Original Article

Cardiac Abnormalities in the Iranian Pediatric and Adolescent Population with Chronic Renal Failure

Ali Akbar Zeinaloo, MD*, Abbas Madani, MD, Mohammad Taqi Haqi Ashtiani, MD, PhD

Children's Hospital Medical Center, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Background: *It has been well documented that left ventricular hypertrophy (LVH) is an independent factor for cardiac death in children. The epidemiologic information reveals that there is a very high prevalence of LVH in children with chronic renal failure (CRF). The purpose of this study was to evaluate the existence of left ventricular hypertrophy, its severity and other cardiac abnormalities in children and young adults with chronic renal failure (CRF), end stage renal disease (ESRD) on hemodialysis (HD) or post renal transplantation (RTx).*

Methods: *Sixty-three patients including 31 females and 32 males aged 1 to 18-year- old with defined causes for renal damage were enrolled in the study. Study patients were distributed in three groups: HD (n=45), CRF (9) and RTx (9). LVH and degree of hypertension were compared with an age and sex-matched control group (63 normal individuals). Left ventricular mass indexed for height (LVM/Ht and LVM/$Ht^{2.7}$) and body surface area (LVM/BSA), and other related parameters were determined by echocardiography in both groups. Laboratory investigations were carried out at a reference laboratory for the study group.*

Results: *The index of LVM/BSA in CRF group was more (r=0.765) than the control group. The HD patients had significantly higher LV systolic and diastolic dimensions. Analysis of variance (ANOVA) showed the influence of groups on subject score on the LVM. A significant effect of groups on the mean score on the LVM was noted. An important finding of this study was the correlation between serum creatinine and LVM in the HD and RTx subjects by both linear and multiple regression analyses. There was also significant difference amongst groups with respect to blood parameters, which is discussed.*

Conclusion: *This study demonstrates that left ventricular hypertrophy and cardiac abnormalities are frequent findings in children with renal impairment or ESRD. The degree of hypertrophy is often severe, particularly following transplantation. Further studies to clarify the relationship between biochemical disturbances and ventricular abnormalities are suggested.*

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Keywords: *Left ventricular mass • Cardiac abnormalities • End stage renal disease • Children and young adult*

Introduction

Chronic renal failure (CRF) is a major cause of morbidity and mortality in children. The prevalence and incidence of chronic renal failure in children has been reported in some countries. For instance, a recent study in Italy reported the

Corresponding Author:** ***Ali Akbar Zeinaloo*, Department of Pediatric Cardiology, Children's Hospital Medical Center (Markaz Tebbi Koodakan), Tehran University of Medical Sciences, Tehran, Iran. 1413914711. Tel: +98 21 66921185, 66911029. Fax: +98 21 88792552. E-mail: zeinaloo@tums.ac.ir.*

