

Carotid Intima-Media Thickness in Children with Chronic Kidney Disease as an Early Predictor of Cardiovascular Diseases

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ABSTRACT

Aim: Cardiovascular problems are very common in children with chronic kidney disease (CKD). To examine early cardiovascular risk factors, notably carotid intima-media thickness (CIMT) and pulse wave velocity (PWV).

Material and Method: Case-control study was conducted in the Department of Pediatric Nephrology Sindh Institute of Urology and Transplantation Karachi from 1st February 2023 to 31st July 2023. Forty two children were enrolled. CIMT and PWV were measured using ultrasonography and pulse wave analysis respectively. The following clinical parameters were also assessed: blood pressure, age, gender, etiology, duration of chronic kidney disease (CKD), estimated glomerular filtration rate (eGFR), serum albumin, calcium-phosphate product, and intact parathyroid hormone (PTH), and vitamin D levels.

Results: The average age was 10.2±3.6 years, with a higher proportion of boys in the cases group (69% versus 47.6%, p-value 0.04). Most patients had normal blood pressure (78.6%), and congenital anomalies were the most common CKD etiology (57.1%). Median eGFR was 30.5 ml/min/1.73 m², with stages 3 and 4 CKD most prevalent. Serum albumin was normal (mean 4.45±0.68), but some cases had a high calcium-phosphate product (7%) and low vitamin D levels (52%). CIMT and PWV did not differ significantly between cases and controls. Echocardiography revealed mild cardiac abnormalities in some cases.

Practical implication: Some patients showed minor left ventricular expansion, while others had mildly depressed GLS and decreased LVEF. Further research should focus on longitudinal studies and explore new biomarkers for early cardiovascular risk detection.

Conclusion: The various clinical characteristics such as blood pressure, mineral and bone diseases, and cardiac abnormalities are common in children with chronic kidney diseases. There were no significant changes in carotid intima-media thickness and pulse wave velocity between the cases and controls.

Keywords: Chronic kidney disease, Carotid intima-media thickness, Cardiovascular disease, Pulse wave velocity

INTRODUCTION

In children with chronic kidney diseases (CKD), cardiovascular problems associated with atherosclerosis are the main cause of morbidity and mortality.¹ Oxidative stress, overweight and obesity, dysfunction of endothelial cells, disease of the bones, vascular calcification (VC), anemia, protein-caloric deficiency, and coagulation problems contribute to the development of atherosclerosis.^{2,3} Children are the perfect candidates to investigate the impact of several other CKD characteristics on the arterial wall because they lack the usual adult-related risk factors for atherosclerosis such as diabetes and dyslipidemia.⁴

Carotid intima-media thickness (CIMT) is indeed considered an important biomarker of atherosclerotic disease. The thickness is assessed using B-mode ultrasonography, and the measurement is the distance in the carotid artery between the media-adventitia and lumen-intima interfaces. This test is used to evaluate the risk of cardiovascular disease and the degree of atherosclerosis.^{5,6} Lopes et al⁷ described that 74.5% of children and adolescents with CKD showed an increase in CIMT using ultrasonography techniques. Furthermore, a meta-analysis of 14 populations (cohort studies) revealed that for each 0.1 mm rise in CIMT, there was a 9% increase in the likelihood of developing cardiovascular disease (CVD).⁸ In their investigation, Litwin et al⁹ discovered a substantial correlation between CIMT and several parameters about the metabolism of calcium and phosphorus. These factors include serum calcium and phosphate products, the total dosage of calcium-based phosphate binding agents, and the mean calcitriol dose averaged across time. This suggests that these factors may play a role in influencing CIMT, possibly through their effects on vascular calcification. Lawal et al¹⁰ found that the following factors predict CIMT in CKD: erythrocyte sedimentation rate, left ventricular ejection fraction (LVEF), and left arterial diameter (LAD). Arterial stiffness can be assessed by measuring the PWV as it travels through a specified arterial segment, like the aorta, with the carotid and femoral arteries commonly used for pulse wave measurement.¹¹

