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ORIGINAL ARTICLE

Improved left ventricular mass index in children after renal transplantation

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Abstract Left ventricular hypertrophy (LVH) is a risk factor for cardiovascular disease, and it is prevalent in children with end-stage renal disease (ESRD) and after renal transplantation (RTx) on cross-sectional studies. Our aim was to compare prospectively left ventricular mass index (LVMI) in children with ESRD, before and after RTx. Thirteen patients aged 1.5–15 years underwent echocardiogram prior to and at least 3 months after RTx, and again in the second year after transplantation. A control group consisted of children with ESRD who remained on dialysis. Systolic and diastolic blood pressure index decreased significantly over the study period only in the children who had undergone RTx. Mean LVMI in children with ESRD decreased from 45.4±12.6 g/m$^{2.7}$ to 34.9±10.4 g/m$^{2.7}$ after RTx (P=0.001), but it remained unchanged in patients who remained on dialysis. The prevalence of LVH decreased from 54% to 8% (P=0.03) after RTx. Systolic and diastolic blood pressure index were correlated with LVMI. Mean body mass index increased during the study period from 17.3±2.5 to 20±4.6 (P=0.05); however, no correlation was found with LVMI. LVH in children with ESRD is potentially reversible after RTx, especially with good control of hypertension.

Keywords Left ventricular hypertrophy · Hypertension · Renal transplantation · Pediatric

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Introduction

The prognosis of pediatric renal transplantation (RTx) recipients has improved dramatically over the past 3 decades, due to the use of more potent immunosuppressive agents and a decline in mortality from infections [1]. However, life expectancy is shortened in comparison with that of the age-matched population, mostly due to cardiovascular disease. Although cardiovascular mortality is significantly reduced in comparison with that of children with end-stage renal disease (ESRD) on dialysis, it remains the leading cause of death in young adults who have undergone RTx, and it is the second most common cause of death in children, after infection [1, 2]. Left ventricular hypertrophy (LVH) is the most common cardiac abnormality observed in pediatric and adult dialysis patients, and has been associated with hypertension and volume overload [3]. However, LVH is prevalent even after successful RTx, in between 7% and 82% of children in various cross-sectional studies [4–8]. LVH is a significant risk factor for cardiovascular mortality, both in the general population and in patients with renal disease [9].

The aim of this study was prospectively to compare left ventricular mass index before and after RTx in children with ESRD, in comparison with children who remained on dialysis, and to seek correlation with blood pressure and clinical characteristics.

Patients and methods

All patients under the age of 18 years followed at our center with ESRD were eligible to participate in the study. Informed parental consent was obtained, and the study was approved by the ethics committee of the Shaare Zedek Medical Center. Each patient underwent a comprehensive echocardiographic evaluation prior to transplantation. Two subsequent echocardiographies were performed, the first at least 3 months after successful RTx, and the second during the second year after transplantation. Patients who had not undergone RTx had repeated echocardiography performed 6 months to 18 months later. Exclusion criteria were congenital or other structural heart disease, and estimated glomerular filtration rate (eGFR) of less than 30 ml/min per 1.73 m^2 body surface area at the first examination after transplantation. Data recorded included age, gender, underlying renal disease, dialysis mode and duration, age at transplantation, source of kidney transplant (living or deceased donor), immunosuppression, including current prednisone dose per weight, use of pulse corticosteroid for rejection, and anti-hypertensive medications. On the days of echocardiographic evaluation, weight and height were recorded and body mass index (BMI) was calculated. Blood pressure was measured in accordance with the recommendations of the Fourth National Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [10], and mean systolic and diastolic measurements were calculated from the values obtained on the day of evaluation and the three previous clinic visits or dialysis sessions (pre-dialysis measurements). These values were then divided by the 95th percentile blood pressure measurements for age, gender and height percentile to produce the blood pressure index (BPI). Estimated GFR was calculated using the Schwartz equation, based on serum creatinine of that day. Mean hemoglobin was calculated as the time-averaged hemoglobin over the 3 months prior to each echocardiography.

