Role of Hypertension and Anaemia in Left Ventricular Remodelling in Patient with Renal Allograft in the First Post-transplant Year

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ABSTRACT
Background: Hypertension (HT) and renal anaemia (RA) are well-established markers of cardiovascular risk in patients with chronic kidney disease (CKD). They appear to be the stimuli for left ventricular hypertrophy (LVH), who significantly participates in cardiac complications in uremic patients. Hypertension is extremely common after kidney transplantation (KTx) and it has been observed in up to 75% of patients. The prevalence of post-renal transplant anaemia (PTA) is variable (up to 30%) and several factors such as graft function contribute towards its pathophysiology.

Aim: The aim of this study was to analyze the impact of blood pressure and anaemia on LV remodelling in first year after transplantation comparing echocardiographic findings before and twelve months after transplantation had done. Methods: In five years retrospective-prospective study we followed up 30 patients with renal allograft in first post-transplant year. During the study values of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), blood hemoglobin (Hgb), serum creatinine and creatinine clearance were monitored monthly.

Results: Before transplantation (Tx) 86% of patients had HT, and RA was confirmed in all patients. Normal echocardiographic findings had 33% of patients and 67% of patients had echocardiographic sings of LVH. Before renal transplantation group with LVH had statistically higher the mean values of blood pressure (MBP) (p=0.053) compared to group with diastolic (LVDDE) (p=0.0047) and systolic-diastolic dysfunction (LVDDDF) (p=0.0046). The values of SBP and DBP positively correlated with LV mass index (LVMi) in the group of patients with LVH (p=0.0007 and p=0.0142). The values of Hgb was statistically higher in group with normal LV mass index compared to LVH (p=0.019), with negative correlation between LVMi and values of Hgb in the patients group with LV hypertrophy (p=0.009). After the first year of transplantation, 63% of patients showed normal LV mass index and 37% remained with echocardiographic findings of the LVH. The values of SBP and values of Hgb in both groups, as well as values of DBP in group of LVH were statistically different in compare with data before transplantation (p<0.05). The positive echocardiographic remodelling of LV significantly correlated with the increase of Hgb values (p=0.05), but without significant correlation with the decrease of the mean SBP and DBP.

Conclusion: These results confirmed that positive echocardiographic remodelling of left ventricle after successful renal transplantation is complex process depended on many risk factors and elimination of uremia-related factors is a priority.

Key words: kidney transplantation, anaemia, hypertension, left ventricular hypertrophy.

1. INTRODUCTION
Cardiovascular diseases (CVD) and risk of poor cardiovascular outcome increase with decreasing renal function and the prevalence of these diseases is being driven to epidemic number (1). For the patient with end stage of renal disease (ESRD) uremic cardiomyopathy is reported to be a predictor of cardiovascular morbidity and mortality. Left ventricular hypertrophy (LVH), as an adaptive response to volume and pressure overload, is a well-established marker of cardiovascular risk in the general population and remains the prevalent form of cardiomyopathy in the renal transplant patients (2). In patients with renal failure, the major reversible risk factors for LVH appear to be hypertension and anaemia (3). Hypertension is extremely common after kidney transplantation. It has been observed in up to 80% to 90% of patients (4, 5).

Some investigators have demonstrated that higher levels of blood pressure (BP) were also correlated with an increased risk of acute graft rejection (6). More effective control of arterial pressure in the transplant patient could improve survival, but prospective outcome trials have not yet been performed.

Anaemia plays important role in development of LV hypertrophy in patient with chronic renal disease and it is important risk factor of cardiovascular morbidity and mortality. The prevalence of post-transplant anaemia (PTA) is variable (13-70%) and depends on several factors which contributing its pathophysiology. After kidney transplantation anaemia increased the risk of...
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Cardiovascular events, especially towards LVH and heart failure which were considered to be the main causes of death after renal transplantation (7, 8, 9). Some recent published studies emphasize that correction of anaemia and hypertension may enable reduction risk of cardiovascular consequences in renal transplant recipients (10).

2. AIM

The aim of the study was to determine the prevalence of hypertension and anaemia in the first year after kidney transplantation, and to examine their impact on the remodeling of the left ventricle.

