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Table and Figures: Tables: 4

Abstract

Hyperparathyroidism and New Onset Diabetes after Renal Transplantation

Background: Secondary hyperparathyroidism (sHPT) persists after renal transplantation in a substantial number of patients. Primary hyperparathyroidism (pHPT) and sHPT are both associated with abnormalities in glucose metabolism, such as insufficient insulin release and glucose intolerance. The association of hyperparathyroidism and diabetes after renal transplantation has, as far as we know, not been studied.

Objective: Our aim was to investigate whether hyperparathyroidism is associated with new-onset diabetes mellitus after transplantation (NODAT) during the first year after transplantation.

Study Design: In a retrospective study, we analyzed data on patient characteristics, treatment details and parathyroid hormone (PTH) in 245 adult non-diabetic patients who underwent renal transplantation between January 2000 and June 2011.

Results: The first year cumulative incidence of NODAT was 15%. The first serum PTH value after transplantation was above normal range in 74% of the patients. In multiple logistic regression analysis, PTH levels above twice normal range (>13.80 pmol/L) were significantly associated with NODAT (OR 4.25, CI 1.13-15.92, P = .03) compared with PTH within normal range (≤6.9 pmol/L). Age between 45 and 65 years (OR 2.80, CI 1.07-7.36, P = .04) compared with age lower than 45 years was also associated with NODAT.

Conclusion: We found a strong association between hyperparathyroidism and NODAT in the first year after renal transplantation. Both conditions are common and have a negative impact on graft and patient survival. Our results should be confirmed in prospective studies.

Introduction

Despite successful renal transplantation hyperparathyroidism persists in many patients,[1, 2] and to date there is no consensus on the optimal parathyroid hormone (PTH) level after transplantation. Previous studies have shown a negative impact of secondary hyperparathyroidism (sHPT) on bone by increasing the risk of osteoporosis and fractures.[3, 4] The ensuing hypercalcemia can lead to interstitial calcification in the allograft with graft dysfunction[5, 6] and soft tissue calcification.[7, 8]

Primary hyperparathyroidism (pHPT)[9, 10] and sHPT[11, 12] are both associated with abnormalities in glucose metabolism, such as glucose intolerance and insufficient insulin release. Furthermore, a higher prevalence of diabetes mellitus (DM) has been reported in patients with pHPT.[13-15]

New-onset diabetes mellitus after transplantation (NODAT) is a common metabolic complication of renal transplantation. Metabolic abnormalities such as insulin resistance and insulin deficiency seem to be part of the pathogenesis.[16] Immunosuppressive agents (corticosteroids and calcineurin inhibitors) are major risk factors.[17] However, several other risk factors such as age, pre-transplant weight, certain infections and genetic predisposition have also been identified or suggested.[18-23]

To the best of our knowledge, the role of hyperparathyroidism in developing NODAT has not been studied. This association could have important implications in the assessment of the individual patient risk of NODAT and in how to handle hyperparathyroidism in transplanted patients. The aim of this study was to examine whether hyperparathyroidism after renal transplantation is associated with NODAT.

Methods

Patients

In a retrospective study, we included all adult kidney allograft recipients with follow-up visits for at least one year at the Department of Nephrology and Transplantation, Skåne University Hospital, Malmö and Lund, respectively, between January 2000 and June 2011. A total of 335 patients fulfilled the inclusion criteria. All patients but one was transplanted at our centre. Altogether ninety patients were excluded from the study because of DM at the time of transplantation ($n = 75$), age under 18 years ($n = 12$) or death ($n = 3$) within the first year post-transplant. Two hundred and forty five patients were included in the study, 122 of them had their follow-up visits in Lund and 123 in Malmö.

Patient characteristics, treatment details and PTH values were extracted from patient charts according to a predefined study protocol. We included only patients who had available PTH measurements within six months from transplantation in the statistical analysis, in all 222 patients.

Definition of NODAT

All cases of DM after the first 14 days after transplantation were defined as NODAT. The physician in charge of the patient established the diagnosis when two separate plasma glucose levels were ≥7.0 mmol/L (≥126 mg/dL) in the fasting condition, or ≥11.1 mmol/L (≥200 mg/dL) in the non-fasting condition or if an oral glucose tolerance test was pathological.