Echocardiography

Echocardiography was performed by a senior pediatric cardiologist using the HP Sonos 4500 machine. Left ventricular mass was assessed by two-dimensional echocardiography. We calculated left ventricular mass index (LVMI) by dividing the LVM (in grams) by height to the power of 2.7 in order to correlate with body size. LVMI greater than two standard deviations from the mean for age was used to define LVH as described by De Simone et al. [11]. As LVMI is higher in young children, a natural decrease in LVMI is expected over time, particularly under the age of 8 years. In order to control for this phenomenon, we calculated the number of standard deviations (SDS) from the mean for age from the data presented by Khoury et al. and used them to compare LVMI over time in each patient [12]. We assessed left ventricular geometry by measuring relative wall thickness (RWT). If RWT was above 0.41, LVH was defined as concentric; otherwise, it was considered to be eccentric LVH [8]. Concentric remodeling was defined as normal LVMI with elevated RWT. An additional control group consisted of 42 age-matched healthy children and adolescents, who underwent echocardiography for evaluation of an innocent murmur, with no abnormal structural findings found on the echocardiogram.

Statistical analysis

Variables are presented as mean ± standard deviation. In order to compare continuous variables when two time points were compared, we used the paired sample *t*-test. When three time points were compared, the repeated measures analysis was applied, using the Greenhouse–Geisser correction. We used the McNemar test to assess change between two time points for dichotomous variables. Association between two continuous variables was estimated by calculation of Pearson's correlation coefficient. Multiple linear regression analysis was used for determination of the effect of more than one continuous variable on LVMI. The comparison of the patient group with healthy controls was performed with the two-sample *t*-test. All tests performed were two-tailed, and a *P* value of 5% or less was considered as statistically significant.

Results

Patients' characteristics

Twenty-seven patients with ESRD were eligible to participate in the study. All were Caucasian: 16 Arab and nine Jewish children. One underwent RTx elsewhere and was lost to follow up, and one died due to fungal peritonitis while on continuous cyclic peritoneal dialysis (CCPD). Thirteen patients with ESRD, aged 1.5–15 years (mean 7.9± 4.9 years), underwent RTx and completed the full evaluation (group 1). The remaining 12 patients were treated with chronic hemodialysis and completed their second evaluation (group 2). The children in groups 1 and 2 did not differ in age, gender or underlying disease.

In group 1, ten patients were treated with chronic hemodialysis, one was on CCPD and two underwent examination immediately prior to pre-emptive living donor kidney transplantation. Estimated GFR for these two patients was 12 ml/min per 1.73 m^2 and 14 ml/min per 1.73 m^2, at the time of pre-transplantation cardiac evaluation. The mean time on dialysis for the remaining patients was 13±

9.7 months (range 1–24 months) at the time of the first examination. Post-transplantation echocardiogram was first performed between 3 and 12 months after RTx (mean 7.5± 3.5 months), and a follow-up echocardiogram was performed during the second year after RTx (mean 17.2± 6.3 months), and at least 6 months later. Initial immunosuppression consisted of tacrolimus and mycophenolate mofetil in all but one patient, who received cyclosporine and azathioprine, as well as prednisone which was tapered to low-dose alternate-day therapy in all but one patient, who was on a steroid-free protocol. Three patients subsequently discontinued mycophenolate treatment, due to BK virus nephropathy in two (3 months and 9 months after RTx) and Epstein–Barr virus (EBV)-related post-transplantation lymphoproliferative disease in one (1 year after RTx). Three other patients received a course of high-dose intravenous injections of methylprednisolone for biopsy proven acute rejection during the study period.

Renal function of the graft was good in all but one of the patients with BK virus nephropathy, whose graft function decreased to an eGFR of 40 ml/min per 1.73 m^2 and stabilized (Table 1).

A significant decrease in systolic and diastolic BPI was observed at both post-transplantation examinations compared with ESRD values, and the frequency of uncontrolled hypertension decreased significantly. There was a trend towards decreased use of anti-hypertensive medications; however, this did not reach statistical significance. Anti-hypertensive treatment consisted of a calcium channel blocker, a beta blocker, or a combination of the two in the majority of patients; only three patients received an angiotensin-converting enzyme (ACE) inhibitor. No change in BPI was seen in the patients in group 2. There was no significant change in hemoglobin levels over the period of observation, though all of the patients had been receiving recombinant erythropoietin therapy prior to transplantation, but none at the last examination. The prednisone dose was significantly lower at the last examination (Table 1). Two patients in group 1 had an arterio-venous fistula for dialysis access; one patient's fistula clotted shortly after transplantation, while the other's remained patent at the last examination. Vascular access for hemodialysis in group 2 was arterio-venous fistula in three patients and tunneled central venous catheter in the remainder.

