Etiology and prognosis of chronic kidney disease in children: Roma ethnicity and other risk factors

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Chapter 7

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

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Submitted

Abstract

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

Methods
We obtained records of all children and adolescents who were followed-up at the tertiary nephrology center 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 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 with LVMI (p=0.03).

Conclusion
LVH is common after pediatric 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 thorough control of (systolic) hypertension and of other risk factors.

Keywords: left ventricular hypertrophy, children, transplantation, chronic kidney disease

Introduction

Pediatric 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, 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 (U.S. Renal Data System 2011). According to these data from the United States 22-32% of this mortality excess may be explained by cardiovascular disease (U.S. Renal Data System 2011). Studies from other countries similarly showed that 40%-50% of all deaths among dialysis and transplantation patients can be attributed to cardiovascular or cerebrovascular causes (Oh et al. 2002; Schwartz et al. 2009). Uremic cardiomyopathy, stiffening of the vessels due to calcifications and premature atherosclerosis all contribute to this excessively increased cardiovascular risk.

Left ventricular hypertrophy (LVH) is nowadays considered to be an early marker of cardiomyopathy in patients with chronic kidney disease (CKD) (Mitsnefes 2012). By the time maintenance dialysis is instituted, 69 to 89% of the pediatric patients have evidence of LVH (Johnstone et al. 1996; Mitsnefes et al. 2001; Mitsnefes et al. 2003; Mitsnefes et al. 2006; Furth et al. 2011). To a certain extent the differences in prevalence of LVH among studies can be explained by the way how LVH is assessed (Foster et al. 2008; Khoury et al. 2009). Some studies suggest improvement after kidney transplantation (KTx) while others do not (Mitsnefes et al. 2001; Becker-Cohen et al. 2008).

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) (Matteucci et al. 1999; Mitsnefes et al. 2001; Kitzmueller et al. 2004; Becker-Cohen et al. 2006; Bullington et al. 2006; Becker-Cohen et al. 2008). In contrast, other studies did not find an association between BP and left ventricular mass (LVM) in children and suggested other contributing factors like body mass index (BMI), hemoglobin level, or the influence of medication (El-Husseini et al. 2004; Mitsnefes et al. 2004). Our center has added to this evidence previously (Hedvig et al. 2010). 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 records of all children and adolescents followed-up at the tertiary nephrology center for children at the Children's University Hospital in Kosice, Slovakia during 2008-2014. Patients who had previously completed echocardiographic studies while on chronic dialysis and had already undergone a successful KTx were eligible for 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 patients with available measurement at approximately 6 months before KTx and with the second one performed approximately 2 years after successful KTx. With this restriction 17 pairs of measurements were available.

Measures

Data and data collection

Date of birth, gender, weight, height, serum creatinine, hemoglobin, blood pressure, medications, cause of ESRD, type of dialysis therapy, donor type (live or cadaveric), and 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; Schwartz et al. 1976) as the Jaffe method was used for the measurement of creatinine. The recently published Schwartz formula was not fitting suitably as it is recommended for an enzymatic measurement of creatinine (Schwartz et al. 2009). 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 hypertension (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004). Uncontrolled hypertension was defined as blood pressure over this 95th percentile despite taking antihypertensive medication. Anemia was defined as hemoglobin below 5th percentile for age and gender (Koshy 2008). Overweight status was defined as previously suggested as BMI over 85th percentile (Barlow et al. 2007).

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 (Devereux and Reichek 1977). The LVM index (LVMI) was calculated by indexing of LVM to height$^{2.7}$, as described previously (DeSimone et al. 1992). In this study, LVH was defined as an LVMI greater than the 95th percentile for normal children and adolescents (DeSimone et al. 1995). A cutoff of 45.0g/m$^{2.7}$ was used for boys and 40.0g/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 (Foster et al. 2008; Khoury et al. 2009). Severe LVH was defined as LVMI >51g/ $m^{2.7}$(Bullington et al. 2006). A clinically important change in the LVMI was defined as a relative change of greater than 20% from the baseline value (Mitsnefes et al. 2001). Relative wall thickness (RWT) was measured to assess the LV geometric pattern (Ganau et al. 1992). Patients with a LVMI >95^{th} percentile and elevated RWT (>0.41) had a concentric LVH, those with a LVMI >95^{th} percentile and normal RWT (<0.41) had an eccentric LVH. Concentric remodeling was defined as an elevated RWT, but with a normal LVMI.