According to our theory, global longitudinal strain, left ventricular mass, lower left ventricular ejection fraction, and left arterial enlargement are echocardiographic markers of left ventricular dysfunction that appear to emerge before CIMT and PWV. This study aims to evaluate the frequency of altered pulse wave velocity (PWV) and enhanced carotid intima-media thickness (CIMT) in children with chronic renal disease who are asymptomatic and not receiving dialysis. Additionally, we aim to investigate the potential association between CIMT and PWV alterations and various factors, including calcium-phosphorus product, anemia, dyslipidemia, glycemic control, and hyperuricemia. The identification of statistically significant connections between these factors and cardiovascular markers may enhance the cost-effective detection of cardiovascular disease in children with CKD.

MATERIALS AND METHODS

The hospital ethics committee approved this case-control research, and the parents or guardians signed informed permission were obtained. The patients were chosen between 1st February to 31st July of 2023 from the pediatric CKD clinic at Sindh Institute of Urology and Transplantation (SIUT) Karachi Pakistan. Cases included children aged 1-18 years with CKD stage 1-5, selected through non-probability consecutive sampling. Exclusions comprised patients undergoing dialysis, those with cardiac disease, and individuals with known primary co-morbidities such as malignancy, vasculitis, coagulation abnormalities, and autoimmune disorders. Healthy siblings of the cases within a similar age group (±2 years) and of either gender were enrolled as controls.

The National Kidney Foundation and The Kidney Disease Outcome Quality Initiative used practice guidelines to identify chronic kidney disease (CKD). Stage I, II, III, IV, and V were determined by estimating the glomerular filtration rate (ml/min/1.73 m²), which had values ≥90, 60–89, 30–59, 15–29, and ≤15, respectively.¹²

A pre-established, structured proforma was used to gather data in an organized manner. Renal functions, bone mineral disorders, anemia, lipid profiles, erythrocyte sedimentation rate, C-reactive protein, and uric acid levels were evaluated in blood

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samples taken from the patients. In our facility, serum creatinine was measured using the Jaffe technique, and the Schwartz formula was utilized to calculate the estimated glomerular filtration rate (eGFR).¹³

At the pediatric echo laboratory at SIUT, skilled technicians performed targeted echocardiography on both cases and controls to evaluate the heart function, Carotid intima-media thickness (CIMT), and Pulse wave velocity (PWV). After each participant's 15-20-minute procedure, a pediatric cardiologist was blind to the exposure group and reviewed all of the studies. The results of the echocardiogram were communicated to the parents after the completion of the procedure.

CIMT was performed using ultrasound according to the Association of European Pediatric Cardiology working group on cardiovascular prevention guidelines.¹⁴ Using 7-12 MHz linear transducers, all vascular examinations were carried out on GE Healthcare Vivid E95 (GE Healthcare, Waukesha, Wisconsin, USA). The images were taken with the neck extended position and away from the transducer. Longitudinal images of both common carotid arteries proximal to the carotid bulb were obtained. Recorded clips were each of minimum 5 seconds duration. After that, the images were examined offline to determine the dimensions and frame rate. A measurement of the common carotid arteries far wall and distal 10mm was made for the CIMT. There were two prominent brilliant lines on the carotid wall, with darker areas in between. Next, 105-110 points were outlined on a pixel basis using the CIMT program, and the average CIMT value for three consecutive cardiac cycles was calculated on each side. The findings of the absolute CIMT assessment were contrasted with those of a sibling who was normal. PWV was obtained using arterial tonometry, (which is the ratio of distance to time. The time needed for the pulse wave to travel from the carotid to the femoral artery was measured, and the distance was calculated as 0.8 times the distance from the common carotid artery to the femoral artery).

Throughout the trial, 180 children visited our department's CKD clinic, and all of them had siblings available to them. Based on a prior investigation by Litwin et al⁹, which documented elevated carotid intima-media thickness (CIMT) in 74.5% of subjects, accompanied by a 12% error margin and a 95% confidence interval, our sample size computation suggested a need of 40 participants.