3. MATERIALS AND METHODS

This retrospective-prospective clinical study was done at Clinic of Nephrology, University Clinical Center Sarajevo. We followed up 30 patients (pts) with renal allograft in first post-transplant year (19 male with the mean age 37.8 ± 9.9 years and 11 females with mean age 35.55 ± 11 years). Two of them received cadaveric and 28 living related kidney allografts. All evaluated patients were on hemodialysis treatment before renal transplantation (27 – 36 months). Patients older than 55 years, with severe vascular disease and heart failure, with acute renal rejection, chronic allograft nephropathy with progressively decreased renal function in first post-transplant months were excluded from the study.

All patients data were collected just before transplantation and in the one month interval after transplantation, in the first post-transplant year with included control of blood pressure, haemoglobin, serum creatinine and creatinine clearance. Systolic blood pressure was measured at monthly clinic visits and measurements were performed after 15 minutes of rest period. Echocardiographic examination was done prior to kidney transplantation and one year after kidney transplantation at Clinic of Cardiology University Clinical Centre Sarajevo. Echocardiographic analysis was performed by M-mod, two-dimension and pulse Doppler examination on echocardiographic apparatus Toshiba.

The criterion accepted for left ventricular hypertrophy was left ventricular mass index (LVMI) >131 g/m² for males, and for female >100 g/m². Anaemia was defined as hemoglobin (Hgb) level less than 120 g/L. Hypertension was defined as values >140 mmHg for systolic blood pressure (SBP) and/or >90 mmHg for diastolic blood pressure (DBP), based on the ESH/ESC Guidelines for the management of arterial hypertension. The immunosuppressive drugs (cyclosporine, mycophenolate mofetil, prednisolone), for all patients were prescribed by accepted protocol, and showed non-toxic effects of drugs during follow up.

Statistical analysis

The data results were analyzed using the descriptive statistics for each parameter that was followed up. Student’s T-test was used to compare arithmetic means of numeric variables of each parameter, with the acceptance of statistical significance at level p<0.05. Logistical regression was used to test the independent relationship between left ventricular mass index with values of systolic and diastolic blood pressure, haemoglobin, and renal function measured by creatinine clearance.

4. RESULTS

In the total group of patients before kidney transplantation, 10 of them (33%) showed normal echocardiographic findings, and 67% of patients had echocardiographic signs of LVH, out of which fourteen (47%) had concentric and 20% had eccentric LV hypertrophy.

At the beginning of the study 20% of patients had normal function of left ventricle, while 80% had dysfunction of left ventricle, out of which 70% had diastolic, and 10% had systolic-diatolic LV dysfunction. All patients with normal mass index in the beginning of this study remained with normal LVMI until the end of this study. Nine of twenty patients with LVH in the beginning of this study had reached normal echocardiographic findings until the end of this study. Normal function at the end of this study had been observed in 57% of patients, while 40% of patients were with DDFLV, and 3% of patients were with SDDFLV. Before transplantation 86% of patients had hypertension. In comparison to LVH group of patients, the group with normal LV (NLV) had statistically lower values of SBP (155.0±21.0 vs. 169.3±15.3 mmHg; p=0.036) and DBP (90.0±7.1 vs. 101.5±8.9 mmHg; p=0.002). In respect of LV functional status, significantly higher values of SBP and DBP were detected in group of patients with LV diastolic dysfunction (DDF) (100.7±10.0 mmHg) and group with LV systolic-diastolic dysfunction (SDDF) (101.7±2.8 mmHg) compared to the patients with normal LV function (p<0.05).

At the beginning of the study LVMI positively correlated with values of SBP (rho=0.590, p=0.0007), as well as with DBP in the group of patients with LVH (rho=0.450, p=0.0142). By the end of the first post-transplant year, the mean value of SBP was decreased significantly in the group of patients with normal mass index of LV (133.9±7.1 vs. 155.0±21.0 mmHg; p=0.015), as well as in the group with HLV (137.1±6.2 vs. 169.7±9.1 mmHg; p=0.0001), while DBP was statistically decreased only in the LVH group until the end of the study (86.9±7.4 vs. 101.0±8.9 mmHg; p=0.012)(Table 1).

