Carotid intima media thickness and endothelial dysfunction in children with chronic kidney disease (CKD) and nephrotic syndrome

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Purpose

Despite significant advances in the care of children and adolescents with chronic kidney disease (CKD), long-term survival of children with CKD remains far lower than for the general population [1]. The most likely cause of this reduction in survival is cardiovascular mortality, related to both accelerated ischemic heart disease and premature development of dilated cardiomyopathy in young adult survivors of childhood-onset CKD. The risk factors for accelerated CVD in children with CKD are traditional risk factors for atherosclerotic disease (e.g. dyslipidemia, diabetes, hypertension, smoking) and uremia-related risk factors which are far more prevalent among patients with CKD which include volume overload, anemia, abnormalities of calcium and phosphorus metabolism, malnutrition and inflammation [2].

Nephrotic syndrome (NS) is a common illness in childhood characterized by edema, hypoalbuminemia, massive proteinuria and hyperlipidemia. Few studies suggest that adults with history of NS have a 5.5-fold increased relative risk of myocardial infarction and a 2.8-fold increased relative risk of coronary death [3]. Persistent hyperlipidemia and proteinuria is common in steroid resistant nephrotic syndrome (SRNS) and hence an atherogenic state is more likely over the years with concordance of additional disease as well as therapy-related risk factors like hypertension, high body mass index, and chronic renal dysfunction.

Changes of early atherosclerosis in children are reflected by increase in carotid intima media thickness in early life and disturbance in flow mediated dilatation. Several studies in children have shown that atherosclerosis can be detected by measuring carotid intima media thickness using high resolution ultrasound [4-6]. The purpose of this study was to examine the prevalence of Dyslipidemia and assess carotid intima media thickness and flow mediated dilatation of brachial artery in children with chronic kidney disease and nephrotic syndrome using high-resolution ultrasound.
Methods and Materials

This was a cross sectional study conducted in the Department of Pediatrics at All India Institute of Medical Sciences, New Delhi. Written informed consent was obtained from the parent or legal guardian of each patient. Study subjects included consecutive cases of CKD III-IV and children with nephrotic syndrome attending Pediatric nephrology clinic or admitted in wards, between 2 to 18 years of age and of either sex. Both old and newly diagnosed CKD patients and children with nephrotic syndrome were enrolled. Children receiving lipid lowering drugs such as HMG CoA reductase inhibitors or who had a family history of premature CVD or active bacterial infection were excluded. 50 healthy controls matched for age and gender without any apparent renal or cardiovascular disease were also studied. The primary objective was to compare the carotid intima media thickness (CIMT) and brachial artery flow mediated dilatation (FMD) between children with CKD stage III-IV, nephrotic syndrome and healthy controls. The secondary objectives were to correlate the lipid profile with brachial artery flow mediated dilatation and carotid intima media thickness and determine risk factors for dyslipidemia and abnormal CIMT and FMD. The prevalence of dyslipidemia was also estimated. Dyslipidemia was defined as any abnormality in the serum levels of low density lipoprotein (LDL), very low density lipoprotein (VLDL), high density lipoprotein (HDL) and triglycerides.

Diagnostic work up

Clinical and demographic details were recorded. Laboratory investigation was carried out after a 12 hour fasting which will include levels of blood urea, creatinine, calcium, phosphorous bicarbonate, serum alkaline phosphatase and albumin. All children underwent a complete lipid profile including total cholesterol, HDL, LDL and VLDL and triglycerides.

Cholesterol and triglyceride were measured by enzymatic end point method. HDL was removed after precipitation of LDL using phosphotungstic acid / magnesium by enzymatic end point method. LDL cholesterol was calculated by Friedwald’s formula.

CIMT measurement

CIMT measurement was carried out as per Mannheim consensus [7]. High resolution B-mode ultrasound with linear transducers with a frequency of 5-12 MHz was used. Ultrasound was obtained with patients in supine position and head turned slightly to the contralateral side. The arterial wall segments were assessed in a longitudinal view, strictly perpendicular to the ultrasound beam, with both walls clearly visualized in order to achieve diameter measurements. Lateral probe incidence was used. Measurements were obtained from the far wall of both common carotid arteries (CCA), at the bulb and the origin of internal carotid arteries. Values from left and right sides were averaged.
As per the definitions of Mannheim consensus, intima media thickness was a double-line pattern visualized by echotomography on both walls of the CCAs in a longitudinal image. It was formed by two parallel lines, which consist of the leading edges of two anatomical boundaries: the lumen-intima and media-adventitia interfaces. All studies were performed on a single ultrasound machine using a multiple frequency scan with standardized image settings including resolution mode and depth of field. DICOM images from the measurements were stored electronically. An independent observer who was blinded to the control group and CKD patients interpreted the CIMT images. The intra-observer coefficient of variation of variation of CIMT measured at our center is reported to be <10%.

