Original Research Article

DIFFERENCES IN CARDIOVASCULAR REMODELING IN KIDNEY TRANSPLANT RECIPIENTS AND PERITONEAL DIALYSIS PATIENTS

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ABSTRACT

Aims: Cardiovascular disease (CVD) is the leading cause of death in dialysis patients as well as in kidney transplant recipients (KTx). Left ventricular hypertrophy (LVH) starts early during chronic kidney disease and is a strong predictor of CVD. We hypothesized that kidney transplant is significantly associated with improvement in cardiovascular reserve. We conducted the prospective study to characterize changes in CV before and after kidney transplantation in patients with ESRD who underwent KTx compared with control individuals who underwent peritoneal dialysis (PD) and who have not undergone a KTx.

Study design: Case-control study.

Place and Duration of Study: Clinic for nephrology Clinical Center University of Sarajevo, Bosnia, and Herzegovina

Methodology: In this case-control study, we included 50 KTx from the Kidney Transplant Outpatient Clinic for nephrology Clinical Center. For each 50 KTx, PD outpatients matched for gender and age were recruited. All patients underwent transthoracic echocardiography and LV (left ventricular) mass (LVM), LV mass index (LVMi), and indices of cardiac function were measured. In the small subgroup of 18 KTx we retrospectively assessed and compared the LVMI measurements, during dialysis and post-transplant period.

Results: The prevalence of LVH was 24% in KTx and 72% in PD patients (*NS*). KTx had significantly lower LVM, LVMi levels, E/A ratio, FS, and LA diameter compared with the PD group, while the EF and other echocardiographic indices did not differ. In the subgroup of 18

KTx, post-transplant LVMi levels were significantly lower in comparison with dialysis LVMi levels.

Conclusion: LVH is the most frequent cardiac abnormality at the time of kidney transplantation. After KTx, the reduction of LVH and diastolic dysfunction were significant. CV remodeling after successful KTx is related to better kidney function and can explain better outcomes for patients with kidney transplants over patients on long-term dialysis.

Keywords: kidney transplantation, peritoneal dialysis, cardiovascular remodeling, echocardiographic measurements

1. INTRODUCTION

Cardiovascular disease (CVD) is highly prevalent and a leading cause of death among patients with chronic kidney disease (CKD) [1]. Left ventricular hypertrophy (LVH)and systolic and diastolic dysfunction are well-recognized indicators of worse cardiovascular outcomes in patients undergoing dialysis. In advanced CKD, the myocardium is exposed to complex metabolic stressors that result from uremia-related inflammation, oxidative stress, renin-angiotensin-aldosterone system activation, calcitriol and klotho deficiency, increased fibroblast growth factor (FGF) 23, and changes in mineral metabolism [2]. This exposure leads to myocyte hypertrophy, reduced myocardial capillarization, and nonvascularized interstitial fibrosis as well as arteriosclerosis and arterial stiffening [3]. Together, these ultrastructural changes reduce pump efficiency and increase cardiac energy expenditure and myocardial oxygen consumption. LVH starts early in the course of CKD and is inversely correlated with renal function [4]. In end-stage renal disease (ESRD), 75% of patients have LVH at the start of dialysis due mainly to hypertension, volume expansion, and anemia.

Kidney transplant is the optimal treatment for ESRD and is associated with reduced cardiovascular morbidity and improved quality of life and survival [5]. Some echocardiographic studies have reported reduced left ventricular mass and improved left ventricular ejection fraction (LVEF), but these findings have been inconsistent. Serial cardiac magnetic resonance imaging has failed to identify significant regression in left ventricular mass after kidney transplant. In some studies, successful kidney transplantation has been associated with significant echocardiographic regression of LVH in KTx (kidney transplant) [5,6], while other studies have shown no positive effect. The expansion and variation of intravascular volume in dialysis patients compared with KTx have been suggested as one of the reasons for the contradictory result [7,8].

The mortality rate in patients with ESRD is much higher than in the general population despite advances in dialysis treatment. Cardiovascular structure and functional abnormalities, such as LVH, left ventricular (LV)

systolic and diastolic dysfunction, accelerated atherosclerosis, arrhythmias, and coronary artery calcification, contribute to high cardiovascular mortality in patients with ESRD [9].

We hypothesized that kidney transplant is significantly associated with improvement in cardiovascular reserve. We conducted the prospective study to characterize changes in cardiovascular before and after kidney transplant in patients with ESRD who underwent kidney transplants compared with control individuals who underwent peritoneal dialysis (PD) and who have not undergone a kidney transplant.

