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The Predictors of Left Ventricular Hypertrophy in Kidney Transplant Recipients

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Abstract

Background: Cardiovascular disease (CVD) is one of the leading causes of mortality among kidney transplant (KTx) recipients. Left ventricular hypertrophy (LVH) is a known important risk factor for CVD in KTx recipients. The current study aimed at evaluating the association of LVH with hypertension, carotid intima media thickness (CIMT), and serum biomarkers.

Methods: The current cross sectional study included KTx recipients; ambulatory blood pressure monitoring, echocardiography, and CIMT measurement were performed. In addition to standard laboratory investigations, high sensitivity C-reactive protein (CRP) and serum homocysteine were measured.

Results: A total of 30 KTx recipients (20 male, 10 female, mean age: 44.53 $\pm$ 13.59 years) were enrolled. One-third had diabetes and 73.3% hypertension. Their mean systolic and diastolic blood pressure (BP) was 132.0 $\pm$ 14.4 and 77.8 $\pm$ 11.3 mmHg, respectively. BP was well controlled, albeit with more antihypertensive agents of 1.5 (interquartile range (IQR): 0 - 4). Their baseline serum creatinine and eGFR were 108.3 (IQR: 66-319) μM/L and 69.8 $\pm$ 20.8 mL/min/1.73 m^2, respectively. Seven patients had LVH and predominantly had diabetes, a higher pulse pressure, and elevated serum homocysteine. Predictors of left ventricular mass index (LVMI) were the incidence of diabetes, higher pulse pressure, serum homocysteine, and the number of antihypertensive agents prescribed. On multivariate analysis, diabetes and pulse pressure were the main predictors of left ventricular mass index.

Conclusions: LVH is common in patients with KTx, especially in the ones with diabetes. Serum homocysteine is a surrogate marker for LVH.

Keywords: Homocysteine, Hypertension, Kidney Transplant, Left Ventricular Hypertrophy, Pulse Pressure

1. Background

Kidney transplantation improves the survival of patients with end-stage renal disease and with the advances in immunosuppression, kidney transplant (KTx) recipients live longer (1). However, cardiovascular disease (CVD) remains the commonest cause of morbidity and mortality in KTx recipients (2, 3). Although KTx recipients have a lower risk of CVD compared with the patients undergoing dialysis, they are at higher risk compared with the general population (3, 4). Kasiske et al. reported that 16% of their KTx recipients developed new atherosclerotic complications during a 10-year follow-up (5). Non-traditional cardiac risk factors that contributed to CVD in KTx recipients include dialysis vintage, reduced graft function post KTx, graft rejection, reduced effect of immunosuppressive drugs, elevated levels of C-reactive protein (CRP), and hyperhomocysteinemia (5, 6).

Studies showed that hypertension is common in KTx recipients and this could be aggravated by the immunosuppressive agents (7). Hypertension plays an important role in the development of left ventricular hypertrophy (LVH) and atherosclerosis. Studies showed that both functional and structural changes occur in the heart in asymptomatic KTx recipients. LVH is a risk factor for premature death and cardiovascular events (8).

The main immunosuppressive agents prescribed to KTx recipients to prevent graft rejection, such as corticosteroids and cyclosporine, increase the risk of hyperlipidemia, hypertension, and diabetes mellitus (9). Immunosuppressive drugs used post KTx can lead to the development of endothelial dysfunction and subsequently increase risk of CVD. Endothelial dysfunction and damage plays a central role in the pathogenesis of hypertension and atherosclerotic CVD. Endothelial dysfunction is a predictor for future cardiovascular events (10). Carotid intima-media thickness (CIMT) of the common carotid

artery is used as a surrogate marker to predict early atherosclerosis (11).

Hyperhomocysteinemia is a well-established cardiovascular risk factor in the general population. (12). Serum homocysteine level is inversely related to renal function and although its etiology is not fully understood, it is perceived to reduce renal clearance of homocysteine (13). Studies showed that nearly 70% of KTx recipients raised serum homocysteine levels (14, 15). Basu et al. demonstrated that the oxidized form of homocysteine in plasma led to endothelial damage (16).

There is no study on the association of LVH with serum homocysteine in KTx recipients. Hence, the current study aimed at determining the predictors of LVH in the studied KTx population and any association between serum homocysteine and LVH.

