Pre-transplant low paratyroid hormone level: A risk factor for post-transplant osteoporosis and arterial stiffness

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ABSTRACT

Objectives: Arterial stiffness is an early marker of arterial calcification. Adynamic bone disease is associated with microinflammation. The aim of this study is to evaluate the relationship between pre-transplant bone activity and post-transplant osteoporosis and arterial stiffness in kidney transplant recipients.

Methods: One hundred and fifty kidney transplant recipients were enrolled into our study. All patients' pre and post-transplant PTH levels, post-transplant lumbar t-scores and pulse wave velocity (PWv) were cross sectionally analyzed. Patients were divided into two groups according to pre-transplant PTH levels; patients with low PTH group (group 1; PTH<100 pg/ml, n: 91) and patients with normal or high PTH group (group 2; PTH>100 pg/ml, n: 59).

Results: Serum PTH levels were slightly increased or stable after transplantation in group 1. In group 2; serum PTH levels was significantly decreased in 76 % of patients; however 24 % of group 2 patients had increased PTH after transplantation. In both groups, an increase in post-transplant PTH >30% was associated with higher serum creatinine and lower GFR levels and higher PWv. The factors influencing lumbar t-score were pre-transplant PTH, age and duration of hemodialysis. Pre-transplant PTH levels, lumbar t-score, age and duration after transplantation were detected as major determinants of PWv.

Conclusions: Pre-transplant low serum PTH level is an important predictor for post-transplant osteoporosis and arterial stiffness. An increase in post-transplant PTH is associated with graft dysfunction and vascular stiffness that point out the importance of close follow-up and improve the PTH levels after renal transplantation.

Introduction

In terms of quality of life, renal transplantation (RT) is the best treatment of choice for patients with end-stage renal disease (ESRD). Despite advances in RT, post-transplant bone disease is a common complication that affects 50% to 80% of all RT recipients (1). The most critical period for bone loss is the first 6 to 12 months of post-transplant period while the most dramatic reduction is in the first 3 months (2). The causes of post-transplant osteoporosis include patient-related factors such as age, gender, and tobacco use, hyperparathyroidism, decreased vitamin D level, immunosuppressive drugs, impaired renal function and adynamic bone disease (3).

Parathyroid hormone is a well-known factor capable of reducing bone density by releasing calcium ions into the blood system, and its negative association with bone density is anticipated (4). Adynamic bone disease is characterized by low-turnover bone with normal mineralization represented by an absence of osteoid accumulation, furthermore it is associated with age and microinflammation (5). Although previous studies demonstrated that patients with secondary hyperparathyroidism experience bone loss after RT, the data about the effect of transplantation on adynamic bone disease is inadequate in the literature (6).

While transplanted patients have survival advantage over patients on dialysis, they still have 4- to 5-fold higher mortality risk compared to the general population. Similar to ESRD patients receiving dialysis, cardiovascular disease is the main cause of death with functioning graft after transplantation (7). In ESRD patients, the extent of arterial calcification is associated with aortic stiffness that is accepted as an early marker of arterial calcification, systemic atherosclerosis and cardiovascular risk (8). Carotid-femoral pulse wave velocity is a noninvasive and reproducible method currently considered as the gold standard for aortic stiffness measurement and a marker of target organ damage in the European Society of Hypertension–European Society of Cardiology guidelines (9). Aortic stiffness and increased wave reflections were reported as independent predictors of cardiovascular events in renal transplant recipients (10). Interestingly, both arterial calcification and arterial stiffening have been observed in patients with osteoporosis without ESRD (11). However, the associations between pretransplant

levels of parathyroid hormone (PTH) and outcomes after kidney transplantation are not clear. (12).

The aim of this study is to evaluate the relationship between pre-transplant PTH levels and post-transplant osteoporosis, arterial stiffness and graft function in RT recipients.

Material and Methods

Among 457 RT recipients, one hundred and fifty patients (93 male; aged 36.3.± 12.6 years) with minimum one year post transplant period were enrolled into our study. Patients with history of coronary heart disease, peripheral artery disease, hyperlipidemia, post-transplant diabetes mellitus, anti-hypertensive drug and tobacco use were excluded from the study. All patients' standard clinical (age, gender, duration of hemodialysis, post-transplant time) and biochemical parameters, pre and post-transplant PTH levels, post-transplant 12th month lumbar t-scores were cross sectionally analyzed.

