

Subject Area:

Cardiac outcomes after successful kidney transplantation

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Cardiac outcomes after successful kidney transplantation

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Abstract

Aim

The aim of this study was to investigate the effects of renal transplantation on cardiac function and morphology in patients with ESRD on regular hemodialysis at the post-transplant period.

Background

End stage renal disease (ESRD) is considered an overall general health issue related to increased morbidity & mortality. The mortality rate among cases with ESRD who have been experiencing dialysis has been approximately seven times higher than for comparable cases in the general population and has been to a great extent related to cardiovascular causes.

Cardiac diseases have been common in cases with chronic kidney disease (CKD). About 75% of cases with CKD who begin dialysis have left ventricular hypertrophy, left ventricle dilatation or diminished left ventricle functional shortening; these cardiac anomalies keep on progressing during the first year of hemodialysis. Besides these changes, impairment of diastolic function has been also expected in these cases. For example, Left ventricular hypertrophy has been a very common pathological condition in cases with ESRD and considered as an independent risk variable for death and cardiac disease. Generally, many risk variables including uremic toxins, fluid retention & chronic volume over-load, anemia, hypoalbuminemia, hyperparathyroidism, arterio-venous fistula and pressure over-load were involved in the pathogenesis for Left Ventricular Hypertrophy in cases with ESRD. Renal transplantation is a well-established treatment for ESRD, allowing most patients to return to a satisfactory quality of life. It is the most acceptable treatment modality for the patients with ESRD, which improves some complications of renal failure such as chronic uremia and volume overload.

Methods

This cross sectional study was done on 40 kidney transplant recipients enrolled from the patients in the NIUN according to the inclusion and exclusion criteria. We compared echocardiographic findings and some cardiac risk factors after transplantation with those done before transplantation.

Results

There was highly significant reduction with respect to serum creatinine, blood urea, phosphorus. Comparison of echocardiographic findings between the pre-transplant period and post-transplant period. Ejection fraction (EF) was significantly increased at the post-transplant period while left ventricular systolic dimension (LVSD), left ventricular diastolic dimension (LVDD), and LVH showed a significant decrease after transplantation.

Conclusions

We have found that cardiac parameters showed significant improvement after transplantation as well as cardiac risk factors including anemia, hyperparathyroidism and volume & pressure overload.

Keywords: Cardiac outcomes, kidney transplantation, echocardiography

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INTRODUCTION

End stage renal disease (ESRD) is considered an overall general health issue related to increased morbidity and mortality [1]. The mortality rate among cases with ESRD who have been experiencing dialysis has been approximately seven times higher than for comparable cases in the general population and has been to a great extent related to cardiovascular issues [2]. Cardiac diseases have been common in cases with chronic kidney disease. About 75% of cases with chronic kidney disease who begin dialysis have left ventricular hypertrophy, left ventricle dilatation, or diminished left ventricle functional shortening. These cardiac anomalies keep on progressing during the first year of hemodialysis [3]. Besides these changes, impairment of diastolic function has been also expected in these cases. For example, left ventricular hypertrophy has been a very common pathological condition in cases with ESRD and considered as an independent risk variable for death and cardiac disease. Generally, many risk variables including uremic toxins, fluid retention and chronic volume overload [4], anemia, hypoalbuminemia [5], hyperparathyroidism, arteriovenous fistula, and pressure overload were involved in the pathogenesis for LVH in cases with ESRD [6]. Renal transplantation is a well-established treatment for ESRD, allowing most patients to return to a satisfactory quality of life [7]. It is the most acceptable treatment modality for the patients with ESRD, which improves some complications of renal failure, such as chronic uremia and volume overload. Kidney Transplant Recipients (KTRs) are inherently subjected to cardiovascular disease as a consequence of long term exposure to different cardiovascular risk variables. The high prevalence and cumulative effect of cardiovascular risk variables prior to, and then after the transplantation can explain the high rate of occurrence of cardiovascular disease [8]. Of the known cardiovascular risk components, hypertension, post-transplantation diabetes, and hyperlipidemia have been related to immunosuppressive treatment following kidney transplantation and also are indicators of chronic rejection [9]. Doppler echocardiogram is a complementary, noninvasive examination, broadly used in the assessment of heart structure and function. The diagnosis of LV abnormalities by Doppler echocardiography is an important step for the characterization of individuals with higher cardiovascular risk, estimating the prevalence of primary heart disease in a population to study its predisposing factors, prognostic impact, and the effect of therapeutic interventions [10].