**Brachial artery FMD**

Flow mediated dilatation of the brachial artery was measured using ultrasound. The baseline diameter of the brachial artery was measured first. A BP cuff was wrapped around the forearm and inflated to suprasystolic pressure and kept for 4.5 minutes. After releasing the cuff, the diameter was measured at 90 sec flow. The change in the diameter of brachial artery from the baseline represented the FMD.

**Sample size estimation**

The prevalence of dyslipidemia in adults with CKD is reported to vary between 60 to 83%. We hypothesized that the prevalence of dyslipidemia in children with CKD is around 60%. By considering an alpha error of 0.05 and power of 0.80, for a precision of 15%, the required sample size for the study was 78.

**Statistical analysis**

Mean and median were used for continuous variables and comparisons were done by student t test or Wilcoxon rank sum test depending on the distribution of the data. Multiple logistic regression was used for identifying risk factors. A p value of < 0.05 was considered significant.
**Fig. 1:** Longitudinal view of common carotid artery (CCA) and carotid bifurcation. The red line corresponds to the end of the CCA.

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Fig. 2: The mechanism of flow mediated dilatation of brachial artery
Results

182 children were studied which included 80 with CKD stage III-IV and 52 with nephrotic syndrome of more than 2 years illness. 50 age and sex matched healthy children served as controls.

**CIMT and FMD in children with CKD**

The mean age of children with CKD, nephrotic syndrome and controls was similar. The chief underlying cause for CKD was posterior urethral valve, reflux nephropathy neurogenic bladder, dysplastic kidney and chronic glomerulonephritis. The estimated prevalence of dyslipidemia (any abnormality in lipid profile was 35%). Abnormality in triglyceride level was more common than abnormality in total cholesterol (r=-0.23, P=0.03) and LDL levels. There was a positive correlation between systolic blood pressure and total cholesterol and triglyceride levels. Estimated GFR and systolic blood pressures were independent predictors of dyslipidemia. There was a negative correlation between total cholesterol triglyceride levels (r=-0.22, P=0.04) and glomerular filtration rate. The median (95% CI) CIMT in CKD was 0.433 (0.411-0.463) mm and in nephrotic syndrome 0.435 (0.407-0.463) mm, which was significantly higher than in controls [0.397 (0.381-0.412) mm] (P=0.008). Median CIMT was correlated with dyslipidemia, blood pressure and BMI. On multivariate regression, total cholesterol, BMI systolic blood pressure and LDL were independent risk factors for increased CIMT in children with CKD. The median (95% CI) brachial artery FMD (%) was lower in CKD [12.4 (10.1-14.6)] and nephrotic syndrome [10.5 (6.4-14.7)] than in controls [16.0 (12.5-19.6)] (P<0.001). Brachial artery FMD was negatively correlated with GFR and systolic blood pressure. The CIMT and FMD in CKD and nephrotic subjects were similar. The serum levels of total cholesterol, triglyceride, LDL, VLDL were significantly higher in CKD and nephrotic syndrome than control while HDL level was significantly lower than in controls.

Table 1 Baseline characteristics of children with CKD (n=80)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>9.5 ± 3.4 (range 3-17)</td>
</tr>
<tr>
<td>Age of onset (yr)</td>
<td>4.2 ± 2.5</td>
</tr>
<tr>
<td>Boys</td>
<td>65 (80%)</td>
</tr>
<tr>
<td>Height for age z score</td>
<td>-3.9 ± 2.3</td>
</tr>
<tr>
<td>Weight for age (WAZ) z score</td>
<td>-1.4 ± 1.8</td>
</tr>
<tr>
<td>Malnourished (WAZ-2 SD)</td>
<td>36 (45%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70 (87%)</td>
</tr>
</tbody>
</table>
Calcium phosphate product 44.8 ± 0.8  
Creatinine (mg/dl) 1.9 ± 1.0 (range 1.1-5.5)  
GFR (ml/min/1.73m²) 35.2 ± 10.7 (range 16-54)  
CKD stage III 62 (77.5%)  
CKD IV 18 (22.5%)  