2. MATERIAL AND METHODS

Patients

In this case-control study, we included 50 KTx from the Kidney Transplant Outpatient Clinic of nephrology Clinical Center University of Sarajevo, Bosnia, and Herzegovina. For each 50 KTx, chronic PD outpatients matched for gender and age were recruited. Exclusion criteria for all patients were any CV event (defined as stroke, peripheral vascular disease, myocardial infarction, and acute ischemic heart disease) occurring within 6 months before study entry, heart failure NYHA stage III and IV, any moderate or severe valvular heart disease, presence of clinical infection and active malignancy. Moreover, in a subgroup of twelve KTx the LVM (left ventricular mass) index (LVMi) measurements were retrospectively assessed at two different time points, the first during the predialysis period and the second during dialysis treatment, and compared with the LVMi estimation during the posttransplant period. All KTx had a functioning allograft for at least six months and received calcineurin inhibitor-based (tacrolimus) immunosuppression. The local hospital Ethical Committee approved the study and patients participated in the study after providing informed consent.

Methods

At study entry, all patients underwent a detailed review of their medical history and careful clinical examination. Additionally, demographic characteristics, co-morbidities (cardiovascular disease, diabetes mellitus, hypertension), medication, and blood pressure (BP) were assessed. Hypertension was defined as systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg, or the current use of antihypertensive medication. A full hematological and biochemical screen was performed, urine protein was measured in a 24-hour urine collection and eGFR (mL/min/1.73 m2) was calculated by the CKD-MDRD formula [10].

Echocardiographic Data

Comprehensive echocardiographic measurements were performed using an ultrasound machine (Toshiba 270SSA) with a 3.75-MHz sector probe by a single experienced cardiologist blinded to clinical information on patients at baseline and the end of the study period. All images were obtained with standard techniques using M-mode, two-dimensional, and Doppler measurements following the American Society of Echocardiography guidelines [11]. The LV mass was calculated using the modified formula proposed by Devereux et al. [12]. Echocardiographic evidence of LVH was defined as LV mass index divided by a body surface area >115

g/m^2 in men and >95 g/m^2 in women. LV systolic function was assessed by calculation of the ejection fraction (EF) using a modified Simpson's method [13], while fractional shortening (FS) was calculated according to the formula described by Lang et al. [14]. LV systolic weakness was defined as EF <50% and FS <30%. Pulsed Doppler echocardiography was used to evaluate transmitral LV filling velocities at the tips of the mitral valve. The peak early-diastolic flow velocity (E) and the peak late-diastolic velocity (A) shown as the E/A ratio was measured by analyzing the transmitral flow. LV diastolic dysfunction was defined as E/A ≤1.

Statistical Analysis

Data were presented as mean and standard deviation (for normally distributed data), median and interquartile range (for not-normally distributed data), or as absolute count and frequency in percent (for binary variables). Chi-square or Fisher Exact Test was used for categorical variables, whereas comparisons of continuous variables among the two groups of patients were analyzed using Student's t-test. Correlations were determined with Pearson's correlation coefficient. Multivariate linear regression analysis (backward method) was performed to determine the factors that were
independently associated with LVMI levels in both groups of patients.
Multivariate analysis in each group included all associations with a P value ≤ .2 in univariate analysis. A P value less than .05 was considered statistically significant. All analyses were performed by using SPSS 21.0 (SPSS, Chicago, IL).

3. RESULTS

The baseline characteristics of the 50 KTx and 50 PD patients are summarized in Table 1. According to the study design, the two patient groups were matched for age and gender. There were no differences in co-morbidities (hypertension, diabetes mellitus, and CVD), and systolic and diastolic BP levels between the two groups (Table 1). Regarding laboratory parameters, there were no significant differences in levels of hemoglobin (Hb), serum total cholesterol, and phosphorus, between the study groups. Twenty-four hours of proteinuria content was significantly lower in the KTx group (*P* .002) and serum calcium was significantly higher compared to the PD group, as expected (*P* .05) (Table 1).
With regards to medication, a significantly higher percentage of KTxwas receiving β-blockers compared to the CKD group (*P* .045 respectively).

