DOI: 10.4149/BLL_2022_040

Bratisl Med J 2022; 123 (4)

248 – 253

CLINICAL STUDY

Left ventricular hypertrophy in children and adolescents before and after kidney transplantation

KOLVEK Gabriel[1], PODRACKA Ludmila[2]

Department of Paediatrics and Adolescent Medicine, PJ Safarik University in Kosice, Kosice, Slovakia.
gabriel.kolvek@upjs.sk

ABSTRACT

BACKGROUND: Left ventricular hypertrophy (LVH) is associated with a premature death in children with chronic kidney disease (CKD). We studied its change over time, related to a successful kidney transplantation (KTx) and assessed whether clinical variables were associated with the left ventricular mass index (LVMI).

METHODS: We obtained the records of all children and adolescents, who were followed-up at the tertiary nephrology centre for children at the Children's University Hospital in Kosice, Slovakia, during 2008–2014, had completed echocardiographic studies while on chronic dialysis and had undergone a successful KTx, n=25. We assessed the longitudinally recorded left ventricular mass index (LVMI) and the presence/absence of LVH, and risk factors for LVH.

RESULTS: The average prevalence of LVH was 23.5 % while on dialysis, and 29.4 % after KTx (p=0.06). Pre-post changes per patient were relatively big. Uncontrolled systolic hypertension was significantly related to LVMI (p=0.03).

CONCLUSION: LVH is common after paediatric KTx and the reversibility of already present LVH seems to be rather problematic. Significant changes of LVMI on the individual level suggest that modification is feasible with a thorough control of (systolic) hypertension and of the other risk factors *(Tab. 3, Fig. 1, Ref. 50)*. Text in PDF *www.elis.sk*

KEY WORDS: left ventricular hypertrophy, children, transplantation, chronic kidney disease.

Introduction

Paediatric end-stage renal disease (ESRD) patients nowadays mostly survive until adulthood and beyond, but this is associated with additional morbidity, too. Transplantation, as an ideal renal replacement therapy option, may be glorified for this dramatic improvement of the long-term outcome. However, the overall mortality remains high. Upon reaching adulthood, dialysis patients live 40–50 years less, and transplant patients 20–25 years less than an age- and race-matched population (1). According to these data from the United States, 22–32 % of this mortality excess may be explained by cardiovascular disease (1). Studies from other countries similarly show that 40–50 % of all deaths among dialysis and transplantation patients can be attributed to cardiovascular or cerebrovascular causes (2–4). Uremic cardiomyopathy, stiffening of the vessels due to calcifications and premature atherosclerosis all contribute to this excessively increased cardiovascular risk (5).

[1]Department of Paediatrics and Adolescent Medicine, PJ Safarik University in Kosice, Kosice, Slovakia, and [2]Department of Paediatrics, Comenius University in Bratislava, Bratislava, Slovakia

Address for correspondence: Gabriel KOLVEK, MD, Department of Paediatrics and Adolescent Medicine, PJ Safarik University in Kosice, Trieda SNP 1, SK-040 11 Kosice, Slovakia.
Phone: +421.55.2354132, Fax: +421.55.6428935

Left ventricular hypertrophy (LVH) is nowadays considered an early marker of cardiomyopathy in patients with chronic kidney disease (CKD) (6). By the time a maintenance dialysis is instituted, 69 to 89 % of the paediatric patients have an evidence of LVH (7–11). To a certain extent, the differences in prevalence of LVH among studies can be explained by the way how LVH is assessed (12, 13). Some studies suggest an improvement after kidney transplantation (KTx), while others do not (14, 15).

Intraindividual changes of the left ventricular mass index (LVMI) over time may be influenced by several factors. Some studies suggested an impact of changes in blood pressure (BP) (7, 14–19). In contrast, other studies did not find an association between BP and left ventricular mass (LVM) in children and suggested other contributing factors, such as body mass index (BMI), haemoglobin level, or the influence of medication (20, 21). Our centre added to this evidence previously (22, 23). The aim of the current study was to describe changes in LVH in children and adolescents with ESRD over time, related to the moment of successful KTx and to assess whether clinical variables are associated with LVMI changes.

