ORIGINAL ARTICLE

Evolution of secondary hyperparathyroidism one year after successful renal transplantation

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Abstract

Background: The natural history of parathyroid function after successful renal transplantation (Tx) as well as the factors predisposing to persistent secondary hyperpathyroidism (sHPT) are not well established, whereas regression of sHPT is not always observed and depends on renal graft function. The aim of the present study was to evaluate the post-Tx natural history of parathyroid function in patients with a well functioning renal graft.

Patients and Methods: One hundred and five (105) patients, which underwent successful renal transplantation, were studied. Sixteen (16) patients had a history of previous parathyroidectomy for severe HPT.

Results: Parathyroid hormone (PTH) mean value presented a significant fall from 373.2±418 to 128±121 pg/ml ($p<0.001$) at 12 months post-Tx. Pre-Tx PTH levels were significantly correlated with 12 months post-Tx levels ($r= 0.46$, $p< 0.001$). Serum calcium did not present significant alterations, whereas serum phosphorus decreased significantly, since the third month post-Tx from 5.9±1.67 mg/dl to 3.2±0.75 mg/dl ($p<0.001$). Renal graft function remained well preserved and mean serum creatinine was 1.59±0.44 mg/dl at the 12th month post-Tx. Eighteen (18) patients presented severe HPT (PTH > 800 pg/ml) at the time of transplantation. In this group of patients, PTH was also significantly decreased, but remained in abnormal levels (PTH > 100 pg/ml) after 12 months post-Tx in 6 cases.

Conclusions: These results suggest an improvement of parathyroid function as measured by PTH levels, during the first year after successful renal transplantation in patients with mild or moderate sHPT. Twelve months' PTH levels depend on pre-Tx levels. However severe pre-existing sHPT may persist even after one year post-Tx in a significant number of patients. Hippokratia 2011; 15 (Suppl 2): 30-32

Key words: calcium, phosphorus, PTH, renal transplantation

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Secondary hyperparathyroidism (sHPT) is a frequent complication of uremia. Ideally, successful renal transplantation (Tx) corrects the endocrine and metabolic imbalances and the main abnormalities responsible for sHPT during the first months[1].

The natural history of parathyroid function after successful renal transplantation, as well as the factors predisposing to persistent hyperparathyroidism is not well established and only a few data are available in the literature on this subject. Renal transplant recipients may present signs of disturbed calcium homeostasis, such as hypercalcemia or bone loss[2-7], whereas regression of sHPT is not always observed and also depends on renal graft function [2,4,8,9] .

The aim of the present study was to evaluate the post-Tx natural history of parathyroid function in patients with well functioning renal grafts one year post-Tx and to identify any possible risk factors for persistent sHPT.

Materials and Methods

One hundred and five (105) patients aged 43.8±12.3 (13-67) years, which were on renal replacement therapy for 64.2±41.3 (8-204) months and underwent successful renal transplantation in our centre from 1998 until 2005 were retrospectively studied. Their original renal diseases included chronic glomerulonephritis (n=40), unknown aetiology (n=31), polycystic kidney disease (n=13), diabetic nephropathy (n=12) and other aetiologies (n=9). Ninety-four patients had undergone cadaveric renal transplantation and 11 patients living related transplantation. All patients received induction therapy with basiliximab and were on triple immunosuppressive regimens with calcineurin inhibitors, mycophenolate mofetil and steroids. Sixteen (16) patients had a history of previous parathyroidectomy for severe sHPT.

Parathyroid hormone (PTH) was measured before renal transplantation and every three months during the first year post-Tx by a RIA technique. Serum creatinine, calcium and phosphorus were measured at least monthly by standard techniques and estimated Glomerular Filtration Rate (eGFR) was calculated by the MDRD formula.

All values are expressed as mean± SD. Analysis of

Months post-Tx	0	3	6	12
PTH* (pg/ml)	373.2±418	206.2±197	138.9±126*	128±121*
Calcium (mg/dl)	9.7±1	10±0.72	10.1±0.7	10.1±0.8
Phosphorus* (mg/dl)	5.9±1.7	2.88±0.75*	3.3±0.7*	3.2±0.75*
Creatinine* (mg/dl)	10.3±2.8	1.56±0.48*	1.63±0.48*	1.59±0.44*

Table 1: Evolution of serum parathyroid hormone (PTH), calcium, phosphorus and creatinine levels during the first 12 months post renal transplantation. (*p< 0.001).

variance (ANOVA) test and correlation analysis by Pearson coefficient were used as appropriate. A p value < 0.05 was considered as statistically significant.

Results

Evolution of serum PTH, calcium, phosphorus and creatinine during the first 12 months post renal transplantation is shown in table 1. Renal graft function remained well preserved with a mean serum creatinine of 1.59±0.44 mg/dl and a GFR of 57±12 ml/min/1.73m^2 at the 12th month post-Tx .

Mean value of PTH decreased significantly from 373.2±418 to 128±121 pg/ml (p<0.001) at 12 months post-Tx (Table 1). Serum calcium did not present significant alterations, whereas serum phosphorus decreased significantly, since the third month post-Tx from 5.9±1.7 mg/dl to 3.2 ± 0.75 mg/dl at 12 months post-Tx (p<0.001) (Table 1).

Pre-Tx PTH levels were significantly correlated with 12 months post-Tx levels (r= 0.46, p< 0.001). Post-Tx PTH levels were positively correlated with serum calcium levels (r= 0.278, p< 0.05) and negatively with serum phosphorus levels (r= - 0.283, p< 0.05) at 12 months post-Tx. There was no significant correlation of PTH levels with serum creatinine, or GFR at 12 months post-Tx.