The data was analyzed through SPSS-23. The t-test was utilized to analyze quantitative data, while the Chi-square tests was

applied to categorical variables. For statistical significance, a cutoff of p<0.5 was utilized. In order to look at the relationship between risk variables and carotid intima-media thickness (CIMT), Univariate and multivariate analyses were performed

RESULTS

The current study included 84 children, 42 in the cases and control groups. The mean ages were comparable between the two groups (10.2±3.6 versus 10.3±3.4 years, p-value 0.96). Nonetheless, a statistically significant distinction was noted, with a great percentage of boys in the cases group [29(69%) versus 20 (47.6%), p-value 0.04]. Concerning blood pressure categories among the patients, 33 (78.6%) were below the 90th percentile, 4 (9.5%) had elevated blood pressure, 2(4.8%) were classified as stage 1, and 3(7.1%) fell into the stage 2 category. Congenital anomalies of the kidney and urinary tract (CAKUT) were among the underlying causes of chronic kidney disease (CKD) in 24 (57.1%), renal stone in 2 (4.8%), nephrocalcinosis in 2 (4.8%), chronic glomerulonephritis in 3(7.1%), and the etiology was unknown in 11 patients (26.2%). The median estimated glomerular filtration rate (eGFR) was 30.5ml/min/1.73m² (interquartile range 17.7-53). A significant proportion of children were in higher stages of CKD, with stage 3 observed in 16 (38%) and stage 4 in 15 (36%). The duration of CKD before enrollment in the study was 42 months (interquartile range 12-72). Serum albumin was well maintained across the entire cohort, with a mean value of 4.45±0.68. A relatively small number of cases, specifically 4(7%), had a calcium-phosphate product greater than 60. High intact parathyroid hormone (iPTH) levels for the CKD stages were found in 39 (93%), and low vitamin D levels were observed in 22 (52%). When comparing cases with an estimated GFR less than or equal to 30mls/min/1.73m² to those with greater than 30mls/min/m², a statistically significant difference was observed only in vitamin D levels p=0.002 (Table 1).

Carotid intima-media thickness (CIMT) measurements taken at the left anterior carotid, left posterior carotid, right anterior carotid and right posterior carotid were within normal limits as shown in table 2. The medians for both cases and controls showed no statistical difference as depicted in Figures 1-2. Additionally, abnormal values were not observed in pulse wave velocity (PWV). Other echocardiographic parameters indicated mild left ventricular (LV) size enlargement in 3 (9.5%) cases, severe heart dilatation in one child (2.3%), and mildly reduced left ventricular ejection fraction (LVEF) in 2 (4.6%). Furthermore, mildly depressed global longitudinal strain (GLS) was noted in 9(21%) cases as shown in table 2 and isolated instances of mild pericardial effusion and moderate pulmonary hypertension were identified.

Table 1: Baseline characteristics of children (n=42)

Variable	eGFR ≤30 ml/min/1.73m ² (n-21)	eGFR >30 ml/min/1.73m ² (n-21)	P value
Age (years)	10.04±3.5	10.5±3.7	0.689
Gender			
Male	13	16	0.317
Female	8	5	
BMI (kg/m ²) (median ± IQR)	14.8 (13.9-19.9)	13.8 (13.0-14.9)	0.087
Blood Pressure			
Below 90 th centile	16	17	0.500
Elevated BP	2	2	
Stage 1 HTN	2	-	
Stage 2 HTN	1	2	
Duration of CKD (years) (median + IQR)	3 (0.9-6)	4 (1.5-6)	0.560
Vitamin D			
Normal	6	9	0.002
High	5	-	
Severe deficiency	1	-	
Mild deficiency	7	1	
Insufficiency	2	11	
iPTH			
Normal	1	2	0.549
High	20	19	
Serum iron			
Normal	13	12	0.753
Low	8	9	
Serum vitamin B12			
Normal	16	16	1.0
Low	5	5	
Serum folate			
Normal	17	14	0.292
Low	4	7	