Table 2 Comparison of CIMT, FMD and lipid profile between CKD, nephrotic syndrome and controls. Values are median and 95% CI

<table>
<thead>
<tr>
<th></th>
<th>CKD* n = 80</th>
<th>Nephrotic syndrome n=52</th>
<th>Controls* n = 50</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum CIMT (mm)</td>
<td>0.433 (0.411-0.463)</td>
<td>0.435 (0.407-0.463)</td>
<td>0.397 (0.381-0.412)</td>
<td>0.008</td>
</tr>
<tr>
<td>FMD (%) increase</td>
<td>11.4 (10.1-14.6)</td>
<td>10.5 (6.4-14.7)</td>
<td>17.0 (14.5-19.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>201.6 (185.9-217.5)</td>
<td>178 (168.1-227.4)</td>
<td>126.6 (105.7-147.5)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>159.4 (132.8-186.0)</td>
<td>128 (91.5-156.5)</td>
<td>80.6 (67.7-93.4)</td>
<td>0.0000</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>121.2 (106.5-135.9)</td>
<td>118 (100-139.4)</td>
<td>45.8 (41.5-50.0)</td>
<td>0.0000</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>31.9 (26.6-37.2)</td>
<td>33.1 (27.7-40.2)</td>
<td>23 (18.0-28.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>48.6 (44.3-52.9)</td>
<td>41 (39.2-42)</td>
<td>84.6 (72.6-96.7)</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

CIMT and FMD in Nephrotic syndrome

Both the cases with nephrotic syndrome and controls were similar in age (10.1±0.03 vs. 9.9±0.04 yr), sex, growth and eGFR. Mean maximum CIMT (95% CI) (in mm) was higher in the NS group (p<0.01). SRNS and SSNS cases were similar [0.441 (0.367 - 0.515) mm] vs. [0.434 (0.404 - 0.464) mm, P=0.36]. Nephrotic children showed significantly lower FMD than controls (P=0.02).

On univariate analysis, CIMT correlated with disease profile at onset (r=0.33, P<0.01), FMD (r=-0.23, P=0.02), male sex (r=0.23, P=0.02), BMI (r=0.23, P=0.02), total cholesterol
(TC) \( r=0.34, P<0.01 \), LDL \( r=0.33, P<0.01 \), VLDL \( r=0.29, P<0.05 \), triglycerides \( r=0.33, P<0.05 \), and creatinine \( r=0.25, P=0.03 \). Multivariate analysis showed TC, LDL, VLDL to be independent predictors. FMD correlated with systolic blood pressure, age and BMI.
Fig. 2: The mechanism of flow mediated dilatation of brachial artery

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**Fig. 3:** B mode ultrasound image using high resolution zoom shows the measurement of intima media thickness of the common carotid artery 2 cm proximal to the bulb

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Fig. 4: B mode ultrasound image using high resolution (5-12 MHz) transducer shows the measurement of brachial artery diameter before the release of BP cuff for assessing the flow mediated dilatation in a case of CKD

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**Fig. 5:** B mode ultrasound image using high resolution (5-12 MHz) transducer shows the measurement of brachial artery diameter after the release of BP cuff for assessing the flow mediated dilatation in a case of CKD

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Conclusion

Premature atherosclerosis as evidenced by significantly increased CIMT and decreased brachial artery FMD was seen in both CKD children and those with nephrotic syndrome when compared with controls. We found that the prevalence of hyperlipidemia was 35% in children with CKD. Results from CKiD study have shown that dyslipidemia is common in children with CKD and is a risk factor for increased CIMT [8]. In our study CIMT was significantly increased in children with CKD as compared to controls. Saygyly et al found that children with ESRD had higher CIMT than controls and CIMT was positively correlated with systolic blood pressure and left ventricular mass [9]. Similarly Groothoff et al found increased CIMT in young adults who had CKD in childhood [10]. We found that FMD was decreased in children with CKD. Kari et al studied normotensive children with advanced CKD and showed decreased FMD as compared to healthy controls [11]. Total cholesterol, BMI systolic blood pressure and LDL were independent risk factors for increased CIMT in children with CKD. In nephrotic syndrome, TC, LDL, VLDL were independent predictors of CIMT while FMD correlated with systolic blood pressure, age and BMI.
References

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