mean incidence of CRF as 12.1 cases per million, and the point prevalence as 74.7 per million of the age-related population.[1] It has been well documented that left ventricular abnormalities are frequent in children with end-stage renal disease. It has been shown that cardiovascular diseases cause 41% of deaths in less than 15- year-old children with renal failure[2,3,4] to our knowledge, little has been written concerning the cardiac abnormalities in RF patients undergoing renal transplantation at a young age across the world. Young patients with end – stage renal disease (ESRD) suffer from an excessive cardiovascular mortality, which is increased 70-fold in patients undergoing dialysis and more than 10-fold after renal transplantation. Chronic renal failure is associated with hypertension, dyslipidemia, hyperphosphatemia, chronic inflammation, uremic toxins, hyperparathyroidism, hypoalbuminemia, hyperhomocysteinemia, severe chronic anemia and acid–base abnormalities which may in time lead to cardiovascular complications. Accelerated coronary arteropathy, manifested as myocardial dysfunction significantly contributes to morbidity and mortality in these children.[5,6,7] the precise pathophysiology of cardiac involvement and myocardial dysfunction in CRF are not clear. To date, no studies adequately illuminate the role of any of these factors in the development of myocardial dysfunction in children. However it has been reported that cardiomyopathy in chronic uremia results from pressure and volume overload,[7,8] and increased patients' survival due to the advances in renal replacement therapy have subjected these children to prolonged exposure to multiple cardiovascular risk factors.[9] Anemia has been associated with an increase in left ventricular mass (LVM) and with increased LV end diastolic diameter (LVdD) in hemodialysis patients and the correction of anemia by erythropoietin was followed by a decreased in ventricular volume and mass. The effect of rHuEpo on the myocyte cells appear to be related to the capacity of erythropoietin to stimulate Na, K^+ -ATPase activity, likely secondary to the activation of tyrosine kinase and protein kinase C.[10,11] Although the etiologies for altered myocardial structure and performance in renal failure are multiple, there is evidence suggesting that disturbance of calcium, phosphorus and vitamin D metabolism caused by secondary hyperparathyroidism may play important roles in uremic cardiovascular disease.[12] Further study demonstrated the high prevalence of LVH in patients with predialysis CRF with concentric hypertrophy as the main pattern of LVH.[13,14,15] It should be noted that a report on management of renal failure in children in Europe indicated that 30% of children on continuous ambulatory peritoneal dialysis and 22% of transplant children had left ventricular abnormalities on echocardiographic examination.[16,17] In Iran, there is no empirical evidence to evaluate LVH in pediatric chronic renal failure and its relation with factors such as anemia, blood pressure, hyperparathyroidism, which may influence Left Ventricular mass index. The purpose of this cross-sectional study was to investigate left ventricular hypertrophy, its severity and other patterns of cardiac abnormalities in children and young adults with chronic renal failure (CRF), end stage renal disease (ESRD) on medication, hemodialysis (HD) or post renal transplantation (RTx).

Methods

Patients

Sixty three CRF patients on hemodialysis (HD) (n=45), CRF on medication (n=9) and RTx (n=9) were studied. Patients consisted of 31 females and 32 males with age between 1 and 18-year old, Inclusion criteria for CRF group were existence of CRF with serum creatinine greater than 2 SD above the mean for age persisting for at least six months and a defined cause for renal damage. The HD group had arterio-venous fistula, and were treated with r-HuEPO (EPReX), folic acid and active vitamin D supplements. In the transplant group, 7 patients had received Living related (matched) grafts and two had cadaveric grafts. The median time following transplantation at the time of study was 2.6 years (range: 0.8-5.2 years). Eight of nine patients in the RTx group used prednisone, Two out of 9 consumed Adalat and four were treated with Cyclosporine and Imuran. Existence of LVH and level of hypertension in the study patients were compared with 63 normal subjects including 29 females and 34 Males aged between 2 and 18 years as the control group.

Design

A cross -sectional study was carried out in a Tehran University affiliated hospital over a two- year period. All echocardiogarphic examinations were performed by an expert pediatric cardiologist using a Vingmed 750 ultrasound machine. M-mode measurements were performed according to recommendations of the American Society of Echocardiography (ASE).[18] Echocardiograms were recorded on the tape by the investigator and two expert pediatric cardiologists examined the tracings to measure the following parameters: left ventricular end diastolic dimension (LVdD), left ventricular end systolic dimension (LVsD), ventricular posterior wall thickness (PWT), interventricular septal thickness (IVS), aortic root (AR) diameter, left atrial (LA) dimension, fractional shortening (FS), Ejection fraction (EF) and diastolic mitral inflow measuring; peak E wave flow and peak A wave flow and E:A ratio(E/A). Diastolic initial inflow velocities were measured by pulsed wave Doppler at the tips of the mitral valve leaflets, with the opening click of the mitral valve just audible.Valvular abnormalities were noted when present.[19] Left ventricular mass was determined by M-mode echocardiography using the following formula: LVM (gm)= $0.8\{1.04[(LVdD + PWT+IVS)^3 - (LVdD)^3\}+0.6$(gm).[20] Left ventricular size was measured at or just below the tips of the mitral valve leaflets at the largest left ventricular internal dimension. LVdD and PWT measurement were made at end-

