

## Large vessel disease in children with chronic kidney disease

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### Abstract

**Objectives:** To assess early atherosclerotic changes using echocardiography and to correlate with the clinical and biochemical parameters associated with chronic kidney disease (CKD).

**Method** A cross sectional study was carried out in a tertiary care hospital over a period of 2 years. All 45 children with CKD registered with the nephrology unit were assessed and 43 without congenital cardiac disease were included. Data regarding onset of CKD, stage of CKD, biochemical profile and carotid intima-media thickness (CIMT) measured by B-mode echocardiography were analysed in these children. Correlation of CIMT with the stage of CKD, biochemical and clinical parameters associated with CKD was the main outcome measured.

**Results:** Ninety percent of the patients had high CIMT. The mean CIMT was more in children with end stage renal disease (ESRD) ( $0.139 \pm 0.009$ cm vs  $0.112 \pm 0.007$ cm;  $p = 0.003$ ). There was a significant difference between the mean CIMT in normotensive patients ( $0.104 \pm 0.008$ cm) and well controlled systolic and diastolic hypertension [ $(0.134 \pm 0.009$ cm) and  $(0.132 \pm 0.009$ cm) respectively]. Mean CIMT in children with uncontrolled systolic and diastolic hypertension group ( $0.152 \pm 0.009$ cm) was higher as compared to the mean CIMT in patients well controlled hypertension and normotensive patients ( $0.116 \pm 0.006$ cm;  $p = 0.0214$ ).

**Conclusions:** CIMT is an echocardiographic marker for cardiovascular disease in CKD. Hypertension is the single most important risk factor associated with large vessel disease.

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### Introduction

Atherosclerosis is a known cause of cardiovascular events in adults<sup>1</sup>. It often starts in childhood and is associated with hypertension, obesity, and dyslipidaemia. Children with chronic kidney disease (CKD) have in addition altered mineral metabolism, which contributes to an increased risk of cardiovascular disease (CVD)<sup>2,3</sup>. The ensuing increased vascular stiffness and blood pressure (BP) also contribute to the increased frequency of hypertension and left ventricular hypertrophy in these children<sup>4</sup>. Early atherosclerotic changes include arterial wall stiffening and increased carotid intima-media thickness (CIMT), which can be reversed. An autopsy study of children with end-stage renal disease (ESRD), demonstrated that soft tissue and vascular calcinosis were highly prevalent<sup>5</sup>. Ultrasonography of carotid arteries is an alternate, noninvasive method of studying cardiovascular disease in adults<sup>6,7,8</sup>. However, CIMT assessment is not yet recommended to screen children at higher cardiovascular risk<sup>9</sup>. There is not much data about CKD in Indian children. This prompted us to conduct a study on large vessel disease in children with CKD and evaluate the various comorbid factors.

### Objectives

1. To evaluate early atherosclerotic changes using echocardiography and
2. To correlate with clinical and biochemical parameters associated with CKD.

### Method

This cross sectional study was carried out in a tertiary care multispecialty hospital in Mumbai after obtaining informed consent from all parents of children with CKD. Ethical approval for study was obtained from the institutional Ethics Committee.

All 45 children diagnosed with CKD as per standard definition<sup>10</sup> and registered in the nephrology unit were screened and 43 were selected for the study, 2 being excluded for having pre-existing cardiovascular disease. The selected patients were separated into 5 categories based on the stage of CKD as per standard terminology. The term end-stage renal disease (ESRD) was used for stage 5 children treated with dialysis or kidney transplantation<sup>10</sup>. This is shown in Table 1.



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**Table 1: Standard terminology for stages of chronic kidney disease**

Stage	Description	GFR (ml/min/1.73m <sup>2</sup> )
1	Renal damage with normal or increased GFR	>90
2	Renal damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	5-29
5	Renal failure	<15 or on dialysis <sup>10</sup>

GFR: Glomerular filtration rate

For estimation of kidney function the following formula was used.  $eGFR = 0.413 \times (\text{height}/\text{Scr})$  if height is expressed in centimeters<sup>11</sup>. We studied their relative differences in occurrence of large vessel disease. The details were recorded in a case proforma designed for the study.