Echocardiographic findings

In group 1, seven patients (54%) with ESRD had LVH, defined as LVMI of more than two standard deviations above the mean for age. Four of them had concentric LVH and three had eccentric LVH. Three additional patients had concentric remodeling, while only three had normal

Table 1 Clinical and echocardiographic parameters (*RTx* renal transplantation, *BPI* blood pressure index, *SDS* standard deviations, *BMI* body mass index, *GFR* glomerular filtration rate, *LVMI* left ventricular mass index, *LVH* left ventricular hypertrophy)

Parameter	Group 1			Group 2	
	ESRD evaluation	First post-RTx evaluation	Second post-RTx evaluation	First dialysis evaluation	Second dialysis evaluation
Age (range) in years	7.9±4.9 (1.5–16)	8.9±5 (2.5–16.5)	9.8±5.1 (3.5–17.5)	6.9±4.7 (1.5–17.5)	8±4.9 (3–18.5)
Years from RTx	−0.47±0.35	0.65±0.28	1.44±0.47		
Systolic BPI	1.11±0.14	0.96±0.1	0.94±0.07*	1.12±0.2	1.21±0.21
Diastolic BPI	1.03±0.17	0.84±0.11	0.78±0.1*	1.03±0.19	1.12±0.27
Uncontrolled hypertension (%)	77	38	8[a]	79	83
Anti-hypertensive drugs[a]	1.45±1.5	1.08±0.9	0.85±0.8	1.21±1.1	1.67±1.4
Mean hemoglobin, g/dl	11.3±1.1	11.8±1	12.4±1.1	11±1.2	11.1±1.4
Mean hemoglobin, SDS	−2.4±2.2	−1.7±1.8	−1.1±1.9	−2.6±1.9	−2.2±1.9
Prednisone dose, mg/kg per day		0.38±0.19	0.21±0.13[c]		
BMI kg/m^2	17.3±2.5	19.1±3.1	20±4.6***	16.3±2.8	16.4±2.7
BMI SDS	0.11±0.97	0.95±0.8	1.18±0.76***	−0.47±1.1	−0.33±1.2
Estimated GFR, ml/min per 1.73 m^2		85.6±24.1	86.3±23.9		
LVMI, g/$m^{2.7}$	45.4±12.6	36.7±11.6	34.9±10.4*	50.9±14.6	49.6±19
LVMI, SDS	1.8±1.6	0.66±1.4	0.46±1.4**	2.2±2	2.3±2.7
LVH (%)	54	23	8[b]	50	50

*$P \leq 0.001$, **$P \leq 0.01$, ***$P \leq 0.05$, comparing all three time points in the group of patients who underwent RTx, using the repeated measures analysis

[a] $P \leq 0.01$, [b] $P \leq 0.05$, comparing second post-RTx examination to ESRD

[c] $P = 0.001$, comparing the two post-RTx evaluations

There were no significant differences between group 1 and group 2 at baseline, or between the first and second examinations of the patients in group 2

geometry. After transplantation, three patients still had LVH at the first examination (all concentric), and only one patient at the second examination after RTx, (P=0.03, compared to ESRD). Four patients had echocardiographic findings consistent with concentric remodeling at the last cardiac evaluation. Mean LVMI decreased from 45.4±12.6 g/m$^{2.7}$ during ESRD to 34.9±10.4 g/m$^{2.7}$ during the second year after RTx (P=0.001). These values were still significantly higher than in the group of healthy controls (mean LVMI 23.4±5.1 g/m$^{2.7}$, P=0.002). The LVMI SDS also decreased significantly from 1.8±1.6 to 0.46±1.4 over the study period (P=0.01) (Table 1). Only two children from group 1 demonstrated an increase in LVMI SDS during the study period. One of them was the patient with decreased eGFR due to BK virus nephropathy and persistent uncontrolled hypertension, while the other patient's LVMI increased but remained within the normal range at 31 g/m$^{2.7}$. Change in LVMI over time in individual patients is shown in Fig. 1.