Immunosuppressive protocol

Interleukin-2 monoclonal antibodies (Daclizumab or Basiliximab) are used as induction therapy at our center since 1999. The standard immunosuppressive protocol (maintenance therapy) mainly consists of a triple therapy comprising steroids, calcineurin inhibitor (cyclosporine or tacrolimus) and mycophenolate mofetil. We aim at target trough levels of tacrolimus between 5 and 8 ng/mL and cyclosporine A between 80 and 100 ng/mL during the first year after the transplantation procedure. In AB0-incompatible transplantations, the tacrolimus target trough levels are higher, 8-10 ng/mL. Steroids are given at the time of transplantation (500 mg methylprednisolone), followed by 1 mg prednisolone/kg on the first day and are then tapered to a level of 20 mg per day at discharge. We aim at maintenance doses of 5 mg per day within six months from transplantation for non-NODAT patients.

Acute rejections (clinically suspected or biopsy proven) were treated with 500 mg methylprednisolone intravenously for three consecutive days. Muromonab-CD3, anti-thymocyte globulin and photopheresis were used in a few cases in addition to methylprednisolon. For the purpose of the present study we defined additional immunosuppressive treatment as patients who underwent AB0-incompatible transplantations and/or had rejection therapies and therefore were exposed to higher total cumulative doses of immunosuppressive medications.

Laboratory analysis

PTH was measured using one step immunometric sandwich method with electrochemiluminescence immunoassay detection technique based on Reuthenium derivate (Roche Diagnostics, Mannheim Germany) in the patients with follow-up visits in Lund. In Malmö, PTH was determined using an Immulite® 2000 Intact PTH immunoassay (Diagnostic Products Corporation, Los Angeles, USA) between June 2002 and December 2011. We

calibrated the Immulite® 2000 samples with the formula:

.7439 x Immulite®2000 PTH value + .7351

to get an estimated value according to the Roche method. This formula is used by the laboratory units at our hospital.

PTH measures

Data on parathyroid hormone were extracted from the charts at the first visit and at approximately one, three, six and twelve months after transplantation, when available. Vitamin D measurement is not part of our clinical routine. We did not collect data on calcium and phosphate because of the retrospective nature of the study, and because laboratory tests were not performed at predetermined dates.

Since PTH was not consistently measured in all patients at all intervals as defined by our protocol, we chose to use the first recorded PTH up to 6 months after transplantation in our main analysis. We did not *a priori* know the nature of any potential association between PTH and NODAT and PTH levels were not normally distributed which justified analyzing different measures of PTH, i.e. as a continuous variable, the six months median, categories based on reference range (normal, above normal but less than twice above normal, and twice above normal) and the natural logarithm.

Statistics

Data are expressed as means and standard deviations for normally distributed variables and median and interquartile range for non-normally distributed variables. One-way analysis of

variance (ANOVA) was used for normally distributed variables and Mann-Whitney U test for not normally distributed variables. Chi-squared Test or Fisher's Exact Test was used for categorical variables. Results were considered statistically significant when $P < .05$.

Logistic regression was used to analyze predictors of NODAT. The model was not able to fit all covariates at once, due to the small number of events of NODAT. Instead we included those covariates with statistically significant associations in single regressions and age and sex. P value for trend was calculated for categorical variables in the multiple logistic regression analysis. To test any interactions, we performed multiple regression analysis with pair-wise covariates.

All statistical analyses were made using SPSS for Windows version 21.0 (IBM Corporation, Somers, USA).

Ethical approval

The study was approved by the Regional Ethics Committee of Lund, DNR 827/2004.

Results

Out of 245 patients 36 developed NODAT, yielding a cumulative incidence of 15% during the first year post-transplantation. In 94% of the cases the diagnosis was made within 180 days after transplantation (range 15-250 days). Patients with NODAT were treated with insulin ($n= 19$), oral diabetic agents ($n = 5$), dietary and exercise counseling ($n = 7$) or modifications in immunosuppressive therapy only ($n = 4$) after the diagnosis was made. Information on therapy was missing in one case.

Patient characteristics, treatment details and PTH values are shown in Table 1. The mean age at transplantation for patients with PTH taken within six months (n = 222) was 50 ± 13 years and the majority was male (65%). The first PTH value after transplantation was above normal range (>6.9 pmol/L) in 74% of the patients.

Patients with NODAT had a tendency to be older (53 versus 49 years) and have higher mean BMI (27 versus 25 kg/m^2), although neither reached statistical significance. PTH values were significantly higher in patients with NODAT than in patients without NODAT.