diastole. LVM was also indexed according to the algometric regression equation described by de Simone et al.[21] This indexes LVM by Ht.$^{2.7}$ LVH was also defined as measurements Greater than the 95% confidence limit following indexing of LVM by Ht.$^{2.7}$ the patients were classified to four groups (Group1: HD, Group 2: RTx, Group3: CRF, Group 4: normal). Direct measurements were compared between subjects and controls for LVM, LVM/Ht, LVM/ Ht$^{2.7}$ and LVM/SA. Body surface area (BSA) was calculated based on the formula: BSA (m^2) $=\sqrt{H * Wt/3600}$ [21] Laboratory investigations including hemoglobin, urea, creatinine, calcium, phosphate, alkaline phosphatase, albumin, triglyceride, cholesterol, parathyroid hormone, glucose, uric acid, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were all carried out at a reference laboratory.

Statistical analysis

All data were analyzed as mean ± SD. Analysis of variance (ANOVA) and Pearson's correlation analysis were used. All tests were considered significant if they met the $P<0.05$ level. In multiple comparisons a P value < 0.01 was considered significant.

Results

Echocardiographic and laboratory abnormalities of 63 patients aged 1 to 18 years old were studied. All cardiac parameters were compared with same age healthy people. The demographic characteristics and main independent varieties of subjects are given in table 1; the causes of the renal disease of the CRF, HD and RTx groups are showed in table 2 and the status of blood pressure in different subjects is presented in table 3,

Table1. Demographic characteristics of the subjects

Groups of samples	HD	RTx	CRF	Control
Number of cases	45	9	9	63
Age (Mean) (yr) ± SD	12 ± 3.98	11.7 ± 4.02	10.1 ± 2.36	10. 6 ± 3.60
Female/Male (%)	21/24 (46.7/53.3)	6/3 (66.7/33.3)	4/5 (44.4/56.6)	29/34 (43.3/56.7)
Height (Mean) (cm) ± SD Min-Max	124.8 ± 14.89 74-153	128.3 ± 22.10 100-160	124.6 ± 12.93 108-144	124.2 ± 21.32 86-178
Weight (Mean)(kg) ± SD Min-Max	25.6 ± 7.28 8.5-42.5	31.1 ± 17.73 14.3-65.2	25.1 ± 6.45 18-39	26.3 ± 10.22 11-75.2
BSA (Mean) m^2 ± SD Min-Max	0.93 ± 0.18 0.56-1.3	1.02 ± 0.35 0.63-1.5	0.92 ± 0.16 0.74-1.2	0.95 ± 0.28 0.54-1.7

HD, Hemodialysis; RTx, Renal Transplantation; CRF, Chronic Renal Failure; BSA, Body Surface Area

Table 2. Causes of renal disease in the cases

Renal disease causes	HD	RTx	CRF	Total
Obstructive uropathy	4	-	-	4
Glomerulonephritis/Nephrosis	14	3	1	18
Urolithiasis	2	-	-	2
Nephrocalcinosis				
Nephronophthisis	1	1	-	2
Neurogenic bladder	2	-	-	2
Reflux nephropathy	6	-	5	11
Hemolytic Uremic Syndrome	5	2	-	7
Syndromes	6	3	2	11
Others	5	-	1	6
Total	45	9	9	63

HD, Hemodialysis; RTx, Renal Transplantation; CRF, Chronic Renal Failure

Table 3. The status of blood pressure in the cases

Blood pressure	HD	RTx	CRF	CONTRL
Mean systolic pressures mm Hg ± SD Min-Max	118.8 ± 24 190-90	144.3 ± 28 120-200	116 ± 26.4 90-160	101 ± 24.2 88-135
Mean diastolic pressures mm Hg ± SD Min-Max	± 17.4 .73 68-99	93. ± 12 70-110	74 ± 16 60-100	69.3 ± 17.3 60-80

HD, Hemodialysis; RTx, Renal Transplantation; CRF, Chronic Renal Failure

Systolic pressure in RTx group was significantly high. The results of biochemical and hematological studies are shown in table 4.