![Table 1](image-url)

| Statistic | SYSTOLIC BLOOD PRESSURE- SBP (mmHg) | DIASTOLIC BLOOD PRESSURE-DBP (mmHg) |
|-----------|-----------------------------------|------------------------------------|
|           | LVN                               | LVH                                |
|           | SBP (0)                           | SBP (1)                            |
|           | (0)                               | (1)                                |
| X±SD      | 155.0±21                          | 133.9±7.1                          |
| t-value   | 2.97                              | 6.04                               |
| p-value   | 0.015                             | 0.0001                             |
|           | LVN                               | LVH                                |
|           | SBP (0)                           | SBP (1)                            |
|           | (0)                               | (1)                                |
| X±SD      | 92±9.1                           | 88.2±6.2                           |
| t-value   | 2.97                              | 4.6                                |
| p-value   | 0.19                              | 0.013                              |

Table 1. Mean values of systolic and diastolic blood pressure before and one year after kidney transplantation according to morphological status of LV. Notes: (0) – at the beginning of study; (1) – at the end of the study.
Renal anaemia was detected in both tested groups at the beginning of this study. The group with LVN had statistically higher values of Hgb compared to LVH group (96.4±11.7 vs 86.9±13.2 g/L; p = 0.019)(Table 2).

| Statistic | LVN | LVH |
|----------|-----|-----|
| X ± SD   | 96.4 ± 11.7 | 86.9±13.2 |
| t-value  | -2.84 | |
| p-value  | 0.0193 | |

Table 2. Mean values of haemoglobin according to morphological status of LV before kidney transplantation

Until the end of this study the mean level of haemoglobin was increased evidently in both groups, 32% in group with normal mass index (137.1±16.6 vs. 96.4±11.7 g/L), and for 35% in group with LV hypertrophy (128.6 ± 9.0 vs. 86.9±13.2 g/L).

At the end of this study, the group with normal morphology of LV reached statistically higher values of creatinine clearance (74.96±13.9 ml/min) compared to LVH group (64.67±8.2 ml/min; p=0.025)(Table 3).

| Statistic | LVN | LVH |
|----------|-----|-----|
| X ± SD   | 74.96 ± 13.9 | 64.67 ± 8.28 |
| t-value  | 2.06 | |
| p-value  | 0.025 | |

Table 3. Mean values of creatinine clearance according to the LV morphological status one year after kidney transplantation

The logistic regression showed that positive echocardiographic remodelling of LV on second echocardiography was significantly associated with each increase of haemoglobin for 1 g/L (OR 0.824; p=0.0194), increase value of creatinine clearance (OR 1.089; p=0.039), but not with decrease with mean values of SBP (OR 1.071; p=0.17) and mean values of DBP (OR 1.049; p=0.451)(Table 4).

| OUTCOME                           | RELATION                        | Odds ratio | p value |
|-----------------------------------|---------------------------------|------------|---------|
| Normal LV mass index on second echocardiography | Each increase of haemoglobin for 1g/L | 0.824 | 0.049   |
|                                   | Each increase of creatinine clearance for 1 ml/min | 1.089 | 0.039   |
|                                   | Each decrease of mean value of systolic blood pressure | 1.071 | 0.17    |
|                                   | Each decrease of mean value of diastolic blood pressure | 1.049 | 0.451   |

Table 4. Predictors’ presence of normal LV appearance on follow up echocardiography

5. DISCUSSION

Renal transplantation is the treatment of choice for the patients with chronic kidney disease (CKD). Compared to patients undergoing dialysis, transplant patients have improved survival, but cardiovascular mortality remains two times higher than in a general population (11). Left ventricular hypertrophy is a major and independent risk factor for cardiovascular morbidity and each of LV abnormalities such as LV systolic dysfunction and LV dilatation worsens the prognosis. Rasic et al. have suggested that the echocardiographic prevalence of LVH among dialysis patients is 50–90%, with LV dilatation in 20–40%, and systolic dysfunction in 16% of patients (12). LV hypertrophy diagnosis has been assessed conventionally by echocardiography, as gold standard for non-invasive and reproducible method of examination.