2. Methods

The current cross sectional study was conducted on KTx patients attending the Transplant Clinic at Universiti Kebangsaan Malaysia Medical Centre (UKMMC). The study was approved by the ethics research committee of UKMMC (code: FF-2014-213). All KTx recipients attending the transplant outpatient clinics from January 2014 to August 2014 were screened. KTx cases transplanted > 6 months, aged > 18 years, with triple-drug immunosuppressive therapy for > 6 months were enrolled. Pregnant females and those with documented CVD were excluded from the study. CVD was defined when 1 or more of the following conditions occur: acute coronary syndrome, ischemic heart disease, congestive cardiac failure, transient ischemic attack, stroke, peripheral vascular disease, and abdominal angina. After obtaining informed consent, demographic data were collected on all subjects including age, gender, race, body weight and height, body mass index (BMI), diabetes, hypertension, duration of KTx, and immunosuppressive regimen. Immunosuppressive regimen was divided into calcineurin inhibitor (CNI) and proliferative signal inhibitor (PSI). The baseline blood investigations for hemoglobin level, renal profile, fasting blood sugar, hemoglobin A1c (HbA1C), fasting lipid profile, high-sensitivity C-reactive protein (hs-CRP), and homocysteine was monitored in the patients. All patients underwent blood pressure monitoring, echocardiogram, and CIMT measurements.

2.1. Blood Pressure

Ambulatory blood pressure monitoring (ABPM) was recorded using the BPRO machine (model T6400, Healthstats). Patients were advised to carry out their usual activities. BP was recorded every 15 minutes during the day and every 30 minutes during the night hours. Mean 24-hour daytime and nighttime systolic and diastolic BP as well as the mean arterial BP were derived from 24-hour ABPM data. More than 80% technically satisfactory readings of ABPM were considered as a successful recording. Hypertension was defined as systolic BP > 130 mmHg or diastolic BP > 80 mmHg, or the use of antihypertensive medications (17). Good control of hypertension was defined as the mean 24-hour ABPM < 130/80 mmHg, regardless of whether on treatment or not (18).

2.2. Echocardiography

Two-dimensional and M-mode echocardiography (Acuson Sequoia 512, ultrasound machine) was performed by an experienced cardiologist who was unaware of the blood pressure findings. Left ventricular mass index (LVMI) was calculated using the Devereux formula (19).

$$LVMI = 0.8\ (1.04\ ([LVIDD + PWTD + IVSTD]^3 - [LVIDD]^3) + 0.6\ g$$

Where LVIDD, PWTD, and SWTD are LV internal dimensions at the end diastole, posterior wall thickness at end diastole, and septal wall thickness at end diastole, respectively.

LVH was defined as LVMI > 104 g/m^2 in females and > 116 g/m^2 in males (20).

2.3. CIMT

CIMT measurements were performed as per the American echocardiography guidelines by a trained sonographer and were verified by a consultant radiologist. Carotid ultrasound was performed using high-resolution B-mode (Siemens SONOLINE G40) with a 7-MHz linear transducer and a transducer aperture of 38 mm. The right and left carotid arteries were scanned at the level of the bifurcation (11). The mean of 3 readings for each side was measured and the maximum CIMT value was recorded for analysis. CIMT values $\geq$ 75th percentile were considered increased and indicative of increased CVD risk. As there were no local CIMT reference values for the general population, the matched age and gender CIMT value from the Carotid Atherosclerosis Progression Study (CAPS) was applied (11).

2.4. Statistical Analysis

The SPSS version 23.0 (Chicago, IL, USA) was used. Normally distributed data were expressed as mean $\pm$ standard deviation (SD) and the Student t test was used to compare those with and without LVH. Non-normally distributed data were expressed as median (IQR) and analyzed using non-parametric tests (the Mann-Whitney U or the Kruskal-Wallis) for quantitative variables. Categorical variables were analyzed using Chi-square. The Pearson and

Spearman Rho correlation coefficients were used to investigate correlations. A sub-analysis on CNI and PSI groups' recordings was performed to evaluate significant differences in BP, LVMI, and serum homocysteine levels between the groups. Univariate and multivariate analyses were performed using multiple linear and binary logistic regression tests. A P value of < 0.05 was considered significant.

2.5. Sample Size Calculation

Sample size calculation was based on a standard statistical approach applied to a wide range of clinical trials (21). Assuming that the prevalence of hypertension in kidney transplant recipients is about 75% - 85% (3, 21), a sample size of 288 patients was needed to detect a statistically significant difference with a power of 80% ($\alpha = 0.05$). However, since it was a pilot study, 10% of the actual sample size; i e, 30 subjects, were recruited.