Table 4. Results of laboratory tests in the cases

Parameters	HD	RTx	CRF	Control
Albumin (g/dl) ± SD	± 0.6.4	± 0.3 4.4	± 0.6 3.6	± 0.3 4.3
Min-Max	5.2-2.2	5-3.9	4-2.5	4.8-3.7
AL-Phospha (u/L) ± SD	± 206 394.8	271.6 ± 52	354 ± 244.9	85 ± 42
Min-Max	999-70	350-200	214-990	25 -115
Hgb (g/dl) ± SD	± 2 8.3	± 0.9 10.8	± 1.3 8.5	12.9 ± 0.8
Min-Max	13-4.7	12-9.8	11-7	14.9-10.8
Urea (mg/dl) ± SD	± 23.3 60	± 11 34	± 18.5 109.4	12 ± 8
Min-Max	110-25	50-14	140-89	22-6
Creatinine (mg/dl) ± SD	± 1.8 6.8	± 0.33 1.3	± 1.6 .6	0.7 ± .4
Min-Max	10.5-3.8	1.8-0.8	10-4.4	1.1-0.3
Triglyceride (mg/dl) ± SD	± 68.35 163.5	± 28.18 132.7	± 75 178.8	90 ± 25
Min-Max	369-57	180-100	364-115	128-31
Cholesterol (mg/dl) ± SD	± 40.5 167.8	± 28.5 197.7	± 31.4 179.4	105 ± 33
Min-Max	279-71	240-160	235-142	187-65
PTH(mg/dl) ± SD	± 191 206.4	± 25 68.2	± 163 174.1	24 ± 12
Min-Max	967-24	110-33	297-80	48-11
Calcium (mg/dl) ± SD	± 8 9.1	± 0.5 8.9	± 1 8.3	8.8 ± 0.6
Min-Max	11-7.6	9.6-8.1	11-6.1	10-8.1
Phosphate (mg/dl) ± SD	± 2.4 6.5	± 0.8 5.1	± 1 6.3	4.2 ± .5
Min-Max	11.7-2.9	6.3-0.9	8-4.8	4.9-3.2
Uric acid(mg/dl) ± SD	6.2 ± 1.5	± 0.9 5.1	± 1 6.1	3.9 ±0.9
Min-Max	9.9-2.5	3.9-6.3	8-4.8	5.8-3.1

HD, Hemodialysis; RTx, Renal Transplantation; CRF, Chronic Renal Failure

Serum concentrations of blood urea and creatinine were significantly increased (P<0.003) in all three groups compared to control group, but these levels in RTx group were significantly lower than HD and CRF. Serum parathyroid hormone level was increased (P <0.05) in the CRF and HD groups compared to control group Hemoglobin level less than 10 g/dl was presented in 20 cases (44%) of the HD, 3 (33%) of the CRF group and one (11%) of RTx group. Triglyceride and cholesterol levels were RTx incrased in all diseased Groups.

There was no significant deference in other laboratory parameters between the patients and control group. Left ventricular dimensions, thicknesses and functional parameters (echocardiographic measurements) are presented in table 5. A consistent difference between the LV, LA and aortic root dimensions of the four groups was not found. However, IVS and PW thickness measurements were greater in the HD and RTx groups.