Aim

The aim was to compare between cardiac functions before and after successful kidney transplantation and to evaluate improvement of cardiac risk factors among KTRs.

PATIENTS AND METHODS

This is a single-centered cross sectional study performed in 40 kidney transplant recipients who underwent successful transplantation during the years from 2012 to 2014 at the transplantation unit of the National Institute of Nephrology and Urology in Cairo and was approved by local ethical committee.

The nature and aim of the work were fully discussed with all patients who agreed to participate in the study. The enrolled patients were 36 males and 4 females, with mean age 31.05 ± 7.95 years. The inclusion criteria of the studied patients were patients who are more than 18 years and younger than 50 years, patients with successful kidney transplantation and normal kidney functions, patients on maintenance hemodialysis for at least 6 months before kidney transplantation. Evaluation will be done at least 6 months after successful transplantation. Whereas the exclusion criteria included patients with abnormal kidney functions after kidney transplantation, patients with congenital heart diseases, patients with irreversible heart diseases, such as dilated cardiomyopathy, and patients with malignant tumors.

All the studied patients underwent

- (1) General examination and full history including age, sex, duration of dialysis in months, duration of transplantation in months, other comorbid conditions, such as hypertension, diabetes, ischemic heart disease, and regular medications including immunosuppressive therapy, antihypertensive drugs, and other medications if present.
- (2) Echocardiography A standard two-dimensional transthoracic echocardiogram was performed at the time of blood sampling assessment and was compared with the one done before kidney transplantation while the patients were still on regular hemodialysis.
- (3) The studied biochemical parameters were ordered for all the studied patients, including, serum creatinine and blood urea (by Intgra 400 plus) Roche Diagnostic (Basel, Schweiz), complete urine analysis (uriscan); Complete blood count (CBC) (by automated blood counter) (Sysmex K × 21, Chuo-ku, Kobe, Japan); Serum Iron and total iron binding capacity (TIBC), transferrin saturation (t. sat.) was calculated [t. sat.=(S. iron/TIBC)×100], serum ferritin, calcium (Ca), phosphorus (PO₄) and parathyroid hormone (PTH); Lipid profile including cholesterol and triglycerides (Intgra 400 plus) Roche Diagnostic and random blood sugar.

Statistical analysis

Data are entered into an excel sheet and statistical analysis was performed using the Statistical Package for Social Sciences version 22.0 (IBM Corp., Armonk, New York, USA). With respect to the main measured parameters the differences between before and after renal transplantation were tested by using paired *t*-test. Categorical variables like gender were analyzed using the χ^2 -test/Fisher's exact test. Pearson's correlation test was applied to estimate and test the relationship between selected variables and echocardiographic findings. Results are expressed as mean \pm SD in addition to min and max. But in case of qualitative variables, it was represented as No. and % within brackets. All *P* values were based on a two-tailed distribution; those less than 0.05 was indicating statistical significance. The statistical analysis was based on the intention-to-treat population.

RESULTS

This cross sectional study was done on 40 kidney transplant recipients enrolled from the patients in the NIUN according to the inclusion and exclusion criteria.

In the current study, the number of men is 36 representing 90% of the studied patients versus 4 women representing 10%, with mean age 31.05 ± 7.95 years and mean weight 69.35 ± 14.84 kg. As comorbid diseases, hypertension was the most prevalent in 33 patients (82.5%), only one patient was diabetic (2.5%) and only one was known to have ischemic heart disease (2.5%) while the other five patients have no history of comorbidities. The number of smoking patients is 12 representing 30% and the hemodialysis duration was 7.5 ± 24 months (Tables 1 and 2).