The mean LVMI in the group of children who remained on dialysis on the first echocardiogram was 50.9±14.6 g/m$^{2.7}$, which was not significantly different from the initial evaluation in the patients who subsequently underwent RTx (45.4±12.6 g/m$^{2.7}$, P=0.3). The LVMI SDS values were also similar in both groups (2.2±2 vs 1.8±1.6, P= 0.52). At the follow-up examination of the children in group 2, the mean LVMI was 49.6±19 g/m$^{2.7}$ and the LVMI SDS was 2.3±2.7, which were not significantly different from baseline values (P=0.35 and P=0.65 for LVMI and LVMI SDS, respectively) (Table 1). There was a strong correlation between LVMI at the first and second examinations in the children in group 2 (r=0.84, P=0.001).

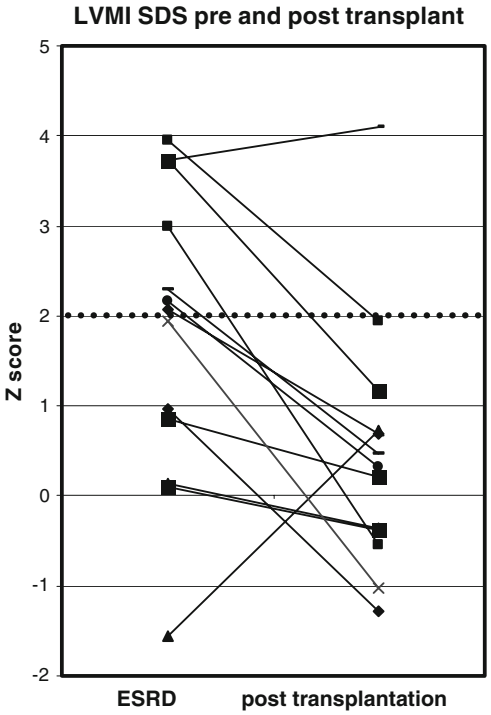

Fig. 1 Individual patient's (*different symbols*) LVMIs expressed in SDS from the mean for age, during ESRD and in the second year after renal transplantation (group 1). The *dotted line* indicates two standard deviations above the mean; values above this are defined as indicating left ventricular hypertrophy

Table 2 Correlation of left ventricular mass index, in number of standard deviations from the mean, with systolic and diastolic blood pressure index at the time of echocardiographic evaluation (*RTx* renal transplantation, *SPBI* systolic blood pressure index, *DBPI* diastolic blood pressure index, *LVMI* left ventricular mass index, *dialysis-1* examination of all patients with end-stage renal disease at the start of the study, *dialysis-2* second examination of children remaining on dialysis, *post-RTx-1* first examination after renal transplantation, *post-RTx-2* second examination after renal transplantation)

LVMI	BPI	Correlation coefficient	P
LVMI dialysis-1, n=27	SBPI	0.41	0.03
	DBPI	0.42	0.03
LVMI dialysis-2, n=12	SBPI	0.61	0.03
	DBPI	0.56	0.06
LVMI post-RTx-1, n=13	SBPI	0.54	0.06
	DBPI	0.56	0.05
LVMI post-RTx-2, n=13	SBPI	0.79	0.001
	DBPI	0.63	0.02
Change in LVMI from ESRD to post-RTx-2, n=13	Change in SBPI	0.25	0.41
	Change in DBPI	0.24	0.43

Correlation between clinical factors and LVMI

Left ventricular mass index was correlated with systolic and diastolic BPI in patients with ESRD as well as after RTx. Although both LVMI and BPI decreased significantly after transplantation, the magnitude of the BPI reduction did not predict the degree of LVMI improvement (Table 2). No correlation was found between age, gender, change in body mass index or SDS, post-transplantation eGFR, prednisone dose, hemoglobin concentration or SDS and change in LVMI. There was a positive correlation between LVMI at the initial examination and on subsequent echocardiograms; however, on multiple regression analysis, only blood pressure index remained positively correlated with LVMI in the children after RTx (R^2=0.86, β=0.48, P=0.017 for SBPI, and β=0.39, P=0.05 for DBPI). In group 2, multiple regression analysis showed that the strongest predictor of LVMI at the second cardiac examination was the initial LVMI (R^2=0.69, β=0.63, P=0.04).