All patients included in the study group were assessed by complete history, physical examination and laboratory evaluation as per standard of care of

the specialty clinic. The parameter studied was B-mode assessment of CIMT with a linear transducer of 12.0-MHz. The segments of common carotid artery 1-2 cm proximal to the bulb were scanned for noting the CIMT. The posterior (far) wall and the distance between the leading edges of the lumen-intima interface and the media-adventitia interface of the B-mode frame were considered to calculate CIMT<sup>12</sup>. (Figure 1)



Figure 1: Zoomed image of B-mode tracing of carotid artery for CIMT estimation, the digital callipers marking the distance between the leading edges of the lumen-intima interface and the media-adventitia interface

In the absence of data for normative cut-off of CIMT in Indians, a value of more than 0.08 cm was taken as abnormal. Although the threshold for abnormal CIMT in children is probably less than 0.08cm, in a study of 32 children with hypertension, 0.08cm defined the high end of the range of values within this selected patient population<sup>13</sup>. Details of treatment with antihypertensive drugs, iron supplements, erythropoietin injections, phosphate binders and calcium and vitamin D supplements were recorded in case proforma and analysed.

*Statistical analysis*

Continuous variables were expressed as means and standard deviations. Discrete variables were expressed as frequencies and percentages. Student's *t*-test was utilized in comparing the means of continuous normally distributed data. Chi-square test was used to test categorical data. Chi-square test for trends / Freeman-Halton extension of the Fisher exact probability test (whichever was applicable) were used to assess categorical data related to the CKD classification.

All statistical tests were 2-tailed, and a *p* value less than 0.05 was taken as statistically significant. Data were analysed using SPSS 13.0 software for Windows.

**Results**

A total of 43 children (35 males) with mean (SD) age of 8 (3.8) years diagnosed with CKD and satisfying the study criteria were included. The mean age of presentation was 4 years and 3 months with 34.8% in the age group 6-10 years. Mean duration of illness was 3.6 (SD 0.6) years. The mean eGFR was 23.22 ml/min/1.73m<sup>2</sup>. Eighty percent belonged to stage IV and V indicating late referral. Fifty five percent of children above 2 years were undernourished (BMI<5%). Reflux nephropathy followed by structural defects including hypoplasia, dysplasia and polycystic disease were the most common aetiological diagnoses. Of the 43, nine (21%) had cardiovascular symptoms such as fatigue, dyspnoea and oedema. These cardiovascular symptoms had a positive predictive value of 88.9% for high CIMT (Table 2).

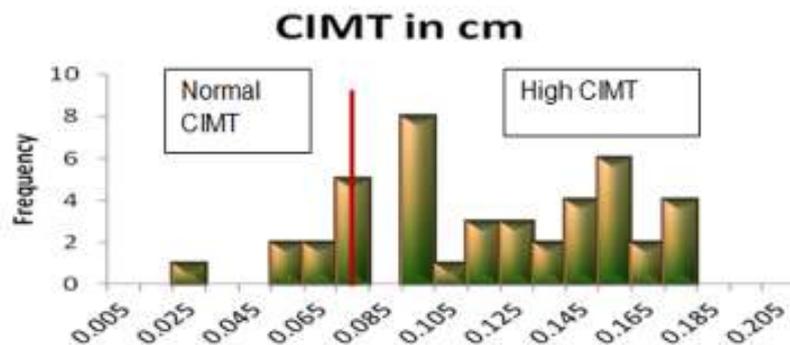
**Table 2: Positive predictive value of cardiac symptoms for underlying large vessel disease**

Data analysed	High CIMT	Normal CIMT	Total
Cardiac symptoms present	8	1	9
Cardiac symptoms absent	31	3	34
Total	39	4	43
Positive predictive value	0.8889		
Likelihood ratio	0.8205		