Table 1. Baseline data of KTx and PD patients

Parameters	**KTx (50 pts.)**	**PD (50 pts.)**	***P***

Sex (M/F) (n)	27/23	31/19	NS
Age	49.5 ± 9.8	53.6 ± 11	NS
CVD (n, %)	11 (22%)	16 (32%)	NS
DM (n, %)	6 (12%)	19 (38%)	NS
Hypertension (n, %)	32 (64%)	41 (82%)	NS
eGFR-MDRD (mL/min/1.73 m^2)	58.5±16.3	16.1±3.12	.05
Proteinuria (mg/24h)	239 (66-424)	403 (256-2296)	.002
Serum albumin (g/L)	32±3.3	26±8.4	.04
Systolic BP (mmHg)	136 ± 17	138±21	NS
Diastolic BP (mmHg)	82±8	84±10	NS
Hb (g/L)	133 ±15	107 ±27	NS
Ca (mmol/L)	2,31±0.5	2.19±0.8	.05
PO4 (mmol/L)	1.67±0.3	1.77±0.7	NS
PTH (pg/ml)	98 (56-137)	148 (107-262)	.05
Cholesterol mmol/L	4.73±0.73	7.05±0.94	NS
Trygliceridemmol/L	1.51±0.40	2.84±0.34	.032
LDL mmol/L	2.90±0.36	4.45±0.86	.04
CRP (mg/L)	1.5 (0.8- 3.3)	5.9 (2.3-11)	<.001
RAAS inhibitor (n, %)	17 (34%)	42 (84%)	.033
Diuretics (n, %)	9 (18%)	24 (48%)	.042
β-blockers (n, %)	34 (94%)	19 (26%)	.045
Ca channel blockers (n, %)	20 (68%)	31 (62%)	NS
Statins (n, %)	22 (44%)	24 (48%)	NS
Erythropoietin (n, %)	9 (18%)	26 (52%)	.023
Duration KTx	2.9 (1.2-4.4)	-	-

(years) (IQR)			
Duration PD (years) (IQR)	-	2.1 (1.0-4.8)	-

Data are expressed as the mean ± SD, number (percentage), or median (range); NS= no significance.

Legend: KTx-kidney transplant; PD-peritoneal dialysis; CVD-cardiovascular disease; DM-diabetes mellitus; eGFR-MDRD-estimated glomerular filtration rate - Modification of Diet in *Renal Disease*; BP-blood pressure; PO4-phosphorous; PTH-parathyroid hormone; LDL-low-density lipoprotein; CRP-C-reactive protein;RAAS-renin-angiotensin-aldosterone system; Ca-calcium.

In the KTx group of all patients, 38 of them (76%) showed normal echocardiographic findings, and 24% of patients had echocardiographic signs of left ventricular hypertrophy. Among patients with LVH, 47% (14 pts) of them had concentric and 20% had eccentric LV hypertrophy. LVH was observed in 72% at least after 12 months of PD treatment.

In the study, both groups had normal average systolic and diastolic heart function, although the PD group had borderline echocardiographic parameters in terms of LV systolic and diastolic dysfunction. KTx group remained with a normal LV mass index, unlike the PD group, as it is shown in Table 2.

Table 2. Echocardiographic Measurements in KTx and PD patients

Parameters	**KTx**	**PD**	***P***
EF (%)	68.1±8.4	56.9±10.0	NS
FS (%)	37.8±7.1	30.8±4.1	<.001
E/A ratio	1.1±0.1	1.0±0.1	.042
LVEDD (mm)	49.6±6.5	52.9±3.6	<.001
LVESD (mm)	35.0±3.5	34.3±3.9	NS
LVMi (g/m^2)	103.2±32.1	140.2±37.8	<.001
LVM (gr)	190.7±68.2	243.8±40.8	<.001
LV volume (mL/m^2)	83.8±21.7	90.2±24.5	<.001
LA Diameter (mm)	40.5±6.7	43.3±5.7	.38

LVH (n, %)	12(24)	36(72)	NS

Data are expressed as the mean ± SD, number (percentage), or median (range); NS= no significance.

Legend: EF-Ejection fraction; FS-Fractional shortening; LVM Left ventricle mass; LVMi Left ventricle mass index; LVEDD - LV end-diastolic diameter; LVESD - LV end-systolic diameter; LA- Left atrium

Examining predictors of LVMi in the KTx group using the model of logistic regression analysis, it was found that diastolic blood pressure and CRP were independent positive predictors and urine proteinuria per day an independent negative predictor of LVMi (Table 3.)