Table 1: Demographic and clinical characteristics of the patients

Age (years)	31.05±7.95 (18-49)
Weight (kg)	69.35±14.84 (41-109)
Gender [n (%)]	
Female	4 (10.0)
Male	36 (90.0)
Smoker [n (%)]	
Yes	12 (30.0)
No	28 (70.0)
HTN	
Yes	33 (82.5)
No	7 (17.5)
DM	
Yes	1 (2.5)
No	39 (97.5)
IHD	
Yes	1 (2.5)
No	39 (97.5)
Duration of dialysis (months) M	12 [7.5-24]

DM, diabetes mellitus; HTN, hypertension; M, median and inter quartile range.

There was highly significant reduction with respect to serum creatinine, blood urea, phosphorus (Fig. 1), PTH (Fig. 2), the random blood sugar (RBS) after transplantation ($P < 0.0001$). The levels of hemoglobin (Fig. 3) and hematocrit (Fig. 4), cholesterol, triglycerides (TGs), and calcium post-transplantation showed a highly significant increase compared to those done before transplantation. With respect to iron profile, there was a significant increase in the levels of serum iron, TIBC, and transferrin saturation as well after transplantation. However, serum ferritin had a significant decrease at post-transplant period compared to the pre-transplant period (Table 3).

Comparison of echocardiographic findings between the pre-transplant period and post-transplant period. Ejection fraction (EF) was significantly increased at the post-transplant period while left ventricular systolic dimension (LVSD), left ventricular diastolic dimension (LVDD), and LVH showed a significant decrease after transplantation.

Table 4 shows correlations of EF with various examined parameters. Before RTx, EF showed significant negative correlation with smoking, hypertension (HTN) (Fig. 5) and Ischemic Heart Disease (IHD) (Fig. 6) while it showed significant positive correlation with hemoglobin level (Fig. 7). But after RTx, it showed significant negative correlation with age, weight, HTN (Fig. 8), and IHD (Fig. 9).

Table 5 shows correlations of LVH with various examined parameters. Before RTx, EF showed significant positive correlation with age, HTN, and creatinine level. But after RTx, it showed significant positive correlation with age, weight, and IHD.

DISCUSSION

Cases with ESRD show an elevated risk of premature cardiovascular mortality. Unlike the general population, sudden, presumed arrhythmic, cardiovascular death, rather than

Table 2: Comparison between biochemical characteristics before and after kidney transplantation

	Before	After	% of change	t	P
Creatinine (mg/dl)	10.2±2.36 (5.4-16.4)	1.08±0.17 (0.7-1.3)	-89.41	24.51**	<0.0001
Urea (mg/dl)	171.08±60.65 (66-311)	30.45±4.01 (24-40)	-82.20	14.77**	<0.0001
Ca (mg/dl)	8.41±0.67 (6.6-10)	9.3±0.46 (8.1-10.4)	10.58	-8.10**	<0.0001
PO4 (mg/dl)	6.05±1.45 (3.6-9.8)	3.36±0.65 (1.8-5.3)	-44.46	9.75**	<0.0001
PTH (pg/ml)	385.89±273.82 (13.6-1290)	116.25±74.1 (42-417)	-69.87	6.12**	<0.0001
Cholesterol (mg/dl)	172.55±40.1 (110-247)	203.75±41.7 (127-324)	18.08	-3.80**	0.001
TGs (mg/dl)	124.3±45.88 (75-305)	158.8±78.05 (77-444)	27.76	-2.86**	0.007
RBS (mg/dl)	93.27±14.23 (71-144)	104.8±13.1 (78-130)	12.36	-5.48**	<0.0001
HgB (g/dl)	9.44±1.41 (7-12.6)	13.77±1.46 (10.1-16.4)	45.9	-14.3**	<0.0001
Hct (%)	28.61±3.27 (22.6-35.2)	41.3±3.26 (31.5-46.4)	44.4	-18.2**	<0.0001
Iron (µg/dl)	81.73±35.61 (24-193)	105.68±31.21 (60-194)	29.30	-4.87*	<0.0001
TIBC (µg/dl)	242.17±39.36 (178-338)	276.18±52.08 (194-417)	14.04	-4.33**	<0.0001
Transferrin sat. (%)	33.27±14.16 (13-79)	37.8±9.33 (24-75)	13.62	-3.13**	0.003
Ferritin (ng/ml)	755.87±1089.5 (36-6601)	466.85±341.3 (124-1627)	-38.24	2.11*	0.041

Hct, hematocrit; PTH, parathyroid hormone; RBS, random blood sugar; TIBC, total iron binding capacity; TGs, triglycerides. *Indicate significant difference ($P < 0.05$). **Indicate highly significant difference ($P < 0.01$).