Table 5. Results of Echocardiographic findings

ECHO parameters	HD	RTx	CRF	Control
STI ± SD Min-Max	± 7.5 36.2 38.4-34	± 5.0 37.7 41.6-34	± 5.5 35.1 -39.3.30	38.8 ± 5.6 41.6-36
LVdD (cm) ± SD Min-Max	± 0.7 4.3 5.6-2.7	± 0.9 4.1 5.4-2.8	± 0.6 3.8 4.9-2.9	3.7 ± 0.5 4.6-2.6
LVsD (cm) ± SD Min-Max	± 0.7 2.8 4.2-1.2	± 0.9 2.9 4-1.8	± 0.4 2.3 2.9-1.7	± 0.4 2.3 3.3-1.2
IVS (cm) ± SD Min-Max	± 0.2 0.9 1.4-0.5	± 0.2 0.9 1.4-0.5	± 0.2 0.7 0.9-0.4	0.6 ± 0.1 0.9-0.4
PWT (cm) ± SD Min-Max	± 0.4 1.1 0.7-1.6	± 0.4 1.1 1.6-0.6	± 0.2 0.9 0.6-1.2	± 0.1 0.7 1-0.5
AR (cm) ± SD Min-Max	2.3 ± 0.3 2.2-2.4	± 0.4 2.3 2-2.7	± 0.3 2.1 2.3-1.8	2 ± 0.4 2.2-1.4
LA (cm) ± SD Min-Max	± 0.5 .3 3.2-2.9	± 0.5 3 -3.5.2	± 0.4 2.7 3.1-2.4	2.5 ± 0.3 2.8-2.3
EF (%)± SD Min-Max	± 7.0 70 72-67	± 9 67 75-60	± 5 74 75-60	72 ± 6.0 74-71
FS (%)± SD Min-Max	34 ± 7 32-26	± 7.0 31 25-37	± 7.0 38 43-33	36 ± 5 37-34
VCF(index) ± SD Min-Max	± 0.3 1.5 1.6-1.3	± 0.2 1.2 1.4-1.1	± 0.2 1.6 1.8-1.4	1.3 ± 0.1 1.4-1.2
E/A (Ratio) ± SD Min-Max	± 0.3 1.2 1.3-1.1	± 0.9 1.7 2.4-0.9	± 0.3 1.4 1.6-1.1	1.3 ± 0.1 1.5-1.1

HD, Hemodialysis; RTx, Renal Transplantation; CRF, Chronic Renal Failure; STI, Systolic Time Interval Of LV; LVdD, Left Ventricular End Diastolic Dimension; LVsD, Left Ventricular End Systolic Dimension; IVS, Interventricular Septal Thickness in diastole; PWT, Posterior Wall Thickness; AR, Aortic Root; LA, Left Atrial Dimension; EF, Ejection Fraction; FS, fractional shortening; VCF, velocity of fiber circumference shortening; E/A, E wave/A wave ratio

In all individuals the IVS: PW ratio was less than one with an average of 0.8:1, showing that the LV enlargement was concentric rather than asymmetric. Although the results of E and A waves` peak velocity and the E/A ratio were within the normal range for all subject groups, an increase in the E wave peak velocity was found in the RTx group and E/A ratio was significantly increased ($P<0.05$). With regard to left ventricular mass, echocardiographic me asurements and comparisons between groups are shown in Table 6.

Table 6. Left Ventricular Mass in the different groups

ID	INDICES	LVM	LVM/Ht$^{2.7}$	LVM/Ht	LVM/BSA
	Mean ± SD	151.8 ± 51.4	84.7 ± 34.1	± 40.3.121	164.6 ± 56.7
HD	Max	309.6	169.0	226	309.9
(N=45)	Min	78.6	24.8	43.5	60.4
	Mean ± SD	164±103.5	± 63 91.3	± 82.6 .130	175.8 ± 118.6
RTx	Max	322.6	207.5	248	346.9
(N=9)	Min	57.9	20.8	50.3	51.8
	Mean ± SD	90.4 ± 29.5	± 9.0 48.8	± 17.5 71.3	96.2 ± 20.6
CRF	Max	136.5	63.5	94.8	124.9
(N=9)	Min	56.6	35.2	48.0	69.1
	Mean ± SD	68.2 ± 26.4	± 15.2 38.3	± 15.8 .54	73.6 ± 22.2
CONTORL	Max	125	71.8	91.6	133
(N=63)	Min	26.4	17.3	24.2	35.6

HD, Hemodialysis; RTx, Renal Transplantation; CRF, Chronic Renal Failure; LVM, Left Ventricular Mass; BSA, Body Surface Area

