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Risk Factors of Post-Transplant Hypertension and Its Effects on Renal Allograft Function and Histopathology

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Abstract

Introduction: Cardiovascular diseases are the leading causes of death after kidney transplantation, one of the major risk factors of which is Post Transplant Hypertension (PTHT), which is often unrecognized and therefore untreated.

Material and Methods: In this study, the incidence and risk factors of PTHT were examined. The effect of blood pressure on graft function and that of renin and aldosterone levels on renal function were assessed. The effect of hypertension on renal histology one year after transplantation was evaluated.

Results: The incidence of PTHT was 42%. Regarding the risk factors, no significant difference was revealed. PTHT was significantly higher in cyclosporine users (P=0.021) than in tacrolimus users. Significant differences were found in case of renal function: serum creatinine (P=0.024) urea (P=0.005) and eGFR (P=0.036) in patients with PTHT. The analysis of renin and aldosterone levels confirmed that renin levels significantly changed serum creatinine (P=0.019) and urea (P=0.027) values. The donor's systolic blood pressure significantly affected the development of arteriolar hyalinosis (normal *vs*. arteriolar hyalinosis; N=13 *vs*. N=56; P=0.023). The incidence of interstitial fibrosis and tubular atrophy (P=0.0001) and acute cellular rejection (P=0.033) was significantly higher in patients with systolic blood pressure one year after the surgery.

Discussion: The harmful effect of newly developed hypertension after transplantation on the graft was seen even one year after transplantation not only in renal function but in morphology as well.

Conclusion: Therefore, we consider it essential to monitor blood pressure regularly and to start antihypertensive therapy if necessary.

Keywords: Immunosuppressive drugs; Kidney function and morphology; Kidney transplantation; Post-transplant hypertension

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Introduction

Post-Transplant Hypertension (PTHT) contributes to the high incidence of cardiovascular mortality as well as to that of interstitial fibrosis and tubular atrophy and late graft failure in renal transplant recipients [1]. The mechanisms are complex and may involve pathogenic factors attributable to the host, allograft, and immunosuppressive drugs. Immunosuppressive agents affect hypertension through a variety of mechanisms, including catecholamine and endothelin induced vasoconstriction, inhibition of nitric oxide induced vasodilatation, and sodium retention. The most significant mechanism in the development of hypertension is due to the hypertension promoting role of calcineurin inhibitors; this effect is more pronounced in case of Cyclosporine (CsA) than in case of Tacrolimus (Tac) [2]. Further important causes of hypertension after transplantation, beyond a progressive decrease in the Glomerular Filtration Rate (GFR), include acute cellular rejection. Calcium channel blockers may be the most useful medications for mitigating calcineurin inhibitor-induced vasoconstriction, and use of such agents may be associated with improvements in GFR. The administration of angiotensin-converting enzyme inhibitors and angiotensin

receptor blockers remains an attractive strategy for many transplant recipients, although some recipients may have significant adverse effects associated with these medications, including decreased GFR, hyperkalemia, and anemia [2].

The primary aim of our study was to assess the incidence of post-transplant hypertension and to evaluate its risk factors and its effect on renal allograft function and morphology.

Our study was approved by the Regional Human Biomedical Research Ethics Committee of the Albert Szent-Györgyi Clinical Center (Reg. No. 18/2020). Each patient was provided with comprehensive information regarding the study.

