EFFECT OF BETTER CONTROL OF HYPERTENSION ON LEFT VENTRICULAR MASS IN LONG TERM RENAL TRANSPLANT RECIPIENTS

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ABSTRACT

Objective: Control of hypertension (HT) can lead to regression of left ventricular mass index (LVMI) especially in the first year of renal transplantation. However, effect of better control of blood pressure (BP) on regression of LVMI in long-term renal transplant recipients is not known. In this study, we aimed to determine whether improved control of HT would decrease LVMI in renal transplant recipients or not.

Methods: Twenty-four nondiabetic renal transplant recipients were included in the final analysis. Patients were categorized into group A (controlled-HT) and group B (uncontrolled-HT) according to their daytime blood pressure levels at the beginning of the study. Antihypertensive drug treatment of patients in group B was modified according to ambulatory blood pressure monitorization (ABPM) and clinical measurements. Echocardiographic examination was performed at baseline and at the end of 24 month.

Results: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) declined significantly ($p<0.01$) in parallel to increased use of angiotensin converting enzyme inhibitor ($p<0.01$) and LVMI remained unchanged in group B (113 ± 34 g / m^2 vs 112 ± 29 g / m^2 at baseline and at the end of 24 month, respectively). Although SBP and DBP did not change significantly in group A, LVMI increased significantly (90 ± 21 g / m^2 to 107 ± 26 g / m^2 at baseline and at the end of 24 month, respectively) in parallel to increase in serum creatinine ($p<0.05$) and decline in hemoglobin levels.

Conclusions: Our results suggest that control of BP is not sufficient either for the regression or maintenance of LVMI in long term renal transplant recipients. However, factors such as low hemoglobin level and worsening of renal function may play critical roles in the progression of LVMI even in patients with well-controlled BP.

Key Words: Renal transplantation, Left ventricular hypertrophy, Hypertension, Ambulatory blood pressure monitoring

INTRODUCTION

Cardiovascular disease is the most common cause of death after renal transplantation (1, 2). Left ventricular hypertrophy (LVH) is an independent predictor of mortality in patients with end-stage renal disease (3). The presence of increased left ventricular mass index (LVMI) in the pretransplant period may also be responsible for the premature death after renal

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transplantation (4). Moreover, increased LVMI in the early posttransplant period was related to increased mortality rate after transplantation (5). Hypertension has a major influence in the development of LVH. Additional factors, such as uremia, hyperparathyroidism, volume overload, high cardiac output state due to anemia, and arteriovenous fistula are also operative in the development of LVH in patients undergoing hemodialysis (6). Although, reduction of LVH has not been a consistent observation (7), it is mostly reported that correction of uremia-related factors and hypertension lead to regression of LVM and normalization of cardiac function, principally during the first year after renal transplantation (8-10). The persistence of hypertension was reported as the most important factor responsible for the failure of further regression of LVMI beyond the second year after renal transplantation (10).

Studies, aimed to investigate the effect of blood pressure (BP) control on the regression of LVMI, were either conducted in the early post-transplant period or study population consisted of the patients with uncontrolled BP (9). There is no prospective report that specifically addressed the effect of better control of HT on LVMI after the first year in renal transplant recipients.

In this study, we aimed to determine whether the improvement in HT control by means of stepped approach with antihypertensive therapy will improve left ventricular structure in renal transplant recipients one year after renal transplantation.

MATERIALS AND METHODS

Study population

Forty-three nondiabetic renal transplant recipients who were followed up at the renal transplant clinic of Marmara University Hospital were candidates for the study. The local ethics committee approved the study protocol and all patients gave written informed consent prior to inclusion to the study. All of the patients underwent echocardiography and ABPM measurement at baseline and at the end of study period. Renal transplant recipients with duration of renal transplantation less than 12 months (n = 5), functional arteriovenous fistula (n = 1), serum creatinine level above 2.0 mg / dl (n = 5), more than 20 % increase in serum creatinine at any time during the preceding 12 months (n = 2) and severe valvular heart disease (n = 1) were excluded from the study. The remaining 29 renal transplant recipients (aged 35 ± 9 years, mean duration of transplantation of 49 ± 32 months) were included in the the study irrespective of their BP levels and LVMI. The duration of renal transplantation was between 13 to 24 months in 10 recipients, between 25 to 36 months in 6, between 37 to 48 months in 3, between 49 to 60 months in 2 and more than 61 months in 8 recipients. The causes of pretransplant renal failure were chronic glomerulonephritis (34 %), hypertensive nephrosclerosis (28 %), chronic pyelonephritis (21 %), and unknown etiology (13 %). Five renal transplant recipients (3 male and 2 female; aged 37 ± 5 years) who had their serum creatinine increased more than 20 % during study period compared to baseline (n = 3), or whose echocardiography was unavailable (n = 2) were excluded from the final analysis at the end of 24 months of follow up.