In unadjusted logistic regression analysis, age between 45 and 65 years compared with age less than 45 years was associated with NODAT. PTH as first value after transplantation, the natural logarithm, median value during the first six months after transplantation and values above twice the upper limit of normal range, respectively, compared with PTH within the normal range, were all associated with NODAT (Table 2).

In adjusted regression analysis including age, sex and PTH, age 45-65 years compared to age less than 45 years was associated with NODAT, with an OR (95% CI) of 2.80 (1.07-7.36, P = .04). PTH above twice the upper limit of the normal range compared with PTH within the normal range was also significantly associated with NODAT, with an OR (95% CI) of 4.25 (CI 1.13-15.92, P = .03). P values for trend showed a linear trend for PTH-categories in relation to the association with NODAT. Moreover, when restricting analyses to two covariates at a time, PTH was associated with NODAT in all analyses (Table 4).

Discussion

Our results show that elevated PTH levels were associated with NODAT in unadjusted regression analysis. This association persisted in the adjusted model including age, sex and PTH. We found that PTH values above twice the upper limit of the normal range were associated with NODAT. Age was also independently associated with NODAT, in line with previous studies.[19, 22]

NODAT is a common complication of renal transplantation[24] and increases the risk of graft failure[25-27] and cardiovascular mortality.[28, 29] The major established risk factors are immunosuppressive agents (corticosteroids and calcineurin inhibitors).[17] Several other risk factors, such as pre-transplant obesity, genetic disposition and certain infections, have also been identified or suggested.[18, 22, 23, 30] Incidence rates of NODAT between 2 and 53% have been reported in the literature.[31] In the present study the one-year cumulative incidence was 15% and the diagnosis was made within 180 days after transplantation in nearly 95% of all cases.

Both pHPT[9, 10, 14] and sHPT[11, 12] have been associated with abnormalities in glucose tolerance, insulin secretion and diabetes. A higher prevalence of DM has been detected in patients with pHPT.[10, 13, 15] Reports on the effect of parathyroidectomy (PTX) on DM in patients with pHPT are contradictory. Some studies have shown a beneficial effect,[15, 32] one no benefit[33] and one partial improvement.[34] In a prospective study Khaleeli et al. found that PTX improved glucose metabolism in patients with pHPT. In those patients who had not yet undergone PTX, an increased prevalence of DM from 22 to 35% and an increased prevalence of glucose intolerance from 41 to 50% were seen. Furthermore, at the first oral glucose tolerance test after PTX the number of patients with DM was reduced by 50%, glucose intolerance by 33%, and normal glucose tolerance increased by 35%, respectively.[13]

Chiu et.al showed that in healthy subjects, plasma iPTH levels were inversely correlated with insulin resistance measured by hyperglycemic clamp.[35] In experimental studies in dogs and rats with hyperparathyroidism insulin release following glucose load was impaired, while PTX normalized the insulin response.[12, 36]

Experimental studies in vitro and in vivo have shown that elevated PTH levels can cause insulin resistance through suppression of insulin signaling in adipocytes via the cyclic adenosine monophosphate (cAMP) pathway.[37, 38] Insulin deficiency related to higher PTH levels are explained by markedly elevated resting levels of cytosolic calcium in the pancreatic islets.[39, 40] In peripheral tissue this increase in intracellular calcium inhibits insulin stimulated glucose uptake and causes insulin resistance.[41, 42]

There is evidence that hypophosphatemia decreases insulin sensitivity[43] and that phosphate supplementation improves glucose tolerance. Phosphate is involved in the energy balance and ATP generation. In vitro studies have demonstrated that pancreatic islets of phosphate-depleted rats had low ATP levels, elevated cytosolic calcium, impaired glycolytic activity and impaired insulin secretion. These effects were normalized after phosphate supplementation.[44]

There are reports of an inverse association between baseline levels of 25-hydroxy vitamin D and subsequent hyperglycemia and insulin resistance.[45] However, these findings have not been confirmed in uremic patients.[46]

Elevated PTH values in conjunction with fibroblast growth factor-23 often induce hypophosphatemia,[47] a condition observed in renal transplant patients but not in patients on dialysis. Thus, hyperparathyroidism and hypophosphatemia along with additional diabetogenic factors such as immunosuppressive agents might induce glucose intolerance and insufficient insulin release and thereby trigger the development of NODAT. The association of PTH levels

and NODAT seems to be dose-dependent, as seen in both P value for trend for PTH in reference range-categories and PTH in the normally distributed form of natural logarithm in our study.