Methods

Patients

We obtained the records of all children and adolescents followed-up at the tertiary nephrology centre for children at the

Children's University Hospital in Kosice, Slovakia during 2008–2014. Patients, who had been prospectively followed by the echocardiographic studies while on chronic dialysis (post-dialysis) and had already undergone a successful KTx were eligible for the analysis (n = 25). Two patients were excluded because of congenital heart defect, leading to a final sample of 23 children. To study the influence of KTx on LVH at the individual level, we followed LVMI over time and compared the patients with an available measurement at approximately 6 months before KTx and with the second one performed approximately 2 years after a successful KTx. With this restriction, 17 pairs of measurements were available.

Measures

Data and data collection

Date of birth, gender, weight, height, serum creatinine, haemoglobin, blood pressure, medications, cause of ESRD, type of dialysis therapy, donor type (live or cadaveric), and the time from KTx were extracted from the medical records. Estimated GFR (eGFR) was calculated using the original Schwartz formula (eGFR = k x height/serum creatinine) (24) as the Jaffe method was used for the measurement of creatinine. The Schwartz formula from 2009 was not fitting suitably as it is recommended for an enzymatic measurement of creatinine. (25). Systolic and diastolic blood pressure (SBP, DBP) were measured using an auscultatory method with an appropriate cuff size, the lowest measurement was used for analysis. Blood pressure over the 95th percentile for age, gender and height defined the hypertension. (26). Uncontrolled hypertension was defined as blood pressure over this 95th percentile despite taking antihypertensive medication. Anaemia was defined as haemoglobin below 5th percentile for age and gender (27). Overweight status was defined as previously suggested as BMI over 85th percentile (28).

LVM was measured by a two-dimensionally guided and M-mode echocardiography (Esaote, MyLab50XVision), by one person, according to the criteria of the American Society of Echocardiography (29). The LVM index (LVMI) was calculated by indexing the LVM to height$^{2.7}$, as described previously (30). In this study, LVH was defined as the LVMI greater than the 95th percentile for normal children and adolescents (31). The cut-off of 45.0 g/m$^{2.7}$ was used for boys and 40.0 g/m$^{2.7}$ for girls older than 9 years. In children younger than 9 years, 95th percentiles were assessed according to the recently published age-specific reference data (12, 13). Severe LVH was defined as LVMI > 51 g/ m$^{2.7}$ (18). A clinically important change in the LVMI was defined as the relative change of greater than 20 % from the baseline value (15). Relative wall thickness (RWT) was measured to assess the LV geometric pattern (32). Patients with the LVMI > 95th percentile and elevated RWT (> 0.41) had a concentric LVH, those with the LVMI > 95th percentile and normal RWT (< 0.41) had an eccentric LVH. Concentric remodelling was defined as an elevated RWT, but with a normal LVMI.

Statistical analyses

Firstly, we assessed the background characteristics of the sample. Secondly, we assessed the LVMI and the presence/absence of LVH. Thirdly, we assessed whether a successful transplantation was associated with major changes in LVMI and compared the LVMI between the patients with and without risk factors. We used the paired Mann – Whitney U-tests to compare the means for continuous variables pre- and post-transplant, and the Fisher's exact test for categorical variables. The p value of < 0.05 was considered statistically significant. Values are expressed as the mean ± standard deviation. SPSS 20.0 and SAS 9.1 were used for the statistical analyses.

Results

Characteristics of the patients

Seventeen patients (10 males) were enrolled in this study, 9 with a congenital primary renal disease. Eleven patients were treated by the means of haemodialysis (HD), 1 was on peritoneal dialysis (PD) and in 5 patients, both modalities were used before KTx. The average time spent on dialysis before KTx was 19 ± 6 months and the average age at transplantation was 11.3 ± 3.6 years. None of the patients included was transplanted pre-emptively,

Tab. 1. Characteristics of patients with echocardiographic measurement before and after KTx.