*CIMT: carotid intima-media thickness*

Of the 43, twenty one were on antihypertensive drugs with 24% requiring more than one antihypertensive medication. Hypertension was noted in 8/43 (18.6%) with systolic hypertension in 14%, 19% and 25% from stages III to V respectively indicating a linear increase with progression of CKD. Diastolic hypertension was noted in 12% of the cases in stages III & IV and 25% in stage V. Despite therapy, 7/21 had uncontrolled hypertension. Eighty percent of cases

were on calcium channel blockers and 23% each on ACE inhibitors and centrally acting antihypertensive drugs, with almost 20% patients requiring more than one antihypertensive medication. Studying the prevalence of large vessel disease in CKD patients, 39/43 (90%) of patients had high CIMT (Figure 2).



**Figure 2: Frequency distribution of CIMT in cm in the study group**  
*CIMT: carotid intima-media thickness*

There was no statistical difference between groups, with large vessel disease seen in all stages of CKD. However, the mean CIMT was significantly more in the ESRD group than in other stages (0.139±0.009cm vs 0.112±0.007cm) (Table 3). There was a significant difference between the mean CIMT in normotensive patients (0.104±0.008cm) and in well controlled systolic and diastolic hypertension (0.134±0.009cm) and (0.132±0.009cm) respectively. Mean CIMT in children with uncontrolled systolic and diastolic hypertension group (0.152±0.009cm) was significantly ( $p=0.021$ ) higher as compared to the mean CIMT in well controlled hypertensive and normotensive patients (0.116±0.006cm). The mean CIMT did not differ significantly in the patients who had uncontrolled systolic and/or diastolic hypertension (0.152±0.009cm) despite therapy and those with good control (0.134±0.009cm) although the mean CIMT was lower in the latter group.

The study did not find any significant association between presence of anaemia, high calcium, high Ca x P product, hyperparathyroidism and proteinuria with CIMT (Table 3). The analysis also revealed that values of CIMT were higher in patients on continuous ambulatory peritoneal dialysis (CAPD) than without, indicating that large vessel disease is worse in patients on dialysis. No significant correlation was found between large vessel disease and anaemia, high calcium, high Ca x P product, hyperparathyroidism, proteinuria, malnutrition, use of calcium containing phosphate binders. Of the 43, twenty seven (63%) had regular follow up in the outpatient department. One child with prolonged duration of illness and stage V CKD died during the study period. The laboratory evaluation revealed anaemia, hypocalcaemia and hyperparathyroidism. The child had a significantly high CIMT.

**Table 3: Association of variables with CIMT**

Variables	CIMT	
	Mean values	p value
<i>Age of presentation</i>	<1 year	0.1146
	>1 year	0.1252
<i>End stage renal disease</i>	Yes	0.1393
	No	0.1127
<i>Stage</i>	Stage 2+3	0.1211
	Stage 4+5	0.1222
<i>Malnutrition</i>	Yes	0.1200
	No	0.1331
<i>Systolic hypertension</i>	Uncontrolled systolic hypertension	0.1529
	No uncontrolled systolic hypertension	0.1160
	Uncontrolled systolic hypertension	0.1529
	Controlled systolic hypertension	0.1346
	Controlled systolic hypertension	0.1346
	No systolic hypertension	0.1041
<i>Diastolic hypertension</i>	Uncontrolled diastolic hypertension	0.1528
	No uncontrolled diastolic hypertension	0.1160
	Uncontrolled diastolic hypertension	0.1529
	Controlled diastolic hypertension	0.1323
	Controlled diastolic hypertension	0.1323
	No diastolic hypertension	0.1043
<i>Anaemia</i>	Yes	0.1265
	No	0.1070
<i>Hypercalcaemia</i>	Yes	0.1150
	No	0.1223
<i>Hypocalcaemia</i>	Yes	0.1222
	No	0.1216
<i>Hyperphosphataemia</i>	Yes	0.1238
	No	0.1213
<i>High calcium phosphorus product</i>	Yes	0.1181
	No	0.1237
<i>Hyperparathyroidism</i>	Yes	0.1213
	No	0.1231
<i>Proteinuria</i>	Yes	0.1192
	No	0.1292
<i>Vitamin D3 supplements</i>	Yes	0.1086
	No	0.1246
<i>Antihypertensive use</i>	Yes	0.1407
	No	0.1041
<i>Alfa calcidol use</i>	Yes	0.1085
	No	0.1278
<i>Calcium containing phosphate binder use</i>	Yes	0.1288
	No	0.1125
<i>Continuous ambulatory peritoneal dialysis</i>	Yes	0.1440
	No	0.1370
<i>Follow up</i>	Irregular	0.1297
	regular	0.1174

