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Factors affecting carotid artery intima-media thickness in children with chronic kidney disease

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ABSTRACT

Introduction: Cardiovascular disease is associated with chronic kidney disease (CKD) in both children and adults. It is difficult to assess cardiovascular status in children for various reasons, such as the lack of clinical manifestations in the early stages of cardiovascular disease. One of the methods for assessing the cardiovascular status of patients is to assess the carotid intima-media thickness (CIMT). However, only limited studies have been conducted on children to date.

Objectives: This study aimed to investigate factors affecting CIMT in children with chronic renal failure.

Patients and Methods: This case-control study evaluated the CIMT of children hospitalized with CKD in Mofid children's hospital (Tehran, Iran) from 2019 to 2021. All children with CKD were selected during the three-year period as the case group of 50 people. The control group was randomly selected from 150 people who were referred to other departments. Medical record information and detailed clinical examinations, laboratory and biochemical tests, and ultrasound examination of CIMT were recorded and analyzed. A significance level of 0.05 was considered.

Results: This study showed, 52% of the patients were boys and the rest were girls ($P=0.80$). The mean age in the patient group was 76.9±10.4 months since the mean age of control group was 32.8±3 months ($P=0.008$). The mean weight in the patient group was lower than in the control group ($P=0.0004$). The median CIMT in the patient group was significantly higher than in the control group (right and left CIMT for the patient group 0.48 mm and for the control group of the right and left carotid 0.41 mm and 0.42 mm, respectively; $P<0.05$). We also found age, weight, mean corpuscular volume (MCV), serum vitamin D and uric acid levels and also blood glucose concentration were correlated with the CIMT ($P<0.05$).

Conclusion: It is concluded that CIMT is a useful method for assessing the cardiovascular status of children with CKD.

Original Article

Implication for health policy/practice/research/medical education:
The aim of this study was to investigate factors associated with carotid artery intima-media thickness of chronic kidney disease (CKD) in children. The median carotid artery intima-media thickness in the patient group was significantly higher than in the control group. We also found age, weight, mean corpuscular volume, serum vitamin D and uric acid levels and also blood glucose concentration were correlated with carotid artery intima-media thickness.

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Introduction

Chronic kidney disease (CKD) is a progressive multifactorial disease characterized by permanent impairment of renal function and/or structure (1). The prevalence of CKD in children is about 15 to 74.7 per million worldwide (2). CKD increases the risk of cardiovascular disease, which increases patient mortality. End-stage renal disease (ESRD) in children is the cause of 35%-50% of deaths (3). This disease causes the internal deposition of calcium and phosphorus, increases blood vessel stiffness, and blood pressure. Elevated blood pressure contributes to left ventricular hypertrophy in children. Therefore, these children are at significant risk of experiencing a cardiovascular event in early adulthood (4).

Assessing cardiovascular risk in children with CKD is difficult because early stages of cardiovascular disease have no symptoms and are asymptomatic (5). Arterial imaging is one of the risk assessment methods for cardiovascular disease that can be detected at the preclinical stage, before the onset of clinical symptoms. The best way to measure the common carotid artery thickness is to use ultrasound and perform a computed tomography (CT) scan to observe the calcification of the coronary artery (4). Extensive epidemiological studies by the American College of Cardiology have identified carotid intima-media thickness (CIMT) as an indicator for assessing the risk of cardiovascular events (6).

Some studies showed that increased intima-media thickness is related to cardiovascular events even in CKD patients, however this association should be investigated in further studies (7-9).

Objectives

The aim of this study was to investigate factors associated with CIMT in children with CKD.

Patients and Methods

Study design

This case-control study was conducted on children hospitalized with CKD in Mofid children's hospital (Tehran, Iran) from 2018 to 2021.

Inclusion criteria were children aged more than two years and less than 18 years suffering from CKD according to the criteria of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guideline (10). Exclusion criteria were primary cardiovascular disease or valvular heart disease and lack of consent to participate in the study.

According to a study by Khandelwal et al (11), taking into account α=0.05, β=0.8 and the ratio of 1:3 case to control, the sample size was calculated to be 200 subjects, including 50 subjects in the case group and 150 subjects in the control group.

All patients in the case group were examined in five groups based on the NKF-KDQI guideline (10). Subsequently, all patients in both groups were examined for CIMT of both sides of the carotids by an experienced radiologist. The data of all patients including age, gender, weight, height, laboratory information, duration of CKD, stage of CKD, and CIMT results, were recorded for each participant and compared between the two groups.