All renal transplant recipients were on triple immunosuppressive treatment consisting of cyclosporine, prednisolone and azathioprine. The serum level of cyclosporine was between 100 and 200 ng / ml. The dose of prednisolone and azathiprine were 5 to 10 mg / day and 1 mg / kg / day, respectively.

Blood Pressure Measurements

Twenty-four hours ambulatory blood pressure monitoring (ABPM) was performed according to the method described previously (11) at baseline and 24 months after the last modification of antihypertensive drugs. ABPM device (Spacelab 90207; Spacelabs Inc., Redmond, WA, USA) was programmed for 24 hours with readings for every 20 minutes from 07.00 to 23.00 and every 30 minutes from 23.00 to 07.00. Monitors were calibrated against a mercury sphygmomanometer at the beginning of each session. According to the baseline recordings, patients were categorized as "controlled HT" (n = 14) with daytime ABPM below 135/85 mm Hg or "uncontrolled HT" (n = 10) with mean daytime ABPM ≥ 135/85 mm Hg according to current definitions and criteria used by Burt and colleagues (12,13). Renal transplant recipients with "controlled-HT" constituted group A, and patients with "uncontrolled-HT" constituted

group B. Antihypertensive medications were modified according to ABPM measurements at baseline and further revised by ABPM measurements or clinical BP measurements at regular intervals during outpatient visits according to recent guidelines (12). Clinical BP was measured from the same upper extremity using a mercury sphygmomanometer with the patient in a sitting position. After 10 minutes of rest, the averages of three consecutive measurements performed 5 minutes apart were accepted as the final BP value.

Echocardiographic assessment

Two-dimensional guided M-mode echocardiography was performed by standard methods using an ultrasound system (Ultramark 9, Advanced Technology Laboratories, Bothell, WA, USA) with a 2.25-MHz transducer. Left ventricular internal dimension (LVID), interventricular septal thickness (IVST) and posterior wall thickness (PWT) were measured at end-diastole according to the American Society of Echocardiography recommendations (14). Left ventricular mass (LVM) was calculated using the thick-wall prolate-ellipsoidal model with correction based on a necropsy validation study by Devereux et al. (15): $0.832 \times [(LVID + IVST + PWT)^3 - LVID^3] + 0.6$. LVM was considered as an unadjusted variable and normalized for body surface area (BSA) as left ventricular mass index (LVMI). BSA was calculated by using the Du Bois formula: $0.007184 \times (\text{weight [kg]})^{0.425} \times (\text{height [cm]})^{0.725}$.

Laboratory measurements

Serum creatinine was measured using a computerized auto—analyzer (Hitachi 717, Boehringer Mannheim, Germany). Blood cyclosporine-A level was analyzed by FPIA assay using a monoclonal antibody (Abbott, IL, USA).

Statistical analysis

All calculations were done using SPSS computer program. Data were expressed as mean ± SD. Comparisons between groups A and B were performed by using Mann Whitney U test. Comparisons within the groups were done using Wilcoxon signed rank test. Fischer's exact test was used for the analysis of categorical variables. A two-tailed p value less than 0.05 were considered significant.

RESULTS

The clinical characteristics and laboratory data of group-A (controlled HT) and group B (uncontrolled-HT) are presented in Table I. There were no significant differences in serum creatinine, hemoglobin, cyclosporine level, the duration of dialysis previous to transplantation and the duration of renal transplantation between the two groups at baseline. Serum creatinine level increased mildly but significantly in group A at the end of 24th month of follow-up ($p<0.05$).