Statistical analyses

First, we assessed background characteristics of the sample. Second, we assessed the LVMI and the presence/absence of LVH. Third, we assessed whether successful transplantation was associated with major changes in LVMI and compared LVMI between patients with and without risk factors. We used paired Mann Whitney U-tests to compare means for continuous variables pre- and post-transplant, and Fisher's exact test for categorical variables. A 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 congenital primary renal disease. Eleven patients were treated by means of hemodialysis (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±6months and the average age at transplantation was 11.3±3.6 years. None of the patients included was transplanted pre-emptively, two received a graft from a living donor. All 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 a 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 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 anemia were present over this period (Table 7.1).

Table 7.1 Characteristics of patients with echocardiographic measurement before and after KTx

	At dialysis (n=17)	After KTx (n=17)	P value
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
Anemia	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

Left ventricular hypertrophy and echocardiographic indices

The average prevalence of LVH in patients while on dialysis was 23.5%, and it was 29.4% after KTx (p=0.06) (Table 7.2). However, per patient substantial changes occurred (Figure 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.

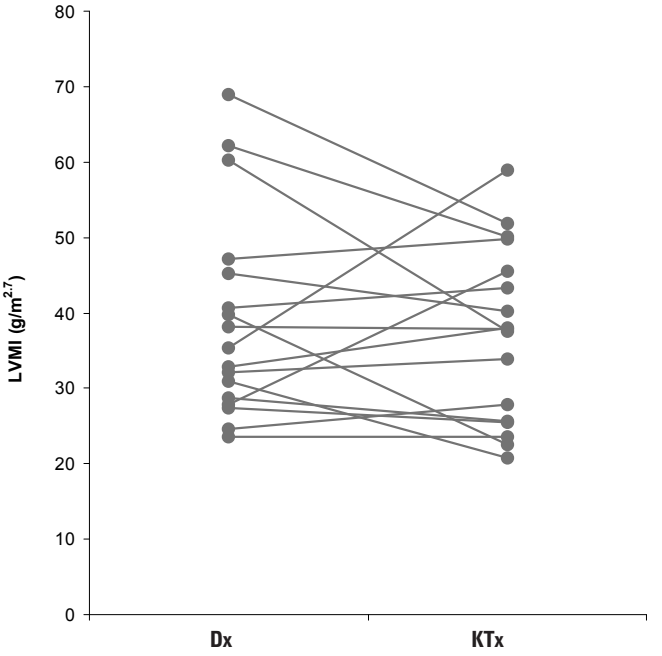
The prevalences of the subtypes of LVH (concentric or eccentric) before and after KTx did not change significantly. LVMI changed more than 20% in 6 patients (35.3%; 4 times decreased, 2 times increased; Figure 1), but the change of the mean LVMI overall was not significant (39.1± g/m$^{2.7}$ vs. 37.2± 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.

Table 7.2 Echocardiographic parameters in patients before and after KTx

	At dialysis (n=17)	After KTx (n=17)	P value
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, $g/m^{2.7}$	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 remodeling	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 ventricule posterior wall thickness at diastole; RWT – relative wall thickness; LVMI – left ventricular mass index; LVH – left ventricular hypertrophy; n.a. – not applicable

Figure 7.1 Intraindividual changes of left ventricular mass index after KTx.



Dx - dialysis
KTx - kidney transplantation

Risk factors

The values of LVMI associated with the absence or presence of clinical variables are shown in Table 7.3. Male gender and uncontrolled systolic hypertension were associated with a higher LVMI with statistical significance.

Table 7.3 LVMI and clinical variables in 34 measurement points

	LVMI	LVMI	P value
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
Anemia; +/-	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 clinical variables were associated with LVMI. We found that LVH remains 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 occur. Six out of 17 patients (35.3%) had a change in LVMI of more than 20% after KTx (four improvements and two worsenings).