Discussion

In this study we found a significant decrease in LVMI and in the prevalence of LVH in children with ESRD after

undergoing successful RTx, but not in those who remained on dialysis. This effect was seen within the first year, persisting, and, in fact, becoming more marked, in the second year after RTx. This is consistent with findings in adults after RTx, especially in those treated with ACE inhibitors [13–15]. However, several studies of children have shown that elevated LVMI is relatively common after RTx. Johnstone et al. found that the prevalence of LVH in children after RTx was greater than in a group of children with chronic renal failure or ESRD [16]. However, in their study, blood pressure values were higher in the group who had undergone transplantation. In a study by Matteuci and colleagues a very high frequency of LVH (82%) was seen, although only 36% had uncontrolled hypertension [6]. Other groups have reported a high prevalence of LVH in children after renal transplantation, but at least half of the patients were hypertensive, and some also had marked anemia [5, 7]. The majority of the patients described in these reports were on cyclosporine-based immunosuppression, and all of the studies were cross-sectional. One study, which looked at the same patients before and after RTx, found no change in LVMI, and an LVH prevalence of 56% at both time points [17]. We have previously described a cohort of 60 children and young adults who had undergone RTx. The mean LVMI was well within normal limits, at 30.9 $g/m^{2.7}$, although it was significantly higher than in healthy controls. Only 7% demonstrated LVH, and a trend towards higher values in patients treated with cyclosporine was observed [4]. In light of the discrepancy between other studies and our previous findings, we adopted a prospective approach to evaluate echocardiographic parameters in children with ESRD. The results of this study are consistent with our previous findings in children after RTx, in that most patients have a normal LVMI. This is despite the fact that most patients had elevated LVMI prior to transplantation. In contrast, patients who remained on dialysis experienced no change in LVMI over a similar follow-up period. No correlation with renal function after RTx was observed; however, all but one of the patients in the study described here had good graft function, with an eGFR greater than 60 ml/min per 1.73 m^2 body surface area. A point of interest is that body mass index increased over the study period, a factor which might have been expected to predispose to increased cardiac mass. We did not observe a correlation between BMI and LVMI.

We found a significant decrease in both systolic and diastolic BPI and in the number of hypertensive patients after RTx. The three children with LVH on the first echocardiogram after transplantation, and the one with persistent LVH at the last examination, all had uncontrolled hypertension. LVMI was positively correlated with blood pressure index in the group as a whole at the first examination and in follow-up examinations in both groups of patients. No correlation was seen between the magnitude of BP reduction and change in LVMI. Uremic cardiomyopathy, found in patients with chronic renal disease and ESRD, has a multifactorial etiology and may be associated with increased circulating concentrations of endogenous cardiotonic steroids and with abnormalities in calcium–phosphate homeostasis, in addition to the impact of hypertension [3, 18]. The correlation between LVMI at the initial examination and on subsequent echocardiograms was not significant after multiple regression analysis had been performed. However, results of regression analysis should be viewed cautiously in small groups of patients.

Cyclosporine use has been associated with hypertension and LVH both in renal transplant recipients and in bone marrow transplant recipients, in comparison with tacrolimus use [19–21]. The increased incidence of myocardial hypertrophy in those studies was not necessarily due to hypertension. Our patients were almost all treated with tacrolimus, which may partly account for the discrepancy between our findings and those of previous studies, in addition to the low frequency of uncontrolled hypertension after renal transplantation. On the other hand, hypertrophic cardiomyopathy has been seen in children treated with high doses of tacrolimus after liver and/or bowel transplantation [22].

The main limitation of this study was its small size; however, the comparison with a matched group of patients who were not fortunate enough to have received a kidney transplant during the study period reinforces the validity of the findings, as does the continuing trend towards improvement of LVMI over 2 years in those who did undergo RTx. The use of standard deviations from the normal value of LVMI for age, avoids the erroneous assumption that LVMI improved, when, in fact, the change observed simply reflected the expected change with age.

In summary, in this prospective study, we demonstrated a significant improvement in LVMI after renal transplantation in children with ESRD, and a low frequency of LVH. This improvement was not observed in children who remained on dialysis. These findings are correlated with blood pressure index. We conclude that LVH in children with ESRD is potentially reversible after renal transplantation, especially with good control of hypertension.

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