Before renal transplantation LVH was common alteration among our patients (67%), only 20% of patients had normal function of LV, while LV diastolic dysfunction was finding in 70% of patients. Until the end of the first post-transplant year normal finding of LV had been observed in 63% of patients compared with 33% at the start. LVH remained in 37% of patients at the end of the study, with LVMI significantly lower compared to the start values (129.4±19.2 vs. 179.9±44.0 g/m², p=0.0018).

Hernandez et al. reported that regression of left ventricular hypertrophy partially starts at the first year after kidney transplantation, with the maximum achieved LV regression within first two years after transplantation, persists between third and fourth year, while long evaluations of this findings are still unknown (2). Study of McGregor et al. was suggested that pre-transplant LVH is predictor of mortality in the first 5 post-transplant years, but without sufficient strength and enough lasting of study to examine whether LVH presence or its development is predictor of death or cardiovascular events in that post-transplant period (13).

Significant anaemia begins to appear in patients who have reduced creatinine clearance. Anaemia is considered as an independent risk factor for progression of renal diseases to the end stage of renal disease. Levin et al. confirmed that anaemia correlated with the presence of cardiovascular conditions, such as congestive heart failure, symptoms of angina, and contributed to the development of LVH and chronic heart failure for each of 0.5 g/dL decreased in Hgb concentration (14). Anaemia of CKD is corrected by restored synthesis of erythropoietin from the graft, but there is an unexpectedly high incidence of anaemia in renal transplant patients. TESAM (Transplant European Survey on Anaemia Management) survey revealed that 38.6% of renal transplant patients were anemic. The most important risk factor for post-transplant anaemia appears to be impaired renal function, also presents of recent infections, use of ACE inhibitors or angiotensin II receptor antagonists, kidney from old donors, use azathioprine or mycophenolate mofetil, and also type of underlying kidney disease (15).

The results of our study show that renal anaemia was detected in all patients before transplantation. Compared with LV morphology status, patients with normal LV before transplantation had significantly higher values of Hgb compared to the patients with LVH (p=0.019). Until the end of the first post-transplant year mean level of Hgb was increased significantly in a group with normal mass index for 32%, and in a group with LV hypertrophy for 35%.

Arterial hypertension, as a potentially modifiable cardiovascular risk factor after renal transplantation, is present in about 50-90% of renal transplant recipients. In our study before transplantation 86% of patients had hypertension. Recently published studies confirmed that increasing levels of systolic and diastolic BP were associated with worsening graft survival over a 7-year period after transplantation. By contrast, maintenance of systolic BP <140 mmHg was connected with improved graft survival at 3 years after transplantation and with reducing...
of cardiovascular mortality at 10 years (16,17). Similarly, high systolic BP is associated with an increased risk of graft loss and all-cause mortality (18).

Our results confirmed positive correlation between values of systolic and diastolic blood pressure and LVMI in the group of patients with LV hypertrophy before kidney transplantation. By the end of the first post-transplant year, the mean values of SBP were significantly decreased in both echocardiographic formed groups of patients compared with values at the beginning of this study. The results of this study also showed that LVMI decreased in first post-transplant year and this decrease was in parallel with better control of blood pressure after kidney transplantation.

Epidemiological studies showed that about 60% of renal transplant patients had GFR lower than 60/ml and about 15% of patients <30 ml/min (19). The results of our study showed that patient with LVH before kidney transplantation had significantly higher serum creatinine values compared to patients with LVN (p=0.023). At the end of this study patients with LV hypertrophy had significantly lower value of creatinine clearance than patients with normal LV mass index (p=0.025). Normalization of LV on follow up echocardiography significantly plays with increase values of creatinine clearance. These findings are in the accordance with the results of other authors (20) and underscore the importance of controlling cardiovascular risk factors in transplanted patients.

6. CONCLUSION

The left ventricular hypertrophy remains the prevalent form of cardiomyopathy in time of kidney transplantation. The significant regression of LV hypertrophy within the first year after renal transplantation is related with correction of anaemia and better allograft function. Better control of blood pressure can improve cardiovascular outcome after renal transplantation.

CONFLICT OF INTEREST: NONE DECLARED.

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