Published prevalences of LVH in CKD children vary widely, from 8 to 82% (Johnstone et al. 1996; Matteucci et al. 1999; Kaidar et al. 2014; Mitsnefes et al. 2001). To a considerable extent differences among studies may be explained by the cutoff used regarding LVH. Recently published cutoffs to define differences from the norm based on age and gender specific 95th percentiles as used were used in this study to denote LVH (Foster et al. 2008; Khoury et al. 2009). Studies using this more conservative approach have reported rather similar prevalences as ours (Becker-Cohen et al. 2008; Kaidar et al. 2014). 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 (Daniels et al. 1995).

Significant changes of LVMI over time on the individual level have been described previously as well (Mitsenefes et al. 2001; Mitsnefes 2004; Bullington et al. 2006). 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 (Becker-Cohen et al. 2006; Becker-Cohen et al. 2008). This decrease was shown to be a consequence of good blood pressure control, not the result of improvement of uremic milieu *per se* (Becker-Cohen et al. 2008). In our study a significant increase of eGFR after KTx was not associated with significant improvement of LVMI (Table 7.1) and no association of LVMI with eGFR was present regardless of patient status (with or without graft; Table 7.3). In contrast, findings of a big Dutch sample of 140 young adults with ESRD from childhood have confirmed that LVMI is significantly higher in patients with poor functioning grafts using a cutoff of 25ml/min/1.73m^2 (Gruppen et al. 2003). Foley and Alvarez 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(Foley et al. 1995; Alvares et al. 1998). Also the duration of the course of CKD before establishing renal replacement therapy may play a fundamental role in the development of LVH (Weaver et al. 2009).

In adults, LVMI correlates with height, lean body mass, BMI, blood pressure, hemoglobin and other factors (Foley et al. 1995; Liao et al. 1997; Devereux and Roman 1999). 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 pathologic circumstances e.g. CKD, due to its relatively rare occurrence in children (DeSimone et al. 1995; Daniels et al. 1995). In our study, patients with uncontrolled systolic hypertension were found to have significantly higher LVMI. This is in accordance with the largest pediatric study on LVH after KTx which showed a relative risk for LVH of 19.7 in hypertensive patients (p=0.004) (El-Husseini et al. 2004). Also studies of Becker-Cohen et al., Johnstone et al. and Kitzmueller et al. found a relation between LVMI and BP and emphasized that good blood pressure control after KTx may lead to a decrease of LVH prevalence (Johnstone et al. 1996; Becker-Cohen et al. 2006; Kitzmueller et al. 2004). 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 (Matteucci et al. 1999). However, a higher cutoff for denoting LVH may have added to over-attribution of LVH in that study. Finally, the previously mentioned Czech study surprisingly did not find relation of blood pressure and LVH even with 24 hour ambulatory blood pressure monitoring (Seeman et al. 2006). In sum, most of the studies relate hypertension with 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 (Bullington et al. 2006). Studies comparing LVMI in obese hypertensive children and in those with hypertension alone showed higher LVMI in obese individuals (Hanevold et al. 2004; Richey et al. 2010). The influence of BMI was, however, not found in the pediatric study of Becker-Cohen (Becker-Cohen et al. 2008).

In this study anemia was found to have no clear association with LVMI. In our previous study anemia had a statistically borderline relation with the increased serum level of brain natriuretic peptide, a marker of heart remodeling. A bigger sample size might have yielded statistical significance as in the study of El-Husseini et al. who showed anemia to independently predict the development of LVH. An eccentric pattern of LVH, that was shown to be a consequence of anemia 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 improvement in the anemia prevalence at the follow-up (Greaves et al. 1994; Hayashi et al. 2000; Mitsnefes et al. 2001; Levin 2002; Bullington et al. 2006).

Strengths and limitations

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

Implications

We found that LVH is 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 control of risk factors for the development of LVH. Thus, rigorous management of (systolic) blood pressure and possibly anemia 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, anemia, obesity and other factors and its duration on geometry of LV and the degree of 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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Conflict of interest statement

None declared.

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