Table 3: Comparison between echocardiographic findings before and after kidney transplantation

	Before	After	% of change	<i>t</i>	<i>P</i>
EF	64.9±6.23 (49-75)	68.2±3.38 (61-77)	5.08	-5.23**	<0.0001
LVSD	3.16±0.43 (2.4-3.8)	2.98±0.42 (2.3-3.8)	-5.70	6.18**	<0.0001
LVDD	5.19±0.62 (3.9-6.4)	4.86±0.56 (3.9-5.7)	-6.36	8.70**	<0.0001
LVH	20 (50.0)	6 (15.0)	35		<0.0001

EF, ejection fraction; LVDD, left ventricular diastolic dimension; LVSD, left ventricular systolic dimension. *Indicate significant difference ($P<0.05$).

**Indicate highly significant difference ($P<0.01$).

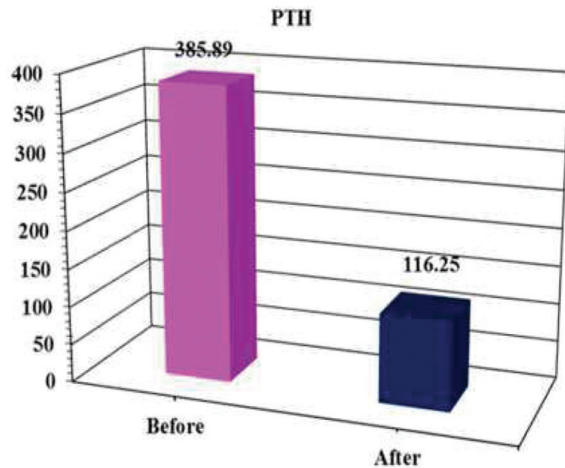


Figure 1: Comparison between serum PO₄ level before and after RTx.

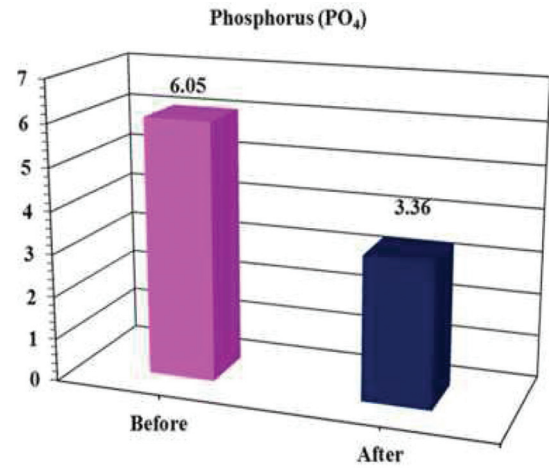


Figure 2: Comparison between serum parathyroid hormone level before and after RTx.

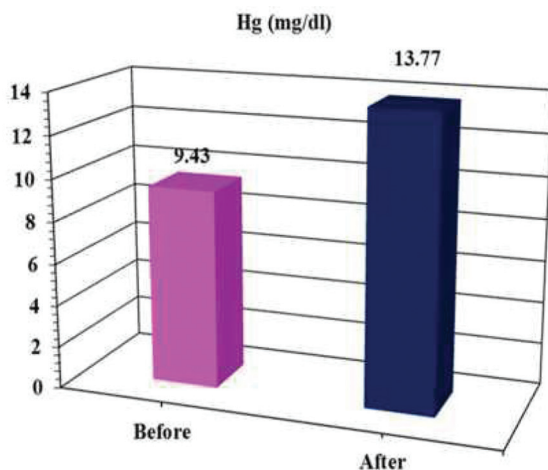


Figure 3: Comparison between Hgb level (g/dl) before and after RTx.