Table 3. Multivariate Regression Analysis of Independent Factors Associated With LVMi in KTx

Variables	**β**	**Sig**	**CI 95% (Lower-Upper Bound)**
Diastolic BP	0.364	0.012	0.353- 2.596
Proteinuria/day	-0.102	1.001	1.641-27.27
CRP	0.453	0.171	1.124-2.200

Legend: LVMi-left ventricular mass index; KTx-kidney transplant; BP-blood pressure; CRP- C-reactive protein

Independent negative predictors of the LVMi in the PD group were 24-hour diuresis (daily collection of urine), hemoglobin, serum albumin level, total cholesterol, and low-density lipoprotein were independent positive predictors of left ventricular remodeling (Table 4.)

Table 4. Multivariate Regression Analysis of Independent Factors Associated With LVMI in PD

Variables	**β**	**Sig**	**CI 95% (Lower-Upper Bound)**
Diuresis/day	-0.002	0.001	0.217- 0.612
Cholesterol	2.395	0.725	2.647-45.433
LDL	3.604	1.011	5.066-26.359
Hemoglobin	-0.418	0.155	0.485-0.893

Serum albumin	-1.111	0.459	0.134-0.809

Legend: L LVMi-left ventricular mass index; PD-peritoneal dialysis; LDL-low-density lipoprotein

4. DISCUSSION

This study provides an integrated assessment of cardiac functional and morphologic changes in PD and kidney transplant patients. CVD accounts for half of the deaths in patients treated with renal replacement therapy, whilst mortality from cardiovascular causes is far higher than in the general population [2,15].

The influence of uremia and dialysis on cardiovascular structure and function was investigated as detailed by studies on patients with chronic renal failure [16,17].

Unlike the limited prognostic value of single surrogate factors of most established clinicopathologic factors (such as age, hypertension, LVMI, and LVEF), measures of the cardiovascular reserve are independently associated with survival in patients with advanced CKD (before and after kidney transplant) and after adjusting for known comorbid factors [18].

There are two parallel processes involved in the development of CVD in ESRD patients. The first process involves cardiac changes including LVH and LV dysfunction as a response to mechanical or hemodynamic overload. The second process involves vascular changes, including atherosclerosis, arteriosclerosis, and vascular calcification. Over the last decade, cardiac abnormalities such as LVH and LV dysfunction and vascular abnormalities, e.g. arterial stiffness, increased intima-media thickness (IMT), and coronary calcification, have been accepted as early markers of cardiomyopathy and atherosclerosis [19]. LV diastolic dysfunction is frequently observed in dialysis patients and results from LVH, cardiac fibrosis, and impaired cardiac relaxation. Also, the presence of LVH and LV systolic dysfunction are well-recognized risk factors for cardiovascular mortality in this population [20].

Considering the large risk, our data may emphasize the importance of early recognition of LV structure and function changes and may have significant therapeutic implications in the treatment of both dialysis and transplant patients. In our study, transplant-associated improvements were significant even after adjusting for age, body mass index, sex, diabetes, CVD, duration of antihypertensive therapy, β-blocker use, and hemoglobin level. Although improvements in uremia and fluid overload were already notable at 2 months after the transplant, were only evident 12 months after the transplant but did not improve in the PD group. This finding is consistent with the incomplete normalization of kidney function after transplant. Taken together, these data suggest that it takes several months for the reversal of cardiovascular molecular and ultrastructural alterations

that may be partially associated with uremia, to reverse sufficiently to result in detectable cardiovascular functional improvement.

Several uncontrolled prospective studies have evaluated pre– and post–renal transplant echocardiographic left ventricular dimensions [21,22].

Some authors have reported significant LVMI regression (but no change in LVEF) in kidney transplant recipients after 12 months. In contrast, are reported no change in LVMI and significant increases in LVEF at a mean of 41 months after transplant among 24 patients [23]. In patients with a pretransplant LVEF of less than 50%, authors reported increases in LVEF 1 and 12 months after kidney transplant. These studies are limited by sample size, the lack of controls not receiving transplants, and the absence of data on the timing of echocardiography with dialysis, given the potential for confounding by intravascular volume or dialysis-induced myocardial stunning [24].

Pathogenetic factors mainly involved in LVH and fibrosis in CKD and ESRD are elevated systolic and diastolic BP, expansion of intravascular volume, and anemia [25].Interestingly, in our PD group of patients, apart from the traditional risk factors, an independent factor associated with LVMI level remained the 24-hours diuresis. Unlike hemodialysis, which is associated with typically marked body water content fluctuations, PD is characterized by its almost steady state, which probably has a major impact on LV function. Also, the data of our study indicate that RRF is lower in ESRD than in PD. Wang [26] has found that RRF may play a role in limiting the increase in cardiovascular remodeling by improving the overall Kt/Vurea and removal of uremic toxins.