Staging for CKD was done as following condition (12):

- Stage 1. Renal damage with a normal or increased GFR (>90 mL/min per 1.73 m^2)
- Stage 2. Mild reduced GFR (60 to 89 mL/min per 1.73 m^2)
- Stage 3. Moderate reduced GFR (30 to 59 mL/min per 1.73 m^2)
- Stage 4. Severe reduced GFR (15 to 29 mL/min per 1.73 m^2)
- Stage 5. Renal failure (GFR <15 mL/min per 1.73 m^2 or dialysis)

Statistical analysis

The data were entered into SPSS version 21 for statistical analysis. To describe qualitative data, frequency and percentage were used, and for quantitative data, mean and standard deviation were presented. To compare the frequency of qualitative variables in the two groups, a chi-square test was conducted. The significance level of all tests was considered less than 0.05. Moreover, Pearson's correlation test was conducted to check the correlation between independent and dependent variables. Independent T-test and one-way analysis of variance (ANOVA) were conducted to compare the mean of dependent variable in subgroups. Linear regression was employed to predict factors related to left and right CIMT.

Results

Fifty patients and 150 controls were examined. Around 52% of the patients were boys and the rest were girls. In the control group, 50% were boys (P=0.80). The mean age in the patient group was higher than in the control group (9.76 ± 4.1 years in the patient group and 8.32 ± 3 years in the control group; P=0.008). The mean weight in the control group was higher than in the patient group (26.04 ± 13.08 kilogram in the patient group and 32.25 ± 9.5 kilogram in the control group) which was statistically significant (P=0.0004). The mean height in the patient group was higher than in the control group (124.44 ± 26.12 centimeters in the patient group and 122.91 ± 12.81 centimeters in the control group). The difference between the two groups was not statistically significant (P=0.58). The data of CIMT between the two groups is shown in Table 1.

The median right CIMT was 0.42 mm in girls and 0.45 mm in boys. In the patient group, the median left CIMT was 0.43 mm in girls and 0.43 mm in boys, where these

Table 1. Carotid intima-media thickness between patient and control groups

Variable	Case, Median (IQR)	Control, Median (IQR)	*P* value*
Right CIMT (mm)	0.48 (0.1)	0.41 (0.05)	<0.001
Left CIMT (mm)	0.48 (0.06)	0.42 (0.05)	<0.001

CMIT, Carotid intima-media thickness.
* T-test.

differences were not statistically significant ($P>0.05$). The correlation between the patients' data and CIMT was presented in Table 2. A negative correlation was observed between the median right CIMT and weight ($P=0.009$), with an increase of one kilogram of weight, the thickness of the right carotid intima-media decreased by 0.18. Age showed a positive correlation with the thickness of both the right and left CIMT, however only the thickness of the left CIMT was found to be statistically significant ($P=0.005$). With each additional year of age, the thickness of the left CIMT increased by 0.19.

The relationship between laboratory findings and CIMT can be observed in Table 3. A statistically significant correlation was found between left CIMT and mean corpuscular volume (MCV). An increase of one unit in MCV resulted in a decrease of 0.28 times in the value of left CIMT. Additionally, a significant correlation was observed between left CIMT and vitamin D levels. With an increase of one unit in vitamin D, the amount of left CIMT decreased by 0.33 times. Moreover, a statistically significant correlation was found between right CIMT and serum uric acid level. An increase of one unit in uric acid level led to a 0.4 increase in right CIMT level. There was also a correlation between right CIMT and blood sugar, where an increase of one unit in the value of blood sugar resulted in a decrease of 0.33 times in the value of right CIMT. However, no significant statistical correlation was observed between other variables and both CIMTs.

We also found no association between CKD duration and CIMT ($P>0.05$). We assessed CIMT in the case group based on CKD stages (Table 4).

It has been observed that the right CIMT in patients diagnosed with stage 3 is 0.06 times lower compared to those with stage 2 of CKD ($P<0.001$). Furthermore, the right CIMT in patients with stage 5 is 0.05 times less than in patients with stage 2 ($P=0.01$). The left CIMT experiences an increase of 0.005 times with each year of age and 0.001 times with each kilogram of weight. In patients with stage 3, the left CIMT is 0.06 times less than in patients with stage 2 of CKD ($P<0.001$). Similarly, patients with stage 5 disease exhibit a 0.05 decrease in left CIMT compared to patients with stage 2 of CKD ($P=0.01$).