In all participants, a venous blood sample was collected after an overnight fast to measure the concentration of the following biochemical variables using standard laboratory techniques: fasting plasma glucose (FPG), creatinine, calcium, phosphorus, albumin, alkaline phosphatase, pre-transplant and post-transplant PTH levels, lipid profile (total cholesterol [C], HDL-C, TGs, LDL-C [low-density lipoprotein C; computed from Friedewald's formula]) and complete blood count.

Body compositions were analyzed with the BIA technique (BCM, Fresenius) that estimates body mass index (BMI).

Pulse wave velocity is defined as the velocity of the arterial pulse for moving along the vessel wall. Pulse wave velocity along the aorta was measured by using two ultrasound or pressure sensitive transducers fixed transcutaneously over the course of a pair of arteries separated by a known distance: the femoral and right common carotid arteries. PWV was calculated from measurements of pulse transit time and the distance, according to the following formula: PWV (m/s)= distance (m)/ transit time (s). Measurement of PWV values was con-ducted after abstinence from caffeine or smoking and after an overnight fast without intake of antihypertensive drugs. PWV was determined by using the SphygmoCor CvMs V9 system and values > 7 m/s was defined as increased (13)

Measurement of bone mineral density (BMD) at the lumbar spine (L2-4) and femoral neck were assessed using dual-energy X-ray absorptiometry (DEXA) (Lunar Expert 1313, Lunar Corp. USA). BMD was calculated from bone mineral content (g) and bone area (cm2), and then expressed in g/cm2.For the DEXA method, osteoporosis and osteopenia were defined according to the World Health Organization definitions (osteoporosis:T score <_2.5; osteopenia: T score between >_2.5 and <_1; normal: T score >_1) (14)

Estimated glomerular filtration rate (eGFR) was calculated based on MDRD formulas; [mL/min per 1.73 m2] = 175 × (serum creatinine [mg/dL])−1.154 × age [years]−0.203 × (0.742 if female).

Patients were divided into two groups according to pre-transplant PTH levels; patients with low PTH group (group 1; PTH<100 pg/ml, n: 91) and patients with normal or high PTH group (group 2; PTH>100 pg/ml, n: 59).

Cyclosporine or tacrolimus, mycophenolate mofetil, and steroids were the primary immune-suppressive agents. All recipients were administrated 500 mg of intravenous methylprednisolone just before restoration of blood flow to the allograft, and the dose of steroid was tapered to 60 mg/day over 4 days. Oral methylprednisolone (30 mg twice daily) was given and tapered by 10 mg every week until the ongoing dose of 10 mg/day was reached. Cyclosporine or tacrolimus therapy was also started immediately after surgery, with dosage subsequently adjusted

Table 1: Demographic characteristics of study population and comparision of pretransplantation and post transplantation parameters of groups

Subject characteristics	Pre-tx low PTH Group (n:91)		Pre-tx high PTH Group (n:59)		P value
	Pre-tx	Post-tx	Pre-tx	Post-tx	
Gender (male/female)	62/29		31/28		NS*
Age (years)	43.7 ± 1.7		44.9 ± 3.1		NS*
Duration of dialysis (years)	10.4 ± 2.6		12.5 ± 1.7		NS*
Post tx time (months)		32.0 ± 2.4		36.1 ±1.7	NS*
Albumin (g/dl)	3.4 ± 0.7	4.2 ± 0.4	3.2 ± 0.6	4.1 ± 0.3	NS*, NS**
Creatinine (mg/dl)	8.4 ± 0.4	1.12 ± 0.6	7.14 ± 0.3	1.02 ±0.6	NS*, NS**
PTH (mg/L)	95.2 ± 7.2	118 ± 14.5	335.8 ± 17.6	179.8 ±11.6	0.008*, 0.024**
Calcium (mg/dl)	9.8 ± 0.3	9.2 ± 0.5	9.4 ±0.7	9.12 ± 0.5	NS*, NS**
Phosphorus (mg/dl)	5.9 ±0.7	2.9 ±0.9	6.2 ±0.4	3.0 ± 0.8	NS*, NS**
GFR (ml/min)	11.3 ± 5.1	110.3 ± 6.2	13.6 ± 1.2	117.2±2.4	NS*, NS**
PWv (ms)		7.6 ± 2.5		6.4 ± 2.0	0.001*
ALP (IU/L)	124 ± 12.5	178.6 ±3.4	138 ± 7.6	176.4 ± 0.3	NS*, NS**
BMI (kg/m2)	21.2 ± 0.4	24.2 ± 0.7	19.8 ± 0.6	23.4 ± 1.2	NS*, NS**
Lumbar t-score (g/cm2)		-3.5 ±0.8		-0.9 ± 0.7	0.001*