3. Results

Thirty KTx recipients (20 males, 10 females; mean age: 44.53 $\pm$ 13.59 years) were enrolled. Their baseline demographics are shown on Table 1. The laboratory parameters of KTx recipients are tabulated on Table 2. Seven of the enrolled KTx recipients had LVH based on the predefined criteria, and majority were not receiving in renin-angiotensin-aldosterone system blockade. The demographics and laboratory parameters were compared between those with and without LVH (Table 3) and those on CNI versus PSI immunosuppressive agents (Table 4). Diabetics had a trend towards higher serum homocysteine (23.10 $\pm$ 5.78 vs. 19.10 $\pm$ 5.02 μM/L, P = 0.06), but there were no significant differences in serum creatinine.

A correlation analysis of LVMI value was performed to patients' demographic and biochemical data. There were significant correlations between LVMI and pulse pressure ($R^2 = 0.542$, P = 0.002), BMI ($R^2 = 0.394$, P = 0.034), serum homocysteine ($R^2 = 0.405$, P = 0.029), and number of antihypertensive agents ($R^2 = 0.374$, P = 0.045)

Serum homocysteine also had a strong correlation with creatinine ($R^2 = 0.517$, P = 0.004).

Predictors of LVMI were the incidence of diabetes, pulse pressure (P = 0.002), serum homocysteine (P = 0.029), and the number of antihypertensive agents (P = 0.045). On multivariate analysis, diabetes (P = 0.014) and pulse pressure (P = 0.008) were the main predictors of LVMI.

Table 1. Baseline Demographics of the Kidney Transplant Recipients

Characteristics	Kidney Transplant (N= 30), %
Age, y	44.53 $\pm$ 13.59
Duration of transplant, mo	91.67 (39 - 311)
Duration on dialysis, mo	21.0 (0 - 129)
Gender, n	
Male	20 (66.7)
Female	10 (33.3)
Race, n	
Malay	9 (30.0)
Chinese	21 (70.0)
Hypertension, n	22 (73.3)
Systolic BP, mmHg	132.0 $\pm$ 14.4
Diastolic BP, mmHg	77.8 $\pm$ 11.3
Mean arterial pressure, mmHg	95.8 $\pm$ 11.1
Mean pulse pressure, mmHg	54.2 $\pm$ 11.8
No of antihypertensive agents, n	1.50 (0- 4)
Diabetes mellitus, n	10 (33.3)
Body mass index, kg/m^2	24.30 $\pm$ 4.03

Table 2. Laboratory Parameters of Kidney Transplant Recipients

Parameters	Mean ($\pm$ SD) /Median (IQR)
Hemoglobin, g/dL	12.67 $\pm$ 1.42
Creatinine, μM/L	108 (66 - 319)
Estimated GFR, mL/min/1.73 m^2	69.83 $\pm$ 20.79
Total Cholesterol, mM/L	5.08 $\pm$ 1.11
High density lipoprotein, mMl/L	1.35 (0.94 - 2.12)
Low density lipoprotein, mM/L	2.93 $\pm$ 1.05
Triglycerides, mM/L	1.36 (0.60 - 4.64)
High-sensitivity C-reactive protein, mg/L	0.7 (0.1- 9.90)
Homocysteine, μM/L	20.43 $\pm$ 5.53
Urine PCI, mg/mM	0.02(0.01- 0.44)
CIMT, mm	0.80 $\pm$ 0.26
LVMI, g/m^2	99.52 $\pm$ 23.83

Abbreviations: CIMT, carotid intima media thickness; GFR, glomerular filtration rate; LVMI, left ventricular mass index; PCI, protein creatinine index.

4. Discussion

CVD remains the leading cause of death in KTx recipients (3). In addition to hypertension, diabetes and dyslipidemia, reduced kidney function, dialysis vintage, hyperhomocysteinemia, and elevated hs-CRP are the established CVD risk factors in KTx recipients (5, 6). These non-traditional risk factors play a role in inflammation and oxidative stress, which in turn lead to atherosclerosis (22).