ABPM data are presented in Table II. Daytime, nighttime and 24-h ABPM measurements were significantly higher in group B compared to group A at baseline. 24-h SBP decreased from 143 ± 12 mm Hg to 126 ± 8 mm Hg ($p < 0.01$) and 24-h DBP decreased from 88 ± 6 mm Hg to 77 ± 7 mm Hg ($p < 0.01$) in group B at the end of follow-up period (Table II). However, 24-SBP and daytime SBP values were still higher in group-B compared to respective values in group A at 24th month. Finally, only 3 patients (30%) had uncontrolled HT according to daytime ABPM values (135/87 mm Hg, 137/77 mm Hg and 135/93 mm Hg, respectively) after 24 months in group B. All of the patients in group A had controlled BP at the end of study period. Number of antihypertensives prescribed in group B increased significantly from 1.5 ± 0.5 at baseline to 2.6 ± 0.5 after 24 months ($p < 0.01$), whereas the number of antihypertensives did not change in group A. The number of patients receiving angiotensin converting enzyme inhibitors (ACEI) were significantly higher in group B than in group A at the end of study period (29% vs. 80%, $p<0.05$) (Table I). There was a significant difference in hemoglobin levels at the end of 24 months between the two groups (12.0 ± 1.7 g/dl vs. 13.9 ± 1.7 g/dl, $p<0.05$).

While the change in LVID index and IVST index remained insignificant in group-A, PWT index (from 4.8 ± 1.1 mm / m^2 to 6.0 ± 0.9 mm / m^2, $P = 0.009$) increased significantly after two years (Table III). As a result, LVMI increased significantly from 90 ± 21 g / m^2 to 107 ± 26 g / m^2 in group A ($p=0.041$). LVID index, IVST index, PWT index did not change in group B. Therefore, LVMI did not change in group B (113 ± 34 g / m^2 vs 112 ± 29 g / m^2) after two years.

Table I: Clinical characteristics and biochemistry of controlled HT (A) and uncontrolled HT (B) groups of renal transplant recipients at baseline and after 24 months.

	Group A (n = 14)		Group B (n = 10)	
	Baseline	24th month	Baseline	24th month
Age (years)	36 ± 9		35 ± 9	
Gender (male / female, n)	8/6		8/2	
Duration of dialysis before Tx (mo)	20 ± 20		24 ± 22	
Duration of renal Tx (mo)	47 ± 27		55 ± 31	
Serum creatinine (mg / dl)	1.32 ± 0.31	1.51 ± 0.47*	1.25 ± 0.33	1.34 ± 0.39
Hemoglobin (g / dl)	12.6 ± 2.0	12.0 ± 1.7	13.5 ± 1.3	13.9 ± 1.7†
Blood cyclosporine-A level (ng / ml)	159 ± 39	163 ± 38	157 ± 25	147 ± 31

Values are expressed as mean ± SD *p< 0.05 vs baseline in group A, †p<0.05 vs group A at 24th month.

Tx: transplantation.

Table II: ABPM and antihypertensive drug data of controlled HT (A) and uncontrolled HT (B) groups of renal transplant recipients at baseline and after 24 months.

	Group A (n = 14)		Group B (n = 10)	
	Baseline	24th month	Baseline	24th month
Uncontrolled HT (%)	0	0	100	30
24-hour SBP (mm Hg)	118 ± 7	118 ± 8	143 ± 12*	126 ± 8†‡
24-hour DBP (mm Hg)	78 ± 5	77 ± 4	88 ± 6*	77 ± 8†
Daytime SBP (mm Hg)	121 ± 8	122 ± 7	143 ± 11*	128 ± 7†
Daytime DBP (mm Hg)	80 ± 5	79 ± 4	89 ± 4§	80 ± 7†
Nighttime SBP (mm Hg)	112 ± 8	114 ± 10	144 ± 20*	121 ± 12†
Nighttime DBP (mm Hg)	72 ± 4	74 ± 6	86 ± 11§	72 ± 10†
Antihypertensive drugs (n)	1.5 ± 0.8	1.5 ± 0.8	1.6 ± 0.8	2.6 ± 0.8&¶
• ACEI	4/14	4/14	1/10	8/10†‡
• Calcium channel blockers	14/14	14/14	10/10	10/10
• α- receptor blockers	2/14	2/14	2/10	5/10‡
• β-receptor blockers	1/14	1/14	2/10	2/10
• Diuretic	0/14	0/14	0/10	0/10
• Others	0/14	0/14	1/10	1/10

Values are expressed as mean ± SD

*p<0.001 vs group A at baseline, †p<0.01 vs baseline, ‡p<0.05 vs group A at 24th month, §p<0.005 vs group A at baseline,

&p<0.0001 vs baseline, ¶p<0.01 vs group A at 24th month,

ABPM: Ambulatory blood pressure monitorization; SBP: Systolic blood pressure; DBP: Diastolic blood pressure,

ACEI: Angiotensin converting enzyme inhibitor.