The proportion of subjects with a value of LVM, LVM/Ht, LVM/BSA and LVM/HT$^{2.7}$ above the 95% confidence interval were significantly increased in HD and RTx groups, but only index of LVM/BSA in CRF group wasincreased compared to the control group. Transplant patients had significantly greater LVM, LVM/BSA and LVM/Ht$^{2.7}$ measurement than matched controls [LVM, 164 g, 67.9 to 322.6 g (mean, range); LVM/BSA, 175.8 g/m^2, 51.8 to 346.9 g/m^2 ,and LVM/Ht,$^{2.7}$ 91.3 g, 20.8 to 207.5 g in transplant patients ; LVM, 68.2 g, 26.4 to 125 g · LVM/BSA,73.5 g/m^2 ,35.6 to 133 g/m^2 , and LVM/Ht,$^{2.7}$38.3 g, 17.3 to 71.8 g for aged and sex matched controls; P‹0.05 , <0.003 and <0.05 respectively. Linear regression analysis of LVM indexed for height correlated with age, height and weight, also clinical and laboratory parameters carried out for each group, there was no significant correlation. Multiple regression analysis was used to assess the effect of independent variables on LVM, LVM/Ht, LVM/Ht$^{2.7}$ and LVM/BSA for the subjects and control groups. In the control group there was a moderate correlation between LVM and indexed LVM with independent varieties (Wt, age, Ht and BSA) (r=0.495) and in CRF the correlation was r =0.765 (except LVM/Ht$^{2.7}$), but this was not evident in other groups. In the RTx group there was a correlation between unindexed LVM and uric acid (r=0.625), cholesterol (r=0.685), triglyceride(r=0.885), creatinine (r=0.660), systolic blood pressure(r=0.715), PTH(r=-0.500), and in HD group this correlation was with creatinine(r=0.595). Analysis of variance (ANOVA) was used to determine the influence of groups on subjects' score on the LVM. A significant effect of groups on the mean score on the LVM (F=25.338; P=0.00) was noted. Post hoc analysis indicated that patients with RTx (X=164; SD=103.5) scored significantly higher than patients with HD (X=151.8; SD=51.4) and CRF (X=90.35; SD=29.5) A two-way between-groups analysis was conducted to explore the impact of sex and age on the LVM.

There was not a statistically significant main effect for sex and the interaction effect did not have statistical significance. Moreover, similar result was noted for height and weight on the LVM. Multiple logistic regression analysis was used to assess the effect of independent variables on LVM, LVM/Ht, LVM/Ht$^{2.7}$ and LVM/BSA The effect of medications on LVH was examined.Glucocorticoids are known to be associated with LVH. Eight of 9 of the RTx Group were the only subjects taking this medication. There was no correlation between LVM/Ht$^{2.7}$ and prednisolone dosage in the RTx group (r=0.48, p>0.05) and no difference in LVM/Ht between those who were or were not on prednisolone ([chi]^2=1.58, p>0.05). Similarly, in the RTx group again, there was no correlation between LVM/Ht and cyclosporine dose (r=0.089, p>0.05). Using multiple logistic regression analysis, no associations were found between the administration of antihypertensive medication and LVM/Ht and LVM/Ht $^{2.7}$ in the transplant group.

Discussion

The etiologies for altered myocardial structure and performance in renal failure are multiple and left ventricular abnormalities of renal failure are frequent in children with