The association of hyperparathyroidism after renal transplantation and NODAT has not been evaluated so far. Bergrem et al. tested 17 different possible risk factors for post-transplant hyperglycemia in a multiple regression model. PTH did not turn out to be associated with glucose derangement. However, they did not study the effect of PTH on the development of diabetes. Hyperglycemia is very common in the immediate period after transplantation,[48] 31% of the patients in the study by Bergrem et al. had elevated glucose levels ten weeks post-transplant.[49]

There are certain limitations in the present study. The retrospective study design is one. We lack data on calcium, phosphate and vitamin D. Albeit, a majority of the patients studied are treated with vitamin D supplements before and after transplantation. Furthermore, we lack information on family history of diabetes mellitus in the patients studied.

This study has several strengths. The patients are well documented and represent a cross-section of Swedish society, as everyone is part of our public health care system. The diagnosis was made by the physician in charge of the patient according to the WHO definition of diabetes, which together with the individualized treatment practiced at our department, ensures a solid and reliable diagnosis of NODAT.

In summary, in this study we show for the first time a strong association between elevated levels of PTH and NODAT. These results are interesting as both conditions have a negative impact on graft survival and patient morbidity and mortality. Hyperparathyroidism remains a problem after renal transplantation and to date there is no consensus on optimal level of PTH after the procedure. Our results need to be confirmed in larger prospective studies.

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Table 1. Patient characteristics, treatment details and PTH values

Factor	All patients (n=222)	NODAT (n=32)	Non-NODAT (n=190)	P
Age at transplantation (years)	*49.7 ± 13.4*	*52.9 ± 9.8*	*49.1 ± 13.9*	.14
Sex, male/female	145/77	21/11	124/66	.97
BMI, kg/m^2	*25.6 ± 4.4*	*26.9 ± 3.7*	*25.3 ± 4.5*	.08
Primary renal disease				
ADPKD	43 (19.4)	7 (21.9)	36 (18.9)	.70
Glomerulonephritis	91 (41.0)	14 (43.8)	77 (40.5)	.73
Nephrosclerosis	14 (6.3)	3 (9.4)	11 (5.8)	.33
Pyelonephritis	12 (5.4)	2 (6.3)	10 (5.3)	.54
Other and unknown	62 (27.9)	6 (18.8)	56 (29.5)	.21
RRT[*]				
Hemodialysis	126 (56.8)	17 (53.1)	109 (57.4)	.65
Peritoneal dialysis	70 (31.5)	9 (28.1)	61 (32.1)	.65
Preemptive	26 (11.7)	6 (18.8)	20 (10.5)	.15
Time in RRT (months)	*27.0 (10.0-53.0)*	*35.0 (8.0-56.8)*	*26.0 (10.0-50.3)*	.07
Number of transplantations, 1/>1	182/40	26/6	156/34	.91
Type of transplantation, LD/DD	88/134	13/19	75/115	.90
Immunosuppressive protocol[†]				
Steroids	216 (97.3)	32 (100.0)	184 (96.8)	.45
Cyclosporine	37 (16.7)	3 (9.4)	34 (17.9)	.23
Tacrolimus	181 (81.5)	28 (87.5)	153 (80.5)	.35

Rapamycin	1 (0.5)	0 (0.0)	1 (0.5)	.86
MMF	217 (97.7)	32 (100.0)	185 (97.4)	.53
Additional immuno-suppressant treatment‡	54 (24.3)	11 (34.4)	43 (22.6)	.15
PTH after transplantation, pmol/L				
first value§	*11.0 (6.4-17.0)*	*13.7(9.1-23.5)*	*10.0 (5.6-16.1)*	.01
log first value	*2.4 (1.9-2.8)*	*2.6 (2.2-3.2)*	*2.3 (1.7-2.8)*	.01
median 6 months	*9.5 (6.4-14.0)*	*12.3 (7.6-18.3)*	*9.3 (5.8-13.3)*	.01

mean ± standard deviation, numbers (percent), *median (interquartile range)*

NODAT, New Onset Diabetes Mellitus After Transplantation .