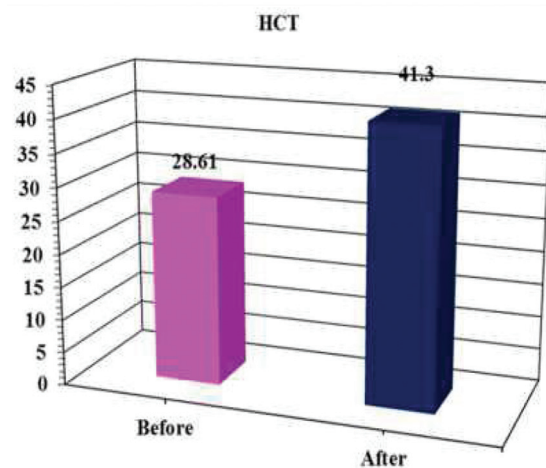


Figure 4: Comparison between hematocrit level before and after RTx.

myocardial infarction or heart failure, has been the most widely recognized reason for death [11]. LVH has been a known marker of cardiac risk in the general population. LVH, which results from volume and pressure overload, has been the most common cardiovascular finding in the cases suffering from ESRD, including kidney transplant recipients (50–70%) [12].

Kidney transplantation has been the most accepted treatment modality for the cases with ESRD, which resolves some hazards of renal failure as chronic uremia and volume overload. It has been observed that successful kidney transplantation positively affects ventricular hypertrophy and could regress LVH and enhance LVEF during the first year post-transplantation [13].

This cross sectional study aims to compare between cardiac functions before and after successful kidney transplantation and to evaluate improvement of cardiac risk factors among KTRs.

The current study was conducted upon 40 patients who underwent successful kidney transplantation and have been on regular hemodialysis three times per week for at least 6 months before transplantation. All the studied patients underwent full history including age, sex, weight, duration of dialysis, time of transplantation, other comorbidities conditions as hypertension, diabetes, ischemic heart disease, and regular

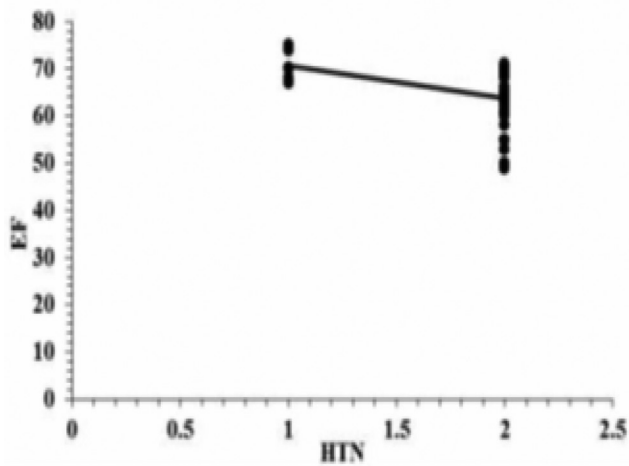


Figure 5: Simple Pearson correlation between hypertension and ejection fraction before.

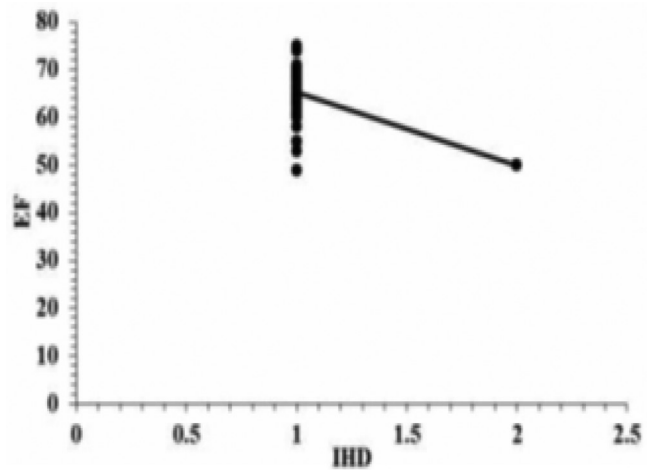


Figure 6: Simple Pearson correlation between IHD and ejection fraction before RTx.