This is a very important result because it suggests the existence of some nondialyzable uremic toxins that may be important in the progression of pathological cardiovascular alteration in this population.

After kidney transplantation, parameters that have been significantly associated with LVM regression are renal function, LVM level before transplantation, adequate control of blood pressure, and anemia [23]. In our KTx group, multivariate analysis showed that independent factors associated with LVMI were diastolic BP.

Our results did not reveal significant differences in regards to systolic and diastolic BP between the two groups of patients, whereas KTx had significantly lower protein excretion in comparison to the PD group. The level of proteinuria has been independently and significantly associated with LVH in KTx patients but not in the PD group, as we showed in our study.

Regarding non-immunosuppressant medication, a significantly greater proportion of KTx and PD patients were receiving β-blockers, statins, and erythropoietin. Randomized trials with CKD and ESRD patients have shown a reduction of sudden cardiac death with the use of a cardioselective β-blocker in ESRD patients with dilated cardiomyopathy, while correction of anemia with erythropoietin had no significant beneficial effect on LVH [27]. Treatment with statins has reduced the risk of a major cardiac event in KTx but its relationship with LVM regression has not been investigated [28]. Based on the existing literature it seems that the significant difference

in LVMi between the two patient groups in our study could not be fully explained by the variation in proteinuria and pharmaceutical treatment. The reversal of volume expansion after successful kidney transplantation and the good control of the modifiable pathogenetic factors for LVH in our RTRs might partially explain our finding of better LVM in this group in comparison with patients undergoing PD.

In the small subgroup of 18KTx we found a significant reduction of LVMI after receiving a well-functioning kidney allograft. Following our results, an important number of other studies have demonstrated significant cardiac alterations after kidney transplantation. One study assessed KTx patients before and 3 months after kidney transplantation and demonstrated significant improvement of the EF and reduction in chamber diameters [29] while another study showed normalization of the FS in the subgroup of patients with systolic dysfunction in addition to a reduction in LVMi and LV diastolic volume [30]. A recent study in KTx showed that more than 50% of patients experienced LV mass regression after kidney transplantation [29]. Also, in this subgroup of KTx we found reduced LVMI measurements in comparison with their predialysis echocardiographic estimations. One possible explanation could be the higher level of post-transplant eGFR compared with the predialysis eGFR. Although we did not find a significant correlation between LVMI and eGFR at any time point, the severity of LVH has been shown in other studies to correlate inversely with residual renal function both in dialysis patients and in KTx[26]. Our finding is limited by the small number of patients and the variability in echocardiographic measurements, but to our knowledge, this is one rarer study that estimated and compared serial LVM measurements in the same patient population starting the monitoring from the early peritoneal dialysis period until the posttransplant phase.

Left ventricular hypertrophy is nowadays considered to be a strong factor for cardiovascular mortality in all groups of CKD patients. Whether successful renal transplantation could reverse LVH remains a debatable issue. Lastly, we found that KTx had significantly lower LVM when compared with PD patients matched for age and residual renal function. Indeed, we showed a reversal of LVH after kidney transplantation. Although our study is limited by the small patient sample, our data might imply that both LVM levels before ESRD and during dialysis may substantially influence post-transplant LVM. There is a compelling need for large, prospective studies to assess the course of LVH at initiation and during the progression of CKD.

5. CONCLUSION

Our study found that partial restoration of kidney function by the transplant was significantly associated with improved cardiovascular functional reserve, without a major change in ventricular structural morphologic features. The study appears to provide insight into cardiovascular structural-functional dynamics and the association of kidney function restoration with cardiovascular physiologic findings.

Left ventricular hypertrophy is the most frequent cardiac abnormality at the time of kidney transplantation. After transplantation, the reduction of LVH and diastolic dysfunction were significant. Cardiovascular

remodeling after successful kidney transplantation is related to better kidney function, with correction of anemia and control of hyperparathyroidism, and can explain better outcomes for patients with renal transplant over patients on long-term dialysis.

CONSENT AND ETHICAL APPROVAL

Informed consent was taken from all patients for the study participation which is performed with the approval of the Ethics committee, Clinical Center University of Sarajevo(04-229-10-2022).

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