Table 2: Characteristics of children in relation to chronic kidney disease

Variable	CKD Stage 2 (n=4)	CKD Stage 3 (n=16)	CKD Stage 4 (n=15)	CKD Stage 5 (n=7)	P value
Age (years)					
1 – 5	-	2	3	-	0.889
6 – 10	2	8	5	3	
11 – 15	2	5	6	4	
16 – 18	-	1	1	-	
iPTH					
Normal	1	1	-	1	0.304
High	3	15	15	6	
Vitamin D					
Severe deficiency	-	-	1	-	0.004
Mid deficiency	-	-	7	1	
Mild deficiency	3	8	-	2	
Insufficiency	1	7	-	1	
Normal	-	1	1	3	
Elevate	-	-	-	-	
LV Size					
Normal	4	14	14	6	0.368
Mildly dilated	-	2	1	-	
Severely dilated	-	-	-	1	
Ejection Fraction					
Normal	3	16	14	7	0.181
Mildly depressed	1	-	1	-	
LV GLS					
Normal	3	15	10	5	0.296
Mildly depressed	1	1	5	2	
CIMT-RCA (normal)	4	16	15	7	.a
CIMT-RCP (Normal)	4	16	15	7	.a
CIMT-LCA (Normal)	4	16	15	7	.a
CIMT-LCP (Normal)	4	16	15	7	.a
PWV (Normal)	4	16	15	7	.a

lpth: intact parathyroid hormone, LV: Left ventricle, LV GLS: left ventricle global longitudinal strain, CIMT-RCA: carotid intima media thickness right carotid anterior, CIMT-RCP: carotid intima media thickness right carotid posterior, CIMT-LCA: carotid intima media thickness Left carotid posterior, CIMT-LCP: carotid intima media thickness Left carotid posterior, a. no statistics computed because CIMT is constant

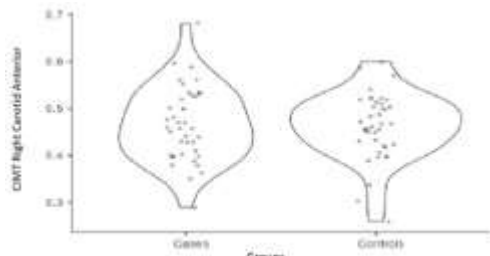


Fig. 1: Median in cases is .435 while in control is .445, IQR in cases is 0.398 to 0.490 while in control is 0.400 -0.492

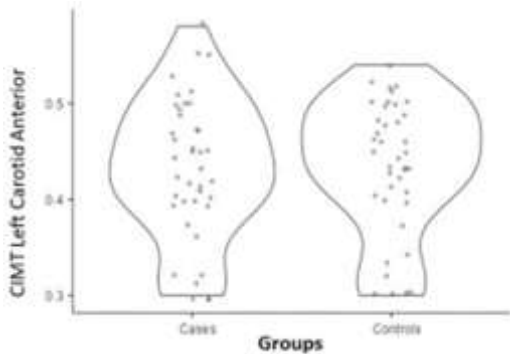


Fig. 2: Median in cases is .460 while in control is .465, IQR in cases is 0.400 to 0.530 while in control is 0.420 -0.510

DISCUSSION

The mean ages of the groups were comparable indicating that age was not a confounding factor in the comparison. However, the gender distribution did show a statistically significant difference, Nevertheless, with a higher proportion of boys in the case group than in the control group. This contrasts with the study of Mitsnefes et al¹⁵, where a similar tendency of a larger proportion of boys (31, 70%) was noted and the average age was 13 years. Where the

mean age was 13 years, and a similar trend of a higher proportion of boys (31, 70%) was observed. In children, Moretti et al¹⁶ observed no association between carotid intima-media thickness (IMT) and age, and they did not find a significant impact of sex on CIMT, which differs from observations in the adult population. Regarding blood pressure categories, a majority of the patients (78.6%) had normal blood pressure. However, a small proportion of patients had elevated blood pressure (14.3%) and did not show a positive correlation with CIMT. In contrast, Brady et al¹⁷ reported a prevalence of 76% for hypertension in their study and showed a positive correlation with CIMT. Jourdan et al¹⁸ calculated the normative values for CIMT, patients with hypertension did not exhibit a significant increase in CIMT.