Patients and Methods

Our study was conducted at the Department of Surgery, University of Szeged, Hungary. Patients were excluded from the study if they did not give consent to participation, had cadaveric kidney transplantation before, had live kidney transplantation, were younger than 18 years of age, or had been transplanted less than one year ago, or had received steroid push therapy. A total of 69 patients were enrolled in the study. PTHT was diagnosed in accordance with the recommendation of the International Society of Hypertension; PTHT was considered to be present if the Blood Pressure (BP) was ≥ 135/85 mmHg [3]. Our study assessed the correlation between Ambulatory BP Monitoring (ABPM), Home BP Monitoring (HBPM), and office Clinic BP monitoring (CBP) in the post-transplant setting. An important aspect in the conduct of these research studies is the care that should be used in the measurement of BP in the clinic. The use of standardized techniques, as used in clinical trials of hypertension with >1 measurement of BP, can provide improved concordance rates between CBP and ABPM. BP was measured four times a day in all patients, and measurements were made in office environment as well, where the mean value of the daily measurements was used. Risk factors of PTHT, such as Body Mass Index (BMI), age, Cold Ischemia Time (CIT), and Human Leucocyte Antigen (HLA) -mismatch were examined. Among the immunosuppressive agents used, the effect of CsA and Tac on the development of PTHT was investigated. Thirty patients received cyclosporine-based and 39 patients received tacrolimus-based immunosuppression. Venous blood sample was collected in a fasting state, during which sodium, potassium, and calcium values were examined considering the systolic and diastolic blood pressure values. We studied whether the systolic or the diastolic blood pressure affected renal function by measuring serum creatinine, urea, and the Estimated Glomerular Filtration Rate (eGFR) values. In addition, the effect of renin and aldosterone levels on renal function parameters were examined. We studied patients whose "zero biopsy" was intact, and in whom we could perform protocol biopsy one year after the transplantation. An ultrasound-guided protocol biopsy was performed (with the patient's prior consent) after the one-year fasting laboratory test. 16-G Tru-Cut needles and a biopsy gun were used to obtain the tissue cylinders. In our studies, we evaluated how the systolic and the diastolic blood pressure values of the donor affected the morphology of our "zero biopsy" specimen. Then, a one-year protocol biopsy was performed in each patient considering the systolic and the diastolic blood pressure values. Morphological examination included standard microscopic staining (hematoxylin and eosin, periodic acid–Schiff, trichrome, and methenamine silver), as well as immunofluorescence staining of frozen section using antibodies against human leukocyte class 2 antigen, Complement 4d (C4d), C3, Immunoglobulin (Ig) G, IgA, and IgM. Embedding for electron microscopy was performed in all cases, and ultrastructural evaluation was performed in some samples. Renal lesions were graded and diagnosed according to the 2003 modification of the Banff classification. Histological changes were classified as Acute Rejection Episode (ARE), Calcineurin Inhibitor toxicity (CNI-tox), and Interstitial Fibrosis/Tubular Atrophy (IF/TA) for grades II and III, compared with grade I, which was considered to be normal. Changes associated with Pyelonephritis (PN) and other diseases, for example, acute tubular necrosis, glomerulonephritis, and BK polyomavirus nephritis were evaluated as well.

Immunosuppressive therapy

The initial daily dose of Tac was 0.20 mg/kg in two portions, and then, the target blood level was (10 to 15) ng/mL for 6 weeks and (5 to 10) ng/mL after Week 6.

The initial dose of CsA was (8 to10) mg/kg daily, in two portions, and then, the target blood level was (1,300 to 1,600) ng/mL in Month 1, (900 to 1300) ng/mL in Months 2 and 3, (750 to 950) ng/mL in Months 4 to 6, and 700 ng/mL afterwards (blood levels were determined two hours after administration).

Laboratory methods

Blood sample collection for the quantification of angiotensin metabolites renin and aldosterone was made after the long interdialytic interval at the pre-filter bloodline site and via cubital venous blood collection after kidney transplantation. Six (6) mL of heparinized peripheral blood was collected from each patient and chilled on ice immediately.

Statistical analysis

Statistical methods. Continuous data were expressed as mean (±) SD. The means of PTHT in groups of normal blood pressure were compared with independent sample *t*-test. The monotonous relationship between the two continuous variable histopathological results was investigated with Spearman's rank correlation coefficient. One-way ANOVA was performed to compare the means of PTHT in groups of normal blood pressure patients. LSD post-hoc comparisons were performed after a significant ANOVA result. Receiver Operating Characteristics (ROC) analysis was applied to investigate the predictive power of the possible risk factors to predict hypertension. Optimal cutoff value of the significant predictors were defined based on the maximum value of the Youden-index, sensitivity and specificity values were calculated based on this optimal cutoff value. A p-value of $p<0.05$ was regarded as statistically significant. Calculations were carried out with the IBM SPSS 26 statistical software.