Patients with severe pre-existing hyperparathyroidism.

Eighteen (18) patients presented severe sHPT (PTH > 800 pg/ml) at the time of transplantation (1074±365 pg/ml). In this group of patients, PTH was also significantly decreased (186±125 pg/ml, p<0.001), but remained in abnormal levels (> 100 pg/ml) after 12 months post-Tx in 6 cases. Only one patient underwent parathyroidectomy due to severe hypercalcemia and graft dysfunction four months post-Tx.

Discussion

Successful renal transplantation restores, at least partially, the main abnormalities responsible for sHPT (vitamin D deficiency, phosphorus retention, hypocalcemia and metabolic acidosis), but information is scarce about the natural course of parathyroid function post-Tx[1,2,5,9,10].

In the present study we retrospectively evaluated data from 105 renal transplant recipients with stable renal function, as reflected by their serum creatinine and calculated GFR. According to our results, there is an improvement of parathyroid function, as measured by PTH levels, during the first year after successful renal transplantation in patients with mild or moderate sHPT. Although our patients' allograft function can generally be considered optimal with a mean eGFR of about 57 ml/min/1.73m^2, this rate is rather insufficient to suppress all of the PTH stimulatory signals and normalize totally parathyroid glands function.

Bonarek et al reported a reduction of parathyroid mass 6 months post-Tx with both static and dynamic tests in 11 renal transplant recipients with good renal function. However normalization of parathyroid function was not complete, possibly due to a slow regression and low parathyroid cell turnover[7].

Bravo et al have prospectively studied 36 patients before and one year post-Tx by ultrasound examination of the parathyroid glands[6]. The authors reported a clinical reduction in gland volume of about 58% in patients with detectable parathyroid glands at the time of Tx that was also accompanied with better allograft function.

Reinhardt et al studied prospectively 129 renal transplant recipients for 2 years dividing the study population in two groups according to optimal or suboptimal renal function with a serum creatinine cut-off of about 1.5 mg/dl[5]. Post-Tx serum PTH levels were significantly higher in the group with impaired allograft function, implicating that the better the graft function, the more complete the reversal of HPT.

Evenepoel et al have retrospectively reviewed the charts from 1165 renal transplant recipients and found that sHPT persisted in 17% of the patients even after 4 years post-Tx[2]. Possible risk factors for persistent sHPT included a long dialysis vintage and elevated serum levels of PTH, calcium and phosphorus at the time of transplantation. Post-Tx PTH serum levels correlated significantly with pre-Tx levels (r=0.52), serum calcium (r=0.30) and serum creatinine (r=0.24). We have also found a rather similar correlation between post-Tx and pre-Tx PTH levels (r=0.46) as well as with serum calcium (r=0.278) but not with serum creatinine, or GFR at 12 months post-Tx. This may be probably due to the smaller sample in our study. However, we found a significantly negative correlation between PTH levels and serum phosphorus that was not examined in the study of Evenepoel et al[2].

In our study, phosphorus levels decreased significantly after 3 months post-Tx. Hypophosphatemia is a

common complication of renal transplantation. Recently, fibroblast growth factor 23 (FGF 23) emerged as its most important mediator, as increased FGF 23 levels, but not PTH levels are independently associated with low serum phosphorus in renal transplant recipients[11]. However, increased PTH may act synergistically to increase phosphaturia in these patients[11].

In the literature the prevalence rates of parathyroidectomy post-Tx range from 0.6 to 5.6%. However there are no evidence-based guidelines for the absolute indications for parathyroidectomy post-Tx, except in cases of calciphylaxis. Although laboratory data, clinical symptoms and imaging data should all taken into account, for most clinicians persistent HPT with hypercalcemia represents the main indication. Besides these, increased alkaline phosphatase activity, unexplained deterioration of allograft function and clinical symptoms such as bone pain and pruritus may serve as additional indications. Evenepoel et al in a retrospective study reported a parathyroidectomy rate of 8.89% per 1000 person-years and female gender, high pre-Tx PTH levels and high pre-Tx calcium as significant risk factors[9]. These authors also reported a deterioration of allograft function after parathyroidectomy, without any alterations in graft survival rates. In our study, only one female patient with high PTH levels pre-Tx underwent parathyroidectomy for persistent hypercalcemia and sHPT, but renal function presented a rapid improvement after the procedure.

The advent of the calcimimetic drugs such as cinacalcet, that has been already been used successfully for the treatment of hypercalcemia and sHPT in the renal transplant recipients[12] will probably reduce parathyroidectomy rates in the near future. However, cinacalcet is a rather expensive therapy and oral pulse calcitriol may result in successful regression sHPT post-Tx with less cost[13].

In conclusion, the majority of renal allograft recipients present a rapid but incomplete decrease of serum PTH levels after successful Tx and renal Tx remains the best option for the treatment of sHPT. Somewhat higher level of PTH should not be regarded as suboptimal, as they may secure a better turnover of the bone and prevent osteopenia after renal Tx. Treatment with vitamin D is preferable, but cinacalcet can be used in selected cases of no other option, such as hypercalcemia or contraindications for parathyroidectomy. However, cinacalcet remains extremely expensive, if applied for a long time and its use has not been justified so far by any large and prospective study in renal Tx.

Conflicts of Interest: None to declare

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