands, perioperative conditions such as volume status and blood pressure would obviously be crucial for adequate management. However, none of the 22 patients were treated in intensive care units or reported a postoperative blood pressure fall or hypovolemia causing acute renal failure. While a study with a control group to compare surgical intervention with PTX is very much needed, the design of such a study would be quite difficult.

In the present study, we aimed to compare PTX patients with no-PTX patients in terms of graft survival with the major concern that no-PTX patients did not have any surgical intervention. On the other hand, by using our global renal TX cohort and assigning these patients a 'virtual PTX date' to enable time-dependent studies, we were able to adjust for major confounders for graft survival such as creatinine at TX baseline, blood pressure, donor age and time between TX and PTX. Interestingly, although graft survival was significantly decreased (60%/6 years) in the PTX group compared to no-PTX by using a univariate Kaplan-Meier approach, this effect was absent in a multivariate analysis adjusted for creatinine at baseline and blood pressure (table 2). However, given the small number of cases, it would be difficult to determine which analysis is correct. Clearly, however, in complex conditions like HPT, the role of influencing covariables, such as those that promote the indications for PTX, must be assessed and enrolled in the analysis.

In patients who did experience significant deterioration in allograft function after PTX, a large proportion of them had an accelerated perioperative calcium drop of >0.5 mmol/l. To our knowledge this phenomenon, first described here, may be regarded as an indirect effect that protects graft function in the context of HPT. Although no data are available on the effects of calcium or PTH on graft function, earlier studies in essential hypertension demonstrated a hyperfiltering effect of both low calcium intake and hypercalciuria resulting in low serum calcium [9]. It could be hypothesized that in TX patients with a comparable metabolic profile, hypocalcemia due to secondary HPT may cause an increased glomerular filtration rate and an accelerated drop of function in the case of withdrawal of the hyperfiltering condition.

In summary, in this retrospective analysis we found a strong relationship between removal of parathyroid glands in HPT and reduced graft function and survival. From a clinical point of view, we would state that in patients requiring PTX, graft function and survival is in danger of worsening. However, many factors contribute to this negative correlation, and it is difficult to differentiate the effects of surgery and anesthesia itself, the removal of the parathyroid glands, or the conditions that led to the indications for PTX. Our study suggests that baseline creatinine, blood pressure, and a peri-PTX drop in serum calcium of >0.5 mmol/l are most important. Thus at this point, we cannot recommend prophylactic PTX based on PTH levels and mild-to-moderate hypercalcemia (<2.8 mmol/l) only, but would discuss PTX early enough if progressive osteodystrophy is present and graft function is still sufficient. Moreover, subcutaneous autotransplantation of remnant glands into the forearm need to be approved for prevention of an overt calcium drop and indirect protection of graft function. Controlled studies for this clinically important topic should be initiated.

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