Results

As a result of our study, PTHT was diagnosed in 29 cases, representing (42%) of the patients. Examining the risk factors for PTHT, no significant difference was found between BMI (P=0.472), age (P=0.289), HLA-mismatch (P=0.576), and gender (P=0.740) (Table 1). No significant difference was found original diseases (Table 2).

Examination of the immunosuppressant agents used showed significantly higher rate of PTHT in case of taking CsA than in case of patients taking Tac (CsA N=30/23 *vs.* Tac N=39/15; P=0.021). No significant difference was found in the electrolyte levels (sodium P=0.252 and potassium P=0.319) examined in terms of systolic and diastolic blood pressure values, but significant difference was found in the renal function parameters (serum creatinine P=0.024,

Table 1: Risks factors of high blood pressure.

	Blood pressure ≥ 135/85 mmHg (N=29) (mean ± SD)	Blood pressure <135/85 mmHg (N=40) (mean ± SD)	P value
Recipient data			
BMI (kg/m²)	31.7 ± 1.6	29 ± 1.9	0.472
Gender (male/female)	13/16	18/22	0.74
Age (year)	54.23 ± 9.23	52 ± 8.23	0.289
Donor data			
HLA-mismatch	2.4 ± 0.45	2.9 ± 1.13	0.567
CIT	11.03 ± 1.57	9.72 ± 2.38	0.623
Age (year)	52.34 ± 1.67	53.82 ± 4.12	0.725
Gender (male/female)	12/17	18/22	0.632
TAC initial daily dose (mean)	8 mg	7 mg	0.179

Abbreviation: BMI: Body Mass Index; HLA: Human Leukocyte Antigen; SD: Standard Deviation; CIT: Cold Ischemia Time; TAC: Tacrolimus

Table 2: Original kidney diseases in the various blood pressure groups.

	Blood pressure ≥ 135/85 mmHg (N=29)	Blood pressure <135/85 mmHg (N=40)	
Polycystic kidney	12	14	0.32
Chronic pyelonephritis	6	9	0.81
Chronic Glomerulonephritis	9	11	0.39
Other	2	6	0.54

Table 3: Effects of blood pressure on the allograft function.

	Blood pressure ≥ 135/85 mmHg (N=29)	Blood pressure <135/85 mmHg (N=40)	P value
Serum creatinine (µmol/L)	230.35 ± 24.69	167.28 ± 12.39	0.024
Urea (µmol/L)	15.78 ± 2.74	9.64 ± 4.25	0.005
eGFR (mL/min/1.73 m²)	39.23 ± 10.23	47.19 ± 8.38	0.036

Abbreviations: eGFR: Estimated Glomerular Filtration Rate

Table 4: Evaluation of possible risk factors for hypertension. ROC analysis results.

	AUC ROC	P-value	95% confidence interval Lower bound	Upper bound
Serum creatinine (µmol/L)	0.59	0.012	0.454	0.726
Urea (µmol/L)	0.632	0.002	0.497	0.766
eGFR (mL/min/1.73 m²)	0.6	0.026	0.464	0.736

urea P=0.005, and eGFR P=0.036) in patients with PTHT (Table 3). ROC analysis revealed that aldosterone is a significant predictor for hypertension (Table 4). Cutoff value was determined only for this significant risk factor. We found 640.5 to be the optimal cutoff value with sensitivity of 71% and specificity of 65.8%.

Serum creatinine (P=0.019) and urea (P=0.027) levels were significantly changed by renin levels, although the eGFR values were similar (P=0.195). No significant difference was seen in case of aldosterone levels in serum creatinine (P=0.206) and urea (P=0.204) values.