Abbreviations: ALP; alkaline phosphatase, GFR; glomerular filtration rate, NS; not significant, PTH; parathyroid hormone, PWv; pulse wave velocity, tx; transplantation
(*) indicated p values between two groups according to pre-transplantation period analysis
(**) indicated p values beween two groups according to post-transplantation first year analysis

to maintain a trough concentration of 200 to 300 ng/mL or 10 to 12 ng/mL, respectively.

Statistical analyses

Statistical analyses were performed by using SPSS software (Statistical Package for the Social Sciences, version 11.0, SSPS Inc, Chicago, IL, USA). Normality of data was analyzed by using a Kolmogorov-Smirnov test. All numerical variables with normal distribution were expressed as the means ± standard deviations (SD), while variables with skew distribution were expressed as medians and interquartile range (IR). Categorical variables were expressed as percentages and compared by chi-square test. Normally distributed numeric variables were analyzed by independent samples t or One-Way ANOVA (Post-Hoc Tukey) tests according to distribution normality A multiple regression analysis was performed to assess the indepen¬-dent determinant of the post-tx PTH, PWV, PTH variability and lomber t-score. Results were considered significant at $p< 0.05$.

Results

Demographic characateristics of study population was given in Table 1. The etiologies of chronic kidney disease was diabetes mellitus (%25), hypertension (%13), glomerulonephritis (%13), polycyctic kidney disease (%5) and others (%44). Between two groups no significant difference was detected by means of demographic characteristics as age, gender, post-transplant follow-up duration, pre-transplant dialysis duration, serum calcium, albumin, alkaline phosphatase creatinine and phosphorus levels, glomerular filtration rate and body mass index values.

The mean serum pre-transplant PTH levels was 95.2 ± 7.2 mg/L and 335.8 ± 17.6 mg/L in group 1 and 2, respectively. The mean post-transplant PTH levels was 118.0 ±14.4 mg/L and 179.8 ± 11.6 mg/L in group 1 and 2, respectively.

In group 1; serum PTH levels was slightly increased or stable after transplantation. In group 2; serum PTH levels was significantly decreased in 76 % of patients; however 24 % of group 2 patients had increased PTH after transplantation.

The mean PWv values was 7.6 ± 2.5 ms and 6.4 ± 2.0 ms in group 1 and 2, respectively.

In both groups, an increase in post-transplant PTH >30% was associated with higher serum creatinine and lower GFR levels (p: 0,001 and 0,003 respectively) and higher PWv (p: 0.001).

In regression analysis, factors influencing lumbar t-score were pre-transplant PTH, age and duration of hemodialysis (p: 0.001, p: 0.001, p: 0.001, respectively). On the other hand, pre-transplant PTH levels (p: 0.001), lumbar t-score (p: 0.0001), age (p: 0.0001) and duration after transplantation (p: 0.02) were detected as major determinants of PWv in regression analysis. Serum creatinine, phosphorus and pulse wave velocity were detected the predictors of post-transplant PTH (Table 2).

Discussion

Renal transplantation is the preferable treatment modality for patients with ESRD because of better survival and quality of life. Despite advances in renal transplantation, post-transplant bone disease is a common complication associated with osteoporosis (1). Previous studies demonstrated that patients with secondary hyperparathyroidism experience bone loss after RT, however the data about the effect of transplantation on adynamic bone disease is inadequate in the literature (6). A study in patients with severe aluminum intoxication evaluated low bone turnover patients and detected an improvement in bone remodeling 6 months after renal transplantation (15). Thus preventing long term bone complications of renal transplantation has become an essential part of post-transplant care.