Table III: Echocardiography of Controlled HT (A) and uncontrolled HT (B) groups of renal transplant recipients at baseline and after 24 months.

	Group A (n = 14)		Group B (n = 10)	
	Baseline	24th month	Baseline	24th month
LVID index (mm / m^2)	28.5 ± 3.2	27.6 ± 3.3	26.3 ± 3.2	25.7 ± 3.3
IVST index (mm / m^2)	5.3 ± 1.2	5.9 ± 0.6	6.4 ± 0.9*	6.0 ± 0.6
PWT index (mm / m^2)	4.8 ± 1.0	6.0 ± 0.9†	5.7 ± 1.0‡	5.9 ± 1.1
LVMI (g / m^2)	90 ± 21	107 ± 26¶	113 ± 34	112 ± 29

Values are expressed as mean ± SD

*p=0.01 vs group A at baseline, †p=0.009 vs baseline, ‡p<0.05 vs group A at baseline, ¶p<0.05 vs baseline.

LVID: Left ventricular internal diameter; IVST: Interventricular septal thickness; PWT: Posterior wall thickness.

DISCUSSION

This study demonstrated that better control of HT did not result in regression of LVMI in long term renal transplant recipients with "uncontrolled-HT" (group B) and maintenance of BP control in the group with "controlled-HT" (group A) did not prevent progression of LVMI after 24 months of follow-up.

Previous studies demonstrated that control of HT resulted in improvement of LVMI LVH in renal transplant recipients in the early posttransplant period (8,9). Rigatto et al. reported that regression of LVMI was an ongoing process during the first 2 years of transplantation and reached a nadir in the third and fourth posttranplant years (10). In contrast to this study, de Lima et al. reported that LVMI continued to regress from 172 g/m^2 to 136 g/m^2 during 40 months of follow-up (16). However, in this study, first echocardiography was performed 12 months after renal transplantation, and the second echocardiography was performed almost 2 years after the first one. This study was quite similar to design of our study in that they also included patients with duration of transplantation more than 12 months. However, in our study, we intended to control HT in the recipients with uncontrolled HT and maintain controlled BP in the recipients with controlled HT. ABPM were done for all recipients at baseline and at the end of 2 years to determine the level of control of HT. ABPM is accepted as the method more closely associated with LVMI compared to clinical measurements following renal transplantation (17, 18).

The increase in LVMI in our renal transplant recipients with controlled HT at baseline was due to increase in the wall thickness of left ventricle. Our findings indicate that control of HT may be a weak factor to influence the course of LVMI in long term renal transplant recipients. The progression in LVMI in this group was probably secondary to significant worsening of renal function and anemia. However, increased use of ACEI and preservation of renal function and hemoglobin level may be responsible from the maintenance of LVMI in patients with "uncontrolled HT". In our study, the decrease in hemoglobin values in group A might explain the increment in LVMI in group A (19).

In this study, we used ABPM measurement for all recipients at baseline and at the end of 2 years. ABPM is accepted as the method more closely associated with LVMI compared to clinical measurements following renal transplantation (17).

A major limitation in this study is that, groups were small to reach a sufficient power to evaluate independent effects of other factors such as decrease in renal function and anemia and the use of ACEI on the structure of left ventricle at long term.

In conclusion, control of HT did not result in regression of LVMI in long term renal transplant recipients. Worsening of renal function and anemia are probably more important risk factors for the maintanence of LVH at long term in renal transplant recipients. Increased use of ACEI would probably effect the left ventricular structure in those patients. Long-term follow-up studies in a large cohort of renal transplant population should be performed in order to investigate whether control of these factors and increased use of ACEI could lead to regression of LVH and have a beneficial effects on cardiovascular outcome.

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