	At dialysis (n=17)	After KTx (n=17)	p
Age, years	10.6±3.6	13.2±3.6	<0.001
Time from KTx, months	-6.6±1.9	25.0±3.4	<0.001
Uncontrolled systolic hypertension	5 (29.4%)	6 (35.3%)	0.03
Uncontrolled diastolic hypertension	4 (23.5%)	3 (17.6%)	0.12
Overweight	1 (5.9%)	3 (17.6%)	0.18
Anaemia	5 (29.4%)	4 (23.5%)	0.05
CaxP >4.4	4 (23.5%)	0 (0.0%)	n.a.

KTx – kidney transplantation; GFR – glomerular filtration rate; BP – blood pressure; BMI – body mass index; CaxP – calcium phosphate product; n.a. – not applicable

Tab. 2. Echocardiographic parameters in patients before and after KTx.

	At dialysis (n=17)	After KTx (n=17)	p
IVSd, cm	0.83±0.16	0.89±0.17	0.03
LVEDiD, cm	3.95±0.69	4.32±0.69	<0.001
LVPWd, cm	0.65±0.13	0.72±0.14	0.23
RWT, cm	0.34±0.08	0.33±0.04	0.80
LVMI, g/m2.7	39.1±13.6	37.2±11.6	0.51
LVH (n, %)	4 (23%)	5 (29%)	0.05
LV geometry (n, %)			
Concentric LVH	0 (0%)	0 (0%)	n.a.
Eccentric LVH	4 (23%)	5 (29%)	0.05
Concentric remodelling	1 (6%)	1 (6%)	1.00
Normal	13 (77%)	12 (71%)	0.28

KTx – kidney transplantation; IVSd – interventricular septal thickness at diastole; LVEDiD – left ventricular end-diastolic diameter; LVPWd – left ventricle posterior wall thickness at diastole; RWT – relative wall thickness; LVMI – left ventricular mass index; LVH – left ventricular hypertrophy; n.a. – not applicable

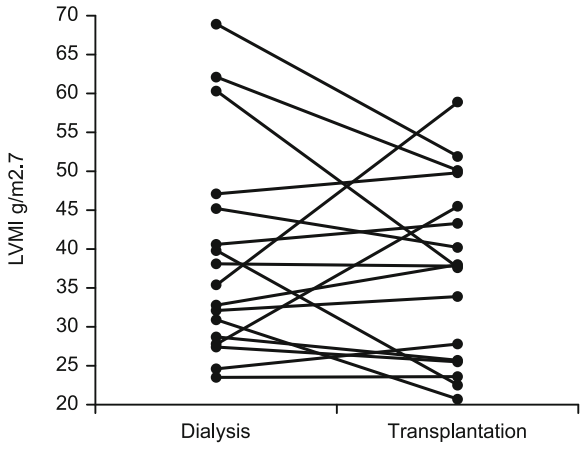

Fig. 1. Left ventricular mass index changes after transplantation. LVMI – left ventricular mass index.

two received the graft from a living donor. All the patients were receiving immunosuppressive therapy consisting of steroids and calcineurin inhibitors (2x cyclosporine, 15x tacrolimus) or sirolimus (1x) and mycophenolate (17x). Three patients had overcome a biopsy proven acute allograft rejection. The initial echocardiography was performed at the mean of 6.6 ± 1.9 months before KTx and the follow-up echo at 25.0 ± 3.4 months after KTx. At that time, the patients were taking on average 2.1 and 1.7 antihypertensive drugs per patient respectively. No significant changes in the number of cases with uncontrolled hypertension, overweight and anaemia were present over this period (Tab. 1).