The research group had a variety of antecedent etiologies of chronic kidney disease (CKD), with congenital kidney and urinary tract defects being the most frequent. These findings are in line with those of Sozeri et al.¹⁹ In our study, most children had advanced CKD (stages 3 and 4) with a median eGFR of 30.5 ml/min/1.73m². The duration of CKD prior to enrollment in the study was relatively long, with a median duration of 42 months. Serum albumin levels were well-maintained in the entire cohort. In our study, a small proportion of cases (7%) had a calcium-phosphate product greater than 60, which did not show a statistically significant correlation with carotid intima-media thickness and pulse wave velocity. This finding contrasts with the results of Mitsnefes et al¹⁵, who demonstrated a significant correlation between CIMT and the calcium-phosphate product in their study. Tamashiro et al²⁰ found No relationship between the increase in vessel calcifications and Ca x P product. PTH (parathyroid hormone) was high in 93% of patients in our research. The association between PTH levels and carotid intima-media thickness (CIMT) was not significant, though. This is not the case with the finding of Garcia-Bello et al²¹, who found a significant positive association in their investigation between CIMT and intact PTH level, who reported a significant positive association between CIMT and intact PTH levels in their study. Ziolkowska et al²² and Poyrazoğlu et al²³ also found negative correlations between CIMT and PTH levels. Vitamin D insufficiency or deficiency was found in 52% of the study group. There was no statistically significant positive correlation between vitamin D deficiency and pulse wave

velocity (PWV) or carotid intima-media thickness. Carotid intima-media thickness measured at various locations was within the normal range and exhibited no notable distinctions between the cases and controls. In the cases group, the median CIMT was 0.435 (IQR 0.398 to 0.490), while in the control group, it was 0.445 (0.400-0.492). Ziolkowska et al²² reported a mean CIMT of 0.4±0.01mm (median 0.4; range 0.36–0.42) in patients, and the average CIMT in the control group was 0.41±0.01mm. We found slightly higher values of CIMT in contrast to Lopes et al.⁷

Likewise, no anomalous pulse wave velocity (PWV), was discovered, suggesting that there was no discernible variation in arterial stiffness among the research groups. In those with early-stage CKD, Sharifi et al⁵ similarly showed that there was no meaningful association between the CIMT and paraclinical. Garcia et al. showed no notable distinction between the left and right sides ($p = 0.94$). Hence, it is suitable to incorporate the mean, left, or right carotid intima-media thickness when calculating normative values for children.²⁴ These findings suggest that CIMT and PWV may not be sensitive markers of early cardiovascular risk in children with CKD in this cohort. However, additional investigations with larger sample sizes and prolonged follow-up durations may be needed to confirm these findings. A small number of patients had minor left ventricular (LV) size expansion, while a subgroup of patients had mildly depressed global longitudinal strain (GLS) and mildly decreased LV ejection fraction (LVEF) these findings were indicated by echocardiographic measures. The necessity of a thorough cardiovascular risk assessment, encompassing cardiac imaging modalities, in children with chronic kidney disease is highlighted by the existence of cardiac abnormalities in spite of normal CIMT and PWV. Future research should focus on longitudinal studies to evaluate the predictive value of CIMT and PWV for cardiovascular outcomes in children with CKD and explore novel biomarkers and imaging modalities for early detection of cardiovascular risk in this population.

CONCLUSION

There were no discernible differences between the cases and controls in CIMT or PWV, this identified potential risk factors such as hypertension, mineral and bone disorders, and subclinical cardiac abnormalities.

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