Table 3. A Comparison of Kidney Transplant Recipients With And Without LVH

Parameters	LVH (n = 7)	Non-LVH (n = 23)	P Value
Age, y	55.3 ± 10.5	41.2 ± 12.9	0.014
Gender, n			
Male	6 (85.7)	14 (60.9)	0.228
Female	1 (14.3)	9 (39.1)	
Diabetes mellitus, n	6 (85.7)	4 (17.4)	0.002
Hypertension, n	5 (71.4)	17 (73.9)	0.556
Blood pressure, mmHg			
Systolic	137.0 ± 19.2	130.5 ± 12.7	0.302
Diastolic	74.4 ± 14.7	78.8 ± 10.2	0.371
Mean arterial pressure	95.3 ± 14.9	96.0 ± 10.0	0.891
Pulse pressure	62.6 ± 13.6	51.6 ± 10.2	0.029
Number of antihypertensive agents, n	2 (0-4)	1 (0-3)	0.386
Duration of dialysis, mo	18 (0, 42)	23.5 (0, 129)	0.328
Duration post transplantation, mo	93.2 (60 - 165)	90.1 (39 - 311)	0.848
BMI, kg/m^2	25.53 ± 4.26	23.91 ± 3.97	0.363
Creatinine, μM/L	90 (67 - 319)	107 (66 - 152)	0.631
Estimated GFR, (mL/min/1.73 m^2	71.00 ± 28.04	69.48 ± 18.84	0.869
Hemoglobin, g/dL	12.51 ± 1.04	12.72 ±1.53	0.741
Fasting blood sugar mM/L	6.60 ± 2.17	5.24 ± 1.82	0.110
Lipid profile			
Total cholesterol mM/L	4.78 ± 1.35	5.24 ± 0.92	0.147
Low density lipoprotein, mM/L	2.68 ± 1.58	3.01 ± 0.85	0.609
High density lipoprotein, mM/L	1.28 (1.09 - 1.61)	1.38 (0.94 - 2.12)	0.532
Triglycerides, mM/L	1.35 (0.67 - 2.00)	1.36 (0.60 - 4.64)	0.266
Hs-CRP, mg/L	1.30 (0.1 - 9.90)	0.70 (0.1 - 12.3)	0.701
Homocysteine, μM/L	25.29 ± 5.12	18.96 ± 4.83	0.006
LVMI, g/m^2	131.2 ± 10.3	89.9 ± 17.4	< 0.001
CIMT, mm	0.93 ± 0.34	0.76 ± 0.23	0.144

Abbreviations: CIMT, carotid intima media thickness; Hs-CRP, high sensitivity C-reactive protein; LVMI, left ventricular mass index.

Table 4. Comparison Among Kidney Transplant Recipients on CNI and PSI

Parameters	CNI (n = 23)	PSI (n = 7)	P Value
Age, y	46.0 ± 15.19	39.71 ± 3.35	0.076
Diabetes Mellitus, n	10 (43.5)	0 (0)	0.038
Hypertension, n	19 (82.6)	4 (57.1)	0.185
Blood Pressure, mmHg			
Systolic	134.3 ± 15.0	124.6 ± 9.6	0.121
Diastolic	79.2 ± 11.7	73.3 ± 8.9	0.239
Mean Arterial Pressure	97.5 ± 11.4	90.3 ± 8.3	0.134
Pulse Pressure	55.0 ± 12.6	51.3 ± 9.1	0.470
No of antihypertensive agents, n	2 (0 - 4)	1 (0 - 2)	0.107
Duration of dialysis, mo	18 (0 - 129)	24 (6 - 30)	0.886
Duration post transplantation, mo	83.6 (39 - 311)	107.2 (55 - 134)	0.666
Body Mass Index, kg/m^2	24.31 ± 4.33	24.26 ± 3.19	0.978
Creatinine, μmol/L	106.5 (66 - 319)	112 (88.5 - 198)	0.335
Estimated GFR, mL/min/1.73 m^2	70.26 ± 20.62	68.43 ± 22.96	0.842
Lipid profile			
Total Cholesterol mmol/L	4.79 ± 1.02	5.99 ± 0.92	0.009
Low density lipoprotein, mmol/L	2.68 ± 0.88	3.71 ± 1.22	0.021
High density lipoprotein, mmol/L	1.38 (0.94 - 2.12)	1.28 (1.21 - 1.43)	1.00
Triglycerides, mmol/L	1.36 (0.6 - 4.64)	1.35 (0.94 - 4.28)	0.413
Hs-CRP, mg/L	0.5 (0.1 - 5.80)	5.4 (0.3 - 9.90)	< 0.001
Homocysteine, μmol/L	20.48 ± 5.31	20.29 ± 6.65	0.937
Urine PCI, mg/mmol	0.02 (0.01-0.39)	0.04 (0.02-0.44)	0.054
LVMI, g/m^2	98.78 ± 25.79	101.94 ± 17.26	0.765
CIMT, mm	0.81 ± 0.29	0.76 ± 0.13	0.632

Abbreviations: CIMT, carotid intima media thickness; CNI, Calcineurin Inhibitor; Hs-CRP, high sensitivity C-reactive protein; LVMI, left ventricular mass index; PCI, Protein Creatinine Index; PSI, Proliferative Signal Inhibitor.