**Discussion**

Large vessel disease occurs very early in CKD children<sup>14,15</sup>. Studies of young adults developing ESRD while still children found an increased frequency of abnormal CIMT, diminished arterial wall compliance and coronary artery calcification which are considered markers of asymptomatic atherosclerosis and predictors of future

symptomatic CVD<sup>15-17</sup>. Ninety percent of the patients in the study had high CIMT including children in earlier stages, suggestive of large vessel disease being universal in CKD patients which is similar to other studies on the same subject<sup>18</sup>. However, only 9/43 (21%) had cardiovascular symptoms. Amongst the symptomatic patients (n=9) fatigue was seen in 66.6%, dyspnoea in 55%

and oedema in 22%. However, the presence of any of the above symptoms has a positive predictive value of 88.9% for high CIMT (Table 2). We did not find any studies which analysed these parameters. Thus large vessel disease in CKD remains predominantly subclinical. When ESRD group was studied separately the mean CIMT was significantly higher than in other stages. This finding is also supported by Milliner *et al.* based on necropsy findings in children with ESRD<sup>5</sup>.

Children with uncontrolled systolic / diastolic hypertension had significantly higher mean CIMTs as compared to others. What was more astounding was the fact that the mean CIMT did not differ significantly in patients who had uncontrolled systolic/diastolic hypertension despite therapy and those with good control, although the mean CIMT was lower in the latter group. Children who were normotensive had significantly lower mean CIMT than those who were normotensive on antihypertensive drugs. The above findings indicate that systolic or diastolic hypertension contributes to large vessel disease which might not revert completely even with good control of BP. Hence, children who are on antihypertensive medication to maintain a particular BP for that age, still have a higher cardiovascular risk in comparison to children with the same BP without using antihypertensive drugs. The difference may also be due to a delay between a faster control of BP with antihypertensive drugs versus a slower effect on the large vessel disease. A cross-sectional CIMT analysis after one year follow-up of 101 children 2–18 years old with mild to moderate CKD found CIMT to be significantly increased among children with CKD, along with prevalence of other cardiovascular risk factors, among which hypertension and dyslipidemia are significantly associated with raised CIMT<sup>19</sup>. Various studies have found greater arterial stiffness and demonstrated that systolic hypertension was the chief determinant of abnormal arterial wall compliance<sup>20-22</sup>.

Based on previous studies<sup>23,24</sup>, we expected to find a correlation between high CIMT and abnormal calcium phosphorus metabolism, but there was no such association found. This can be due to the fact that many children had normal levels of serum calcium and phosphorus. Only 30% of children had an average serum phosphorus value that was above the published Kidney Disease Outcomes Quality Initiative cut-offs for medical therapy<sup>25</sup>. This could be due to the fact that almost 58% were on calcium containing phosphorus binders. Only 3 children had an elevated calcium-phosphorus product, lending further proof to this hypothesis. The study found no significant association between CIMT and anaemia, hyperparathyroidism, or proteinuria.

This study has some limitations. The cross sectional nature of the study limits the ability to infer causality. The small sample size limits the generalizability of the study.

### Conclusions

CIMT is an important echocardiographic marker for cardiovascular disease in CKD. Hypertension is the single most important risk factor associated with large vessel disease.

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