end-stage renal disease. The main finding of this study was that the proportion of subjects with a value of above the 95% confidence interval LVM, LVM/Ht, LVM/BSA and LVM/$Ht^{2.7}$ were significantly increased in HD and RTx groups ,but only index of LVM/BSA in CRF group was increased compared to the control group. Transplant patients had significantly greater LVM, LVM/BSA and LVM/$Ht^{2.7}$ measurement than matched controls. In this study the most common causes of CRF were glomerulonephritis (GN) (28.5%), reflux nephropathy (17%) and Hemolytic Uremic Syndrome (HUS) (11%). Radi M, et al[22] studied 202 Jordanian children with mean age of 7.5 year with CRF and reported the urological abnormalities and malformations as the etiologic diseases in 42% of the of cases with CRF and hereditary renal disorders in 29.7%, GN in 14.4% and HUS in 4.5%. As shown in table 3, the transplant patients were more likely to be hypertensive than those in other groups. A greater proportion of individuals in this group required anti-hypertensive medication. Hypertension usually causes concentric ventricular hypertrophy which was found in this study. In the RTx group there was a correlation between unindexed LVM and systolic blood pressure(r=0.715), however, this study did not reveal a significant correlation between blood pressure and indexed LVM. Furthermore the AR and LA Dimensions were increased in the RTx group more than other diseased groups. Johnstone et al[13] reported that AR dimension was not increased in the RTx group more than other diseased groups. In hypertensive heart disease the AR is usually dilated. Fagard et al[23] on reviewing the literature found that correlation coefficients between LVM or LVM/Ht and blood pressure in the normal population were commonly less than 0.5, but this study suggests that hypertension is not the dominant cause of LVH in the under 18 renal transplanted patients. In our study transplant patients had significantly greater LVM, LVM/BSA and LVM/$Ht^{2.7}$ measurement than matched controls. Daniels et al[24] studied 334 young persons between the ages of 6 and 23 and determined the distribution of LVM, LVM corrected for height and LVM corrected for body surface area according to sex, no data were provided for LVM according to age. De Semine et al[25] determined 95% confidence intervals for LVM according to sex and height in 444 individuals ranging from four months to 23 years of age. In their studies the indexing of LVM to $Ht^{2.7}$ reduced the variability in LVM caused by weight differences better than indexing LVM to Ht or SA. It is well recognized in the pediatric age range that age, height and weight are all significantly associated with LVM. Johnstone et al [13] investigated 72 cases of children and young adults(less than 27 years old) with chronic renal failure and ESRD. In their study Left ventricular mass indexed for height was significantly increased in the chronic peritoneal dialysis (CPD) and transplant groups and further analysis using LVM/$Ht^{2.7}$ confirmed their finding and demonstrated an Increase in LVM in all three subject groups.

In contrast, in our study linear regression analysis of LVM indexed for height revealed no significant correlation and with multiple regression analysis, in the control group there was a moderately correlation between LVM and indexed LVM with independent varieties and in CRF the correlation was r=0.765 but this was not evident in other groups. Hemodialysis can alter cardiovascular function due to the presence of increased cardiac output associated with an arteriovenous fistula and to the larger changes in intravascular volume the patients experiencing pre- and post-dialysis.[26] in dialysis patients, lower hemoglobin levels are associated with increased requenc of LVH, possibly through renin-angiotensin activation. There is a 30% increased risk of developing LV mass for each 0.5 g/dl drop in hemoglobin.[27] In ESRD patients, the effect of rHuEpo on LVH may be dependent upon the degree of anemia prior to initiation of rHuEpo therapy.[28] Kyle J et al have suggested rHuEpo is safe and effective in reducing LVH and increasing hemoglobin level.[11] All the children studied by Morris et al were anemic (Hb < 9.0) and they had shown reduction in left ventricular mass following treatment with recombinant human erythropoietin.[2] In our study, a hemoglobin level of less than 10 g/dl was detected in 20 cases (44%) in spite of r- HuEpo (EPReX) and folic acid therapy in all of them. In our opinion, although erythropoietin has been used in all HD patients, there are two questions: the first is whether all the cases have received sufficient doses of rHuEpo and the second one is how the level of hemoglobin was prior to initiation of rHuEpo therapy. Left ventricular hypertrophy was found most frequently after renal transplantation. Renal transplantation resulted in correction of uremia, anemia and secondary hyperparathyroidism. These consequences would be expected to reduce the severity of LVH. The transplant patients were more likely to be hypertensive than those in the other groups. Most of the RTx group was on prednisolone at the time of the study and all had prednisolone in the first nine months following transplantation. Despite lack of a clear relationship between LVM indexed to Ht or $Ht^{2.7}$, there may have been an additive effect of steroid as reported in infants with lung disease or studies on exercise-induced cardiac hypertrophy.[30] Two of the patients in the Transplant group were treated with antihypertensive drugs and none of these patients received an angiotensin converting enzyme (ACE) inhibitor. The incidence of renin-angiotensin-aldosterone mediated hypertension is high in transplant patients, originating from the native kidneys, graft artery stenosis or chronic rejection.[31] there is a significant body of evidence in experimental animals that renin-angiotensin can cause myocardial hypertrophy and fibrosis.[32] Angiotensin converting enzyme inhibitors would be expected to block this effect. This class of drug is avoided after transplantation because of the possibility of existence of a relative stenosis in the single graft renal artery resulting in impaired renal functionusing induced by the ACE inhibitor. The result of this research is consistent with Johnstone et al[13] study. In our study, despite the more frequent finding of LVH in the RTx