Multiple factors contribute to hypertension in chronic kidney diseases. The activation of the renin-angiotensin-aldosterone system due to renal ischemia and increased levels of endothelial vasoconstrictors in the uremic milieu are amongst them. After kidney transplantation, blood pressure is expected to decline as patients regain their kidney function. However, studies demonstrated that the immunosuppressive agents used to prevent rejection may ultimately elevate the blood pressure and this is in keeping with the current study findings (7). Hypertension plays an important role in the development of atherosclerosis and is associated with increased CIMT (23, 24). As shown in the current study, majority of patients had increased CIMT. Studies showed that KTx recipients have

a higher prevalence of subclinical atherosclerosis measured by CIMT, compared with the general healthy population (4). The authors previous study demonstrated that KTx recipients had a higher prevalence of increased CIMT compared with their matched controls thereby increasing their cardiovascular risk (25). Endothelial dysfunction and ongoing chronic inflammation due to multiple risk factors, including immunosuppressive therapy exposure, play an important role in premature development subclinical atherosclerosis in KTx recipients (10). Nonetheless, no significant differences was found in CIMT between the patients with and without LVH. The reported literature showed conflicting results; despite patients with chronic kidney diseases and the ones undergoing hemodialysis had increased CIMT, they did not have continual LVH (26). However, LVMI was independently associated with increased cardiovascular mortality in patients undergoing hemodialysis (26).

In patients with hypertension, ambulatory blood pressure parameters are reported to correlate better with LVMI and have better predictive value of LVH than casual BP readings (27, 28). This could be due to the fact that majority of KTx recipients are non-dippers (28, 29). Seven of the current study patients had LVH, and LVH is strongly linked to the chronic kidney disease due to both pressure and volume overload (30, 31). LVH also occurs in diabetic cardiomyopathy; in the current study, LVMI was significantly higher among patients who developed diabetes after transplantation (32). Patients with diabetes also had higher LVH values than the ones without diabetes that was in agreement with Sezer et al. findings (33). Patients with LVH had a higher pulse pressure, but this could be confounded by the presence of diabetes.

The results of the current study demonstrated that serum homocysteine is elevated in KTx recipients and consistent with others (15). Studies showed that in the general population, a 25% lower homocysteine level is associated with a 11% lower risk of coronary artery disease and a 19% lower risk of stroke (34, 35). Furthermore, Veeranna et al. showed that adding homocysteine levels to the Framingham risk score enhances the prediction of risk in individuals at intermediate CVD risk (36). The results of the present study indicated that serum homocysteine was strongly correlated with serum creatinine. Several studies showed the inverse relationship between serum homocysteine and creatinine clearance/renal function (13).

The present study also found that serum homocysteine levels increased in those with LVH and correlated with LVMI; hence, it can be used as a good surrogate marker for LVH when echocardiogram is not accessible. Hyperhomocysteinemia promotes LVH through both vascular and non-vascular mechanisms. Homocysteine stimulates growth and collagen production on vascular smooth muscle cells (37). Although homocysteine is associated with CVD, homocysteine lowering interventions did not show any significant reduction on myocardial infarction, stroke or death by any cause when compared with the placebo (38).

Interestingly, no difference was found in hs-CRP between those with and without LVH. Winkelmayer et al. demonstrated that patients with eccentric hypertrophy had lower hs-CRP compared with those with concentric hypertrophy (39). All the 7 patients with LVH evaluated in the current study had concentric hypertrophy. In KTx recipients, there is a J-shaped relationship between hs-CRP and mortality suggesting that patients with a very low hs-CRP may be at higher risk for CVD and death as reported by Winklemayer (39).

The current study compared PSI and CNI, but did not find any differences in terms of LVH and CIMT among the patients. Although patients on PSI had higher cholesterol, in line with the literature (40), they also had a significantly higher hs-CRP level and further analyses indicated a positive correlation between hs-CRP and UPCI ($P = 0.025$). Proteinuria is a well-recognized phenomenon in patients receiving PSI and it is not possible to explain whether the hs-CRP is the causal or effect of the proteinuria.

The small sample size was the main limitation of the current study, worsened by the fact that only few patients had LVH. The study also did not have CIMT and LVMI pre-transplantation reference values to assess the effects of transplantation on these parameters.

In conclusion, serum homocysteine is a surrogate marker for LVH in patients underwent renal transplantation, especially the ones with diabetes.

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Footnotes

Conflict of Interest: None.

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