BMI, Body mass index, taken ± 3 months from transplantation date (missing in 16 patients, including 3 of those with NODAT)

ADPKD, Autosomal dominant polycystic kidney disease

LD/DD, Living donor/deceased donor

MMF, Mycofenolatmofetil

*RRT, renal replacement therapy, type of therapy at the time of transplantation,

†Percentages do not add to 100.0% since patients had one or more treatments.

‡AB0-incompatibility and/or rejection therapy.

§88% of values measured within 3 months from diagnosis.

Table 2. Predictors of NODAT, logistic regression (unadjusted)

Factor		Odds ratio (95% CI)	P
Age, years	<45	1.00	
	45-64	3.27 (1.26-8.44)	.02
	65-74	1.39 (.32-5.95)	.66
Sex	Female	1.00	
	Male	1.02 (.46-2.24)	.97
BMI, kg/m^2	≤25.00	1.00	
	25.01-30.00	1.99 (.81-4.87)	.13
	>30.00	2.64 (.85-8.19)	.09
RRT[*]	dialysis	1.00	
	preemptive	1.57 (.22-1.84)	.40
Number of transplantations	1	1.00	
	>1	1.06 (.41-2.77)	.91
Type of donor[†]	LD	1.00	
	DD	1.05 (.49-2.25)	.90
CNI treatment	cyclosporine A	1.00	
	tacrolimus	2.07 (.60-7.22)	.25

Additional immunosuppressant treatment[‡]	no	1.00	
	yes	1.79 (.80-4.00)	.16
	≤6.90	1.00	
PTH, after transplantation, pmol/L	6.91-13.80	3.21 (.87-11.81)	.08
	>13.80	4.57 (1.26-16.53)	.02
	first value[§]	1.05 (1.01-1.08)	.01
	log first value	2.29 (1.27-4.13)	.01
	median value	1.06 (1.01-1.11)	.01

NODAT, New Onset Diabetes Mellitus After Transplantation

BMI, Body mass index, taken ± 3 months from transplantation date (missing in 16 patients, including 3 of those with NODAT)

[*]RRT, renal replacement therapy

[†]LD/DD, Living donor/deceased donor

CNI, Calcineurin inhibitor

[‡]AB0-incompatibility and/or rejection therapy

[§]Within 6 months, 88% of values measured within 3 months from diagnosis.

Table 3. Predictors of NODAT, multiple logistic regression

Factor		Odds ratio (95% CI)	*P*	*P* value for trend
	<45	1.00		.49
Age, years	45-64	2.80 (1.07-7.36)	.04	
	65-74	1.09 (.24-4.94)	.91	
	Female	1.00		
Sex	Male	1.22 (.53-2.81)	.63	
	≤6.90	1.00		.03
PTH after transplantation, pmol/L*	6.91-13.80	2.82 (.76-10.54)	.12	
	>13.80	4.25 (1.13-15.92)	.03	

NODAT, New Onset Diabetes Mellitus After Transplantation.

*First record up to 6 months after transplantation. 88% of values measured within 3 months from diagnosis.

Table 4. Predictors of NODAT, pair-wise multiple logistic regression analysis

Factor		Odds ratio (95% CI)	P
Age, years	<45	1.00	
	45-64	2.79 (1.06-7.34)	.04
	65-74	1.07 (.24-4.85)	.93
PTH after transplantation, pmol/L*	≤6.90	1.00	
	6.91-13.80	2.88 (.75-10.46)	.13
	>13.80	4.06 (1.10-15.03)	.04
Sex	Female	1.00	
	Male	1.24 (.55-2.82)	.60
PTH after transplantation, pmol/L*	≤6.90	1.00	
	6.91-13.80	3.23 (.88-11.91)	.08
	>13.80	4.83 (1.13-17.75)	.02
BMI, kg/m^2	≤25.00	1.00	
	25.01-30.00	1.84 (0.74-4.57)	.19
	>30.00	2.12 (0.65-6.86)	.21
*PTH after transplantation, pmol/L	≤6.90	1.00	

6.91-13.80	4.21 (0.90-19.78)	.07
>13.80	5.34 (1.15-24.84)	.03

NODAT, New Onset Diabetes Mellitus After Transplantation

[*]Within 6 months, 88% of values measured within 3 months from diagnosis.

BMI, Body mass index, taken ± 3 months from transplantation date (missing in 16 patients, including 3 of those with NODAT)