Left ventricular hypertrophy and echocardiographic indices

The average prevalence of LVH in the patients while on dialysis was 23.5 %, and it was 29.4 % after KTx (p = 0.06) (Tab. 2). However, per patient substantial changes occurred (Fig. 1). Out of 4 children, who initially had LVH (2 severe LVH), 1 converted to normal LVMI. Out of 13 children with initially normal LVMI while on dialysis, two developed LVH after transplantation (one of them severe LVH). Of the two patients, who initially had severe LVH, 1 continued to have severe LVH at the second evaluation, the other one improved but continued to have LVH. One more patient had severe LVH at the second evaluation, in this patient, LVH was not present before KTx.

The prevalence of the subtypes of LVH (concentric or eccentric) before and after KTx did not change significantly. LVMI changed more than 20 % in 6 patients (35.3 %; 4 times decreased, 2 times increased) (Fig. 1), but the change of the mean LVMI overall was not significant (39.1 ± g/m$^{2.7}$ vs 37.2 ± g/m$^{2.7}$, p = 0.51). A significant increase in the mean value of the interventricular septum thickness (IVS) and left ventricular end-diastolic diameter (LVEDD) was observed after KTx.

Risk factors

The values of LVMI associated with the absence or presence of clinical variables are shown in Table 3. Male gender and uncontrolled systolic hypertension were associated with a higher LVMI with a statistical significance.

Tab. 3. LVMI and clinical variables in 34 measurement points.

	LVMI	LVMI	p
Gender; males/females	43.3±12.2	28.8±6.1	<0.001
Systolic hypertension; un/controlled	53.5±13.4	37.7±10.3	0.04
Diastolic hypertension; un/controlled	47.1±19.2	38.6±8.7	0.22
Anaemia; +/-	44.6±10.5	36.7±11.7	0.13
Overweight; +/-	53.7±9.3	38.5±11.2	0.07
CaxP; >4.4 / <4.4	41.5±15.7	39.8±11.5	0.77
CKD; stage 5 / stage 1-4	39.1±13.6	38.9±11.2	0.97

LVMI – left ventricular mass index; CKD – chronic kidney disease

Discussion

We followed the changes in LVMI in children and adolescents with ESRD over time, connected them with successful KTx and assessed whether the clinical variables were associated with LVMI. We found that LVH remained a common problem in ESRD children and adolescents even after a successful KTx, and that overall, the prevalence of LVH did not change significantly after transplantation. On dialysis, 23.5 % of children had LVH compared to 29.4 % after KTx. On the individual level, substantial changes occurred. Six out of 17 patients (35.3 %) had a change in LVMI of more than 20 % after KTx (four improvements and two worsening).

The published prevalence of LVH in CKD children varies widely, from 8 to 82 % (3, 15, 17, 33). To a considerable extent, differences among the studies may be explained by the cut-off used regarding LVH. Recently published cut-offs to define the differences from the norm based on age and gender specific 95th percentiles were used in this study to denote LVH (12, 13). Studies using this more conservative approach have reported rather similar prevalence as our study (14, 34) The use of the old criteria in our study would have led to a prevalence of 41.2 % and 47.1 % before and after KTx, respectively (35).

Significant changes of LVMI over time on the individual level have been described previously as well (15, 18, 36.) The core issue, the predictors of the change of LVM, are however not yet understood. One might assume that a substantial increase in glomerular filtration rate after KTx would *per se* lead towards a considerable regression of hypertrophy in a vast majority of the individuals. However, only studies of Becker-Cohen showed a substantial overall decrease of LVMI after KTx (14, 16). This decrease was shown to be a consequence of good blood pressure control, not the result of improvement of uremic milieu *per se (*14). In our study, a significant increase of eGFR after KTx was not associated with a significant improvement of LVMI (Tab. 1) and no association of LVMI with eGFR was present regardless of patient status (with or without graft) (Tab. 3). In contrast, findings of a big Dutch sample of 140 young adults with ESRD from childhood have confirmed that LVMI is significantly higher

in the patients with poor functioning grafts using the cut-off of 25 ml/min/1.73 m^2 (37). The studies of Foley, Alvarez as well as recent Japanese cohort of 26 paediatric patients have emphasized the malignant influence of the prolonged uremia onto the myocardial architecture what underlines the essential importance of a short waiting time for KTx (38–40). Also the duration of the course of CKD before establishing a renal replacement therapy may play a fundamental role in the development of LVH (41).