Examining the morphological differences in the "zero biopsy" results, the systolic blood pressure of the donor significantly affected the development of arteriolar hyalinosis (normal *vs.* arteriolar hyalinosis; N=13 *vs.* N=56; P=0.023). However, diastolic blood

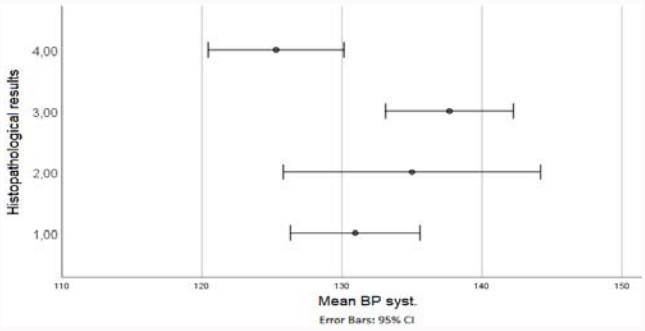

Figure 1: Histopathological results on systolic blood pressure. Histopathological results 1: Other disease; 2: Calcineurin inhibitor-toxicity; 3: Interstitial fibrosis and tubular atrophy; 4: Normal.

pressure did not significantly affect graft morphology, P=0.119.

Interstitial fibrosis and tubular atrophy (P=0.0001) and acute cellular rejection (P=0.033) were significantly more common in PTHT patients than in non-hypertensive patients in accordance with the results of the protocol biopsies performed one year after transplantation (Figure 1).

Discussion

The incidence of PTHT after kidney transplantation was 42%, similar to the results of other clinical trials. Kasiske et al. [4] have found in their study the incidence of PTHT to be between 43.5% and 54.6%. Among the risk factors, BMI, gender, age, and HLA-mismatch did not differ significantly. Linderman et al. [5] have detected that the only 2 exceptions were individuals from the province of Tibet, with an unadjusted increase in systolic blood pressure per unit BMI of 0.56 (95% CI, 0.44-0.68) mmHg/(kg/m²), and individuals taking antihypertensive medications, with an unadjusted increase in systolic blood pressure per unit BMI of 0.34 (95% CI, 0.29-0.39) mmHg/(kg/m²). Corticosteroid therapy is not a major contributor to chronic hypertension in transplant recipients due to the rapid tapering of the dose, but steroids (in high doses) may contribute to the disease early after transplantation or during pulse rejection therapy. It is difficult to assess the contribution of calcineurin inhibitors to the development of hypertension after kidney transplantation, due to the major physiological alterations developing after transplantation and concurrent factors contributing to hypertension. These factors include delayed graft function, volume overload, steroid treatment, and the presence of hypertension prior to kidney transplantation [6]. Besides calcineurin inhibitors and steroids, a variety of pre- and post-transplant factors were shown to predict the occurrence of hypertension following renal transplantation. No significant difference was found in the electrolyte levels between patients with PTHT and normotensive patients, but there was a significant difference in renal function parameters. Cosio et al. [7] have performed a multivariate analysis of renal allograft survival, in which they have studied 547 cadaveric transplant recipients and demonstrated a relationship between mean arterial blood pressure (averaged over the first 6 months after transplantation) and allograft survival only in African American recipients [8,9]. Although these analyses have been adjusted for the serum creatinine value at 6 months, the instability of renal function and blood pressure due to frequent episodes of acute rejection in this time frame may have been the reason that no association has been observed in white recipients. Their analyses demonstrate that elevated blood pressure adversely affects allograft

survival for both African American and white recipients. Evaluation of the donor's blood pressure and the histology with "zero biopsy" confirmed a significantly higher incidence of arteriolar hyalinosis. The one-year protocol biopsy showed a significantly higher incidence of acute cellular rejection, interstitial fibrosis, and tubular atrophy in patients with post-transplant hypertension.

The European guidelines for the treatment of post-transplant hypertension have not yet been put forward. The National Kidney Foundation Task Force on cardiovascular disease recommends a target value of ≤ 135/85 mmHg for patients with renal disease without proteinuria and a target value of ≤ 125/75 mmHg for patients with proteinuria [10].

In summary, the harmful effect of newly developed hypertension after transplantation on the graft was evident even one year after transplantation not only in case of renal function but in case if morphology as well [11,12]. Therefore, we consider it to be very important to monitor BP regularly and to start antihypertensive therapy, if necessary, as it may not only maintain the function of the graft, but it might also increase the long-term survival of the patients.

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