Moreover; patients with chronic kidney disease have a higher risk of cardiovascular disease compared with the general

Table 2: Determinants of post transplantation PTH, variability of PTH, PWv and lumbar t-score

Subject characteristics	Mean ±SD	P value
Post-tx PTH (mg/l)	84.2 ± 18.8	
GFR (ml/min)	1.2 ± 0.5	0.032
Creatinine (mg/dl)	3.1 ±0.8	0.028
Phosphorus (mg/dl)	6.7 ± 0.9	0.002
PWv (ms)		0.001
PWv (ms)		
Age (year)	42.2 ± 2.7	0.001
Pre-tx PTH (mg/L)	212.4 ± 14.7	0.001
Lumbar t-score (g/cm2)	-2.8 ± 0.5	0.001
Duration after tx(months)	34.2 ± 1.8	0.02
PTH variability*		
Pre-tx PTH (mg/L)	212.4 ± 14.7	
Lumbar t-score		
Pre-tx PTH (mg/L)	212.4 ± 14.7	0.001
Duration of dialysis (years)	11.4 ± 1.2	0.001
Age (years)	42.2 ± 2.7	0.001

Abbreviations: GFR; glomerular filtration rate, PTH; parathyroid hormone, PWv; pulse wave velocity, SD: standart deviation, tx; transplantation

population, even after adjustment for traditional cardiovascular disease risk factors. Arterial stiffness has been proposed as a non-invasive cardiovascular disease risk factor. Although the risk of cardiovascular disease is attenuated after kidney transplantation, the impact of kidney transplantation on arterial stiffness still remains unknown (16).

This study aimed to evaluate the relationship between pre-transplant bone activity and post-transplant osteoporosis and arterial stiffness in renal transplant recipients. Our results confirmed that PWv levels; as an indicator of arterial stiffness was significantly higher in patients with adynamic bone disease. Besides, pre-transplant PTH levels were negatively correlated with lumbar t-scores; in consequence pre-transplant adynamic bone disease designates post-transplant osteoporosis. Notwithstanding in our study, age and pre-transplant PTH levels were detected as predictors of PWv in renal transplant recipients. We believe this might be as a result of the relation between adynamic bone disease and microinflammation that can predict cardiovascular calcification.

As well-known, bone remodeling homeostasis is defective after transplantation (2). Published studies showed a decrease in bone formation besides elevated bone resorption that leads to osteoporosis. In a previous study, low turn-over bone disease was detected as a significant risk factor for coronary calcification during early years of hemodialysis (17). London et. al. investigated the association between vascular calcification and low bone turn-over (18). Although previous studies reported an inverse relation between aortic calcification and bone density in ESRD patients, they declined the association between the extent of aortic calcification and low bone activity (19).

A significant finding that we observed, post-transplant increased PTH was associated with low GFR values with high PWv. In most patients, a decrease in PTH occurs by about 1 year after renal transplantation. However some renal transplant recipients continue to have elevated levels of PTH. A previous study evaluated serum PTH levels on 121 patients undergoing renal transplantation. In conclusion they declined elderly patients and longer duration on dialysis before transplantation was risk factors for post-transplant hyperparathyroidism (20). In Akaberi et. al.'s study, PTH remained elevated in long term renal transplant patients with good graft function (21). This conflicted result may be explained by they consider GFR > 35 ml/min to define good graft function. In a recent study, different from previous studies and our results, graft function did not show any association with serum PTH level (12).

It is well known that nutritional status parameters as serum albumin, dietary protein and vitamin D are the important predictors of bone mineral density (21). Previous studies have shown that reduced bone mineral density is associated with arterial stiffening in healthy postmenopausal women. Masugata H. et. al. detected an association between bone mineral density and arterial stiffness in hypertensive patients (22). They also declined that hypertensive patients with increased arterial stiffness may have a high risk of bone fractures due to osteoporosis. Several studies have recently demonstrated that postmenopausal women with osteoporosis or low bone mineral density have impaired arterial endothelial function, increased carotid wall thickness and elevated arterial stiffness indicating that the development of osteoporosis might increase the risk of advanced atherosclerosis (23).

Present study has some limitations. First; the study population has small sample size thus our results should be interpreted with caution. Second, we didn't examine the the mean dosage of active vitamin D received in both groups and lifestyle as exercise that could affect BMD. Finally, we employed DEXA in the evaluation of post-transplant bone disease, but it is well known that bone biopsy provides the only reliable information about bone remodeling.

In conclusion, pre-transplant low serum PTH level is an important predictor for post-transplant osteoporosis and increased arterial stiffness thus an optimum iPTH level should be defined for patients on the transplant waiting list. On the other hand, an increase in post-transplant PTH is associated with graft dysfunction that point out the importance of close follow-up and treatment of high PTH levels after transplantation.

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