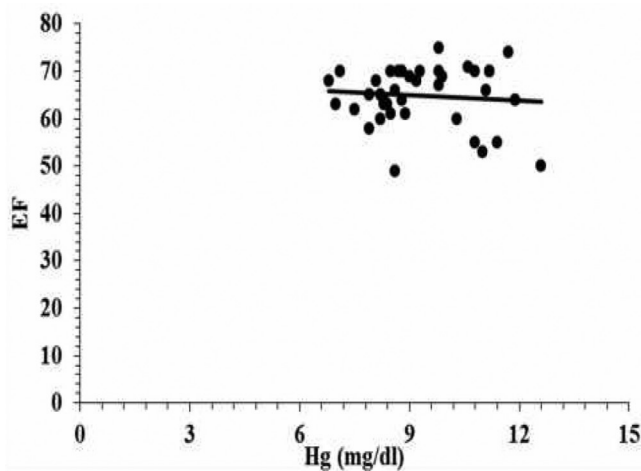


Figure 7: Simple Pearson correlation between Hg level and ejection fraction before RTx.

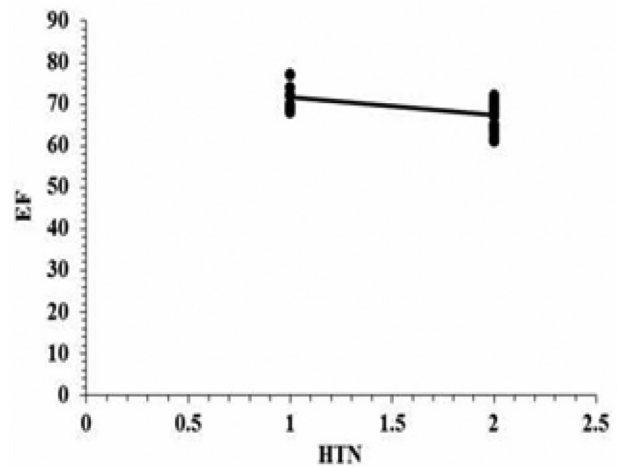


Figure 8: Simple Pearson correlation between hypertension and ejection fraction after.

medications. Also the patients got to have echocardiography and measurement of the studied biochemical parameters at least 6 months after transplantation.

In the current study, with respect to echocardiographic findings, the prevalence of LVH was significantly decreased after kidney transplantation. Also, there were significant improvements in cardiac morphologic parameters including LVDD, LVSD, and in EF. Ferreira *et al.* [14], found that presence of LVH was 75% and 59% before renal transplantation and after 3 months of follow-up in 24 patients aged mean 33 ± 10 years. In another study, the presence of LVH decreased from 70% to 40% at mean 3.2 months of post-transplant period [15]. Similarly, in our study we observed a high prevalence of LVH and a significant decrease in this prevalence from 50% to 15% after transplantation. Also Iqbal *et al.* [16], showed that LVH was significantly decreased after kidney transplantation, whereas some studies did not observe this improvement as in Patel *et al.* [17], which revealed that renal transplantation is not associated with regression of left ventricular hypertrophy.

Another important finding in the current study was a significant increase in LV systolic functions after kidney transplantation. This might be the result of an improvement in the hypervolemic state during the dialysis period after transplantation. Similar findings were observed by Bialostozky *et al.* [18], who found that the percentage of patients with low LVEF decreased from 53% to 20% and mean LVEF increased from 48% to 58% after renal transplantation in 30 patients with ESRD. In contrast to our findings [19], observed nonsignificant increase of EF post-transplantation as it detected an increased mean LVEF (57.33%) after transplantation in comparison to values before (53.83%). Similar to LVEF, LV diameters were improved including LVDD and LVSD, which were significantly lower in the post-transplant period compared with the pre-transplant period. These findings possibly resulted from an improvement in volume overload after transplantation [20]. Similarly found a significant decrease in LV diameters and LAD after kidney transplantation [21]. They also showed that renal transplantation diminishes hypertrophy and improves left ventricular systolic and diastolic function. The current study also showed that

LV diastolic and systolic functions significantly improved after renal transplantation in patients with ESRD. In general,