In adults, LVMI correlates with height, lean body mass, BMI, blood pressure, haemoglobin and other factors (39, 42, 43). In children, increasing height and lean body mass seems to be a driving force of growth of the mass of the left ventricle, but less is known about the factors and mechanisms and their importance under the pathologic circumstances e.g. CKD, due to its relatively rare occurrence in children (31, 35). In our study, patients with an uncontrolled systolic hypertension were found to have a significantly higher LVMI. This is in accordance with the largest paediatric study on LVH after KTx, which showed a relative risk for LVH of 19.7 in hypertensive patients ($p = 0.004$) (20). Also the studies of Becker-Cohen et al, Johnstone et al and Kitzmueller et al found a relation between LVMI and BP and emphasized that a good blood pressure control after KTx may lead to a decrease of LVH prevalence (7, 16, 19) On the other hand, Matteuci et al. reported a very high prevalence of LVH (82 %) despite a relatively low prevalence of hypertension (36 %) what might suggest the importance of other factors. They themselves hypothesized that hypertension may not be sufficient for the development of LVH in recipients of grafts (17). However, a higher cut-off for denoting LVH may have added to over-attribution of LVH in that study. Finally, the previously mentioned Czech study surprisingly did not find the relation of blood pressure and LVH even with 24 hours ambulatory blood pressure monitoring (45). In sum, most of the studies relate hypertension to LVH although data are scarce and sometimes contradictory.

No association between LVMI and overweight was found in our sample. In the study of Bullington et al, BMI independently predicted the presence of LVH, what was explained as being a consequence of hypercirculation frequently seen in overweight individuals (18) Studies comparing LVMI in obese hypertensive children and in those with hypertension alone showed a higher LVMI in obese individuals (46, 47) The influence of BMI was, however, not found in the paediatric study of Becker-Cohen (14)

In this study, anaemia was found to have no clear association with LVMI. In our previous study, anaemia had a statistically borderline relation with the increased serum level of brain natriuretic peptide, a marker of heart remodelling. A bigger sample size might have yielded a statistical significance as in the study of El-Husseini et al. who showed anaemia to independently predict the development of LVH. An eccentric pattern of LVH, that was shown to be a consequence of anaemia according to some studies, dominated in our sample. This was similar to the studies of Mitsnefes et al and Bullington et al, where the eccentric pattern of LVH was more common than the concentric one even after the improvement in the anaemia prevalence at the follow-up (15, 18 ,48–50).

Strengths and limitations

The strength of this study is that it covers all the patients from one region of eastern Slovakia although the number of patients for analyses was small. Information is based on the records from one centre, which led to a large consistency in the way of recording. The limitation was that blood pressure was not measured by the means of 24 hours ambulatory blood pressure monitoring. The effect of KTx may change in time due to a better care, thus perhaps some underestimation may have occurred of the effects of current KTx.

Implications

We found that LVH was a common problem after pediatric KTx. Although we did not find a major change in LVMI after KTx overall, we found relatively many changes at the individual level. This suggests differences in the control of risk factors for the development of LVH. Thus, rigorous management of (systolic) blood pressure and possibly anaemia or other risk factors may have a positive impact on cardiovascular morbidity and mortality in recipients of KTx in childhood and adolescence. Larger longitudinal studies are needed to precisely identify the impact of uncontrolled BP, anaemia, obesity and other factors and its duration on geometry of LV and the degree of a possible reversibility of LVH when correction of these factors occurs.

Conclusion

In summary, we demonstrated that LVH is common after pediatric KTx. Despite the overall poor reversibility of LVH after transplantation, significant changes of LVMI are present on the individual level which might be explained by a different control of (systolic) hypertension and other risk factors.

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Received October 24, 2021.
Accepted November 19, 2021.