group, an increase in the E wave peak velocity was found and E/A ratio was significantly increased (P<0.05). This may be a reflection of recovery of diastolic function in these patients. It has been shown that renal transplant recipients have less severe diffuse intermyocardiocytic fibrosis than patients with advanced chronic renal failure, suggesting some improvement with correction of uremia.[33] the combination of interstitial fibrosis and a reduction in capillary density may cause restrictive changes in myocardial compliance and ischemia. An important finding of this study was the correlation between serum creatinine and LVM in the HD and RTX subjects showed by both linear and multiple regression analyses, but no correlation was detected between urea level and unindexed and indexed LVM in diseased groups. Johnstone et al[13] reported correlation between serum creatinine and LVM in the CRF patients. Biochemical study in the cases (as shown in Table 4) revealed high levels of PTH, phosphate, alkaline–phosphatase, cholesterol, triglyceride, LDL, uric acid and hypocalcaemia or normocalcaemia in HD and CRF groups. In RTx group, uric acid, calcium and phosphate were within normal limits and PTH declined to near normal level. In the RTx group there was a correlation between Unindexed LVM and systolic blood pressure(r=0.715), uric acid (r=0.625), cholesterol(r=0.685),triglyceride(r=0.885),creatinine(r=0.0), PTH (r=.500).

Hyperphosphatemia is a predictable consequence of ESRD. There is growing evidence to suggest that abnormalities in serum phosphate, calcium–phosphate product and parathyroid hormone (PTH) levels are resulting in vascular and visceral calcification leading to increased risk of cardiovascular morbidity and mortality in these patients.[34] Secondary and tertiary hyperparathyroidism are often found to be independent risk factors for uremic calcification. PTH contributes to cardiovascular complications in many ways. It has a permissive role in arteriolar wall thickening myocardial interstitial fibrosis,[35] promoting hyperlipidemia and hypertension.[36] both primary and secondary hyperparathyroidism and their marker and elevated alkaline phosphatase level are also Associated with LVH and increased LV mass index. The mechanisms by which hyperparathyroidism could favor LVH are theoretically several and include direct trophic effects on myocardial cells and on interstitial fibroblasts and indirect effects such as an increase in blood pressure via hypercalcemia, anemia, and large and small vessel changes. PTH induces these changes by increasing protein synthesis and induction of creatine kinase and an elevation of the basal levels of cytosolic calcium on cardiac myocyte and induces toxic effects on the heart.[12,37] We believe many effects of PTH on myocardiocytes, cardiac small vessel cells, calcium accumulation and metabolism, myocardial hypertrophy and fibrosis could be reversed or prevented by Ca-channel blockade. Many investigators suggest the use of calcium channel blockers early in the course of renal insufficiency since it may be beneficial in reducing cardiovascular accumulation of calcium, thus decreasing the risk of calcifying of the myocardium, conduction system and small resistance arteries, thereby reducing the risk for myocardial ischemia, heart failure, arrhythmia, and death. Proper management of hyperparathyroidism would reduce the serum level of lipids and their pathologic effects on cardiac and vessel structures. Moreover, efforts should be made to reduce PTH secretion through strict phosphorus and oral supplementation with calcium or vitamin D derivatives into a range that is normal for uremic patients.

Conclusion

This study demonstrates that left ventricular hypertrophy is a frequent finding in children with renal impairment or ESRD. The degree of hypertrophy is often severe, particularly following transplantation. The finding of increased LVM could not be directly associated with hypertension even though hypertension was commonly found after transplantation, suggesting that other factors may be more important. Factors other than hypertension and uremia such as toxic effect of hyperparathyroidism and hyperphosphatemia, persistent profound chronic anemia, hyperlipidemia, are important. Follow-up Studies are required to determine the precise roles of these factors and the significance of increased LVM in premature cardiovascular morbidity and mortality among pediatric patients with chronic renal disease .Further studies to clarify the relationship between biochemical disturbances and heart abnormalities is suggested.

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