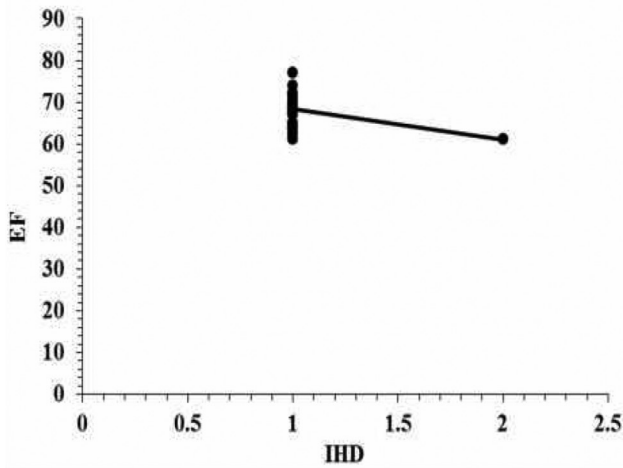


Figure 9: Simple Pearson correlation between IHD and ejection fraction after RTx.

correction of the uremic state by renal transplantation leads to improvement of LV structure and function. Another study, assessing 50 individuals before and 3 months after renal transplantation, demonstrated significant improvement of the ejection fraction and reduction of the chamber diameters [22]. This increase is reported in other studies as well [13,23,24].

In contrast, our results do not go in agreement with the study done by Patel *et al.* [17], which included 50 kidney transplant recipients showing that there was no difference in any of the cardiac parameters measured including ejection fraction, left ventricular mass index (LVMI), corrected end diastolic and end systolic volumes, before transplantation or at follow-up. Only there was a small reduction in LVMI (−3.6%/year) in dialysis patients and a small increase associated with transplantation (2.8%/year). However, none of the measured cardiac parameters achieved statistical significance.

In general, several risk factors including uremic toxins, fluid retention and chronic volume overload, renal anemia, hypoalbuminemia, hyperparathyroidism, arteriovenous

Table 4: Simple Pearson’s correlation between ejection fraction and selected variables and its statistical significance

	Before	After
Age		
<i>r</i>	−0.238	−0.360*
<i>P</i>	0.139	0.022
Weight		
<i>r</i>	−0.23	−0.346*
<i>P</i>	0.153	0.029
Sex		
<i>r</i>	−0.182	−0.13
<i>P</i>	0.262	0.424
Smoker		
<i>r</i>	−0.335*	−0.268
<i>P</i>	0.034	0.094
HTN		
<i>r</i>	−0.425**	−0.486**
<i>P</i>	0.006	0.001
IHD		
<i>r</i>	−0.388*	−0.346*
<i>P</i>	0.013	0.029
Creatinine (mg/dl)		
<i>r</i>	−0.274	−0.125
<i>P</i>	0.088	0.443
HgB (g/dl)		
<i>r</i>	0.461**	0.215
<i>P</i>	0.003	0.182
Cholesterol (mg/dl)		
<i>r</i>	0.06	0.168
<i>P</i>	0.713	0.299
TGs (mg/dl)		
<i>r</i>	−0.208	0.137
<i>P</i>	0.198	0.398

HTN, hypertension; TGs, triglycerides. *Correlation is significant at the 0.05 level (two-tailed). **Correlation is significant at the 0.01 level (two-tailed).

Table 5: Simple Pearson’s correlation between LVH and selected variables and its statistical significance

	Before	After
Age		
<i>r</i>	0.388*	0.523**
<i>P</i>	0.013	0.001
Weight		
<i>r</i>	0.215	0.430**
<i>P</i>	0.183	0.006
Sex		
<i>r</i>	0.167	0.14
<i>P</i>	0.304	0.389
Smoker		
<i>r</i>	0.218	0.183
<i>P</i>	0.176	0.257
HTN		
<i>r</i>	0.329*	0.193
<i>P</i>	0.038	0.232
IHD		
<i>r</i>	0.16	0.381
<i>P</i>	0.324	0.015
Creatinine (mg/dl)		
<i>r</i>	0.348*	0.131
<i>P</i>	0.028	0.028
HgB (g/dl)		
<i>r</i>	0.183	−0.025
<i>P</i>	0.258	0.877
Cholesterol (mg/dl)		
<i>r</i>	0.09	0.025
<i>P</i>	0.582	0.88
TGs (mg/dl)		
<i>r</i>	−0.001	0.268
<i>P</i>	0.995	0.094

HTN, hypertension; TGs, triglycerides. *Correlation is significant at the 0.05 level (two-tailed). **Correlation is significant at the 0.01 level (two-tailed).

fistula, and pressure overload have been accused in the pathogenesis of LVH in patients with ESRD [25]. Although there are beneficial cardiovascular effects of kidney transplantation, the prevalence of LVH remains high in renal transplant patients, and it may contribute to the high cardiac mortality rate observed in this population [26]. Successful renal transplantation improves some risk factors for LVH as uremia, anemia, and hyperparathyroidism, but others including patent arteriovenous fistula, dyslipidemia, and hypertension may persist or worsen after transplantation. Furthermore, immunosuppressive drugs, such as calcineurin inhibitors, especially cyclosporine and steroids that have hypertensive adverse effect, play an important role in the development or persistence of LVH after renal transplantation. With respect to these risk factors, our study showed significant decrease of serum creatinine and blood urea. A significant improvement of anemia parameters including hemoglobin level and iron profile was observed after transplantation. Also, we observed that hyperparathyroidism parameters including PTH, Ca, and PO_4 were meaningfully improved after renal transplantation. However, there has been a significant increase of blood glucose level and lipid profile including cholesterol and triglycerides post-transplantation, most probably due to use of immunosuppressive drugs following transplantation. Dyslipidaemia is common, partly due to the hyperlipidaemic effect of corticosteroids, cyclosporine, tacrolimus, and mammalian target of rapamycin (mTOR) inhibitors. These results were also observed in Ćit *et al.* [27], which showed that levels of serum total cholesterol and high-density lipoprotein were significantly increased at 12 months after transplantation compared with the pretransplant period. The levels of hemoglobin, albumin, and low-density lipoprotein were significantly increased at 12 month after transplantation.

However, levels of blood urea nitrogen, serum creatinine, phosphorus, intact parathyroid hormone (iPTH), and calcium x phosphorus product (CaxP) were significantly decreased at the late post-transplant period compared with the pre-transplant period. Another study Deng *et al.* [28], which included 48 kidney transplant recipients revealed systolic blood pressure, heart rate, BUN, and creatinine post kidney transplantation were significantly lower than pre- kidney transplantation, while glucose was higher than pre- kidney transplantation as in our study. The same results were observed in Souza *et al.* [13]. However, Deng *et al.* [28] showed no significant difference in hemoglobin pre-kidney and post-kidney transplantation. Also there was no significant change in hemoglobin and calcium levels after transplantation in any of the 40 patients included in the study done by Souza *et al.* [13].

CONCLUSION

Our current study showed improvement of cardiovascular risk factors, such as anemia and hyperparathyroidism in the post-transplantation period. Also significant improvement of

cardiac parameters including EF, LVH, LVSD, and LVDD was observed after kidney transplantation. On the basis of these data, we conclude that renal transplantation had beneficial effects not only on diastolic functions but also on systolic functions and cardiac morphology in the post-transplant period. Compared with ESRD patients on dialysis therapy, KTRs showed better outcomes and we could observe better performance of cardiac function in a period after renal transplantation.

Recommendations

- (1) Renal transplantation is the treatment of choice for ESRD patients and is increasingly the preferred method of renal replacement therapy. It has better outcomes than any other modalities of renal replacement therapy. However, further prospective studies are needed to determine other outcomes of renal transplantation rather than cardiac ones.
- (2) Screening for cardiovascular risk in both ESRD patients and KTRs is very important for better survival and outcomes among these patients. Screening will allow nephrologists to identify, with acceptable sensitivity and specificity, patients at higher risk for cardiovascular events.
- (3) Our findings further support the use of echocardiography as a baseline simple, noninvasive, and no radiologic test for evaluation of cardiac function and morphology for risk stratification of both dialysis patients and KTRs, as recently suggested in the international guidelines by the Kidney Disease Improving Global Outcomes panel of experts.

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Conflicts of interest

There are no conflicts of interest.

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