Table 2. Correlation between CIMT by weight, height, and age

Variable		Right CIMT	Left CIMT
Weight (cm)	Pearson's correlation	-0.18	-0.06
	P value	0.009	0.35
Height (kg)	Pearson's correlation	-0.05	0.06
	P value	0.42	0.38
Age (y)	Pearson's correlation	0.10	0.19
	P value	0.13	0.005

CMIT, Carotid intima-media thickness.

Table 3. Correlation between laboratory studies and CIMT

Variable		Right CIMT	Left CIMT
Hemoglobin (g/dL)	Pearson's correlation	-0.17	-0.06
	P value	0.24	0.66
HCT (%)	Pearson's correlation	-0.11	-0.09
	P value	0.43	0.50
MCV (fL)	Pearson's correlation	0.01	-0.28
	P value	0.91	0.04*
Calcium (mmol/L)	Pearson's correlation	-0.22	-0.22
	P value	0.12	0.11
Phosphorus (mmol/L)	Pearson's correlation	-0.17	-0.01
	P value	0.22	0.91
Ca×P	Pearson's correlation	-0.23	-0.10
	P value	0.10	0.45
Vitamin D 25OH (ng/mL)	Pearson's correlation	-0.006	-0.33
	P value	0.96	0.03*
ALP (U/L)	Pearson's correlation	0.08	0.24
	P value	0.56	0.09
Uric acid (mmol/L)	Pearson's correlation	0.40	-0.10
	P value	0.004	0.48
GFR (mL/min)	Pearson's correlation	0.008	0.09
	P value	0.95	0.53
Blood pressure (mm Hg)	Pearson's correlation	0.05	-0.06
	P value	0.72	0.65
BUN (mg/dL)	Pearson's correlation	0.05	-0.12
	P value	0.69	0.38
Creatinine (mg/dL)	Pearson's correlation	0.03	0.07
	P value	0.79	0.61
ESR (s)	Pearson's correlation	0.12	0.18
	P value	0.40	0.20
CRP (mg/L)	Pearson's correlation	0.20	-0.23
	P value	0.16	0.10
Blood sugar (mg/dL)	Pearson's correlation	-0.33	-0.10
	P value	0.01*	0.47
Triglyceride (mg/dL)	Pearson's correlation	-0.11	-0.01
	P value	0.47	0.93
Cholesterol (mmol/L)	Pearson's correlation	-0.02	-0.07
	P value	0.86	0.63

CMIT, Carotid intima-media thickness; HCT, Hematocrit; MCV, Mean corpuscular volume; RBC, Red blood cell; ALP, Alkaline phosphatase; GFR, Glomerular filtration rate; BUN, Blood urea nitrogen; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 4. Evaluation of CIMT across different stages of chronic kidney disease

Stage	Right CIMT, Mean (SD)	*P* value*	Left CIMT, Mean (SD)	*P* value*
2	0.53 (0)	0.84	0.53 (0)	0.58
3	0.46 (0.03)		0.46 (0.03)	
4	0.49 (0.13)		0.49 (0.04)	
5	0.47 (0.08)		0.47 (0.08)	

CMIT, Carotid intima-media thickness.
* T-test.

Discussion

This study was conducted to determine affecting factors of carotid artery intima-media thickness in children with CKD. In our study, 50 children with CKD were compared with 150 children without CKD. Children with CKD had a higher value of CIMT than children without CKD. Besides, it was found that there were correlations between CKD and CIMT by age, weight, MCV, vitamin D level, uric acid level, and blood glucose level. It is advisable to conduct periodic measurements of CIMT in children affected by CKD. CIMT serves as a noninvasive diagnostic technique for the evaluation of generalized atherosclerosis. Consequently, it is posited that CIMT constitutes a commendable indicator for the manifestation of cardiovascular disease. One of the risk factors associated with cardiovascular disease is CKD. Therefore, in the context of this study, we assessed the correlation between CKD and CIMT in children with CKD.

In the study by Mudi et al, 72 children with CKD underwent CIMT. It was found that the mean age of children with CKD was 10.8 ± 3.5 years and male to female ratio was 2:1. The median CIMT was 0.505 mm. The duration of the disease, hemoglobin, and estimated glomerular filtration rate (eGFR) were associated with CIMT (13). In the current study, it was found that the mean age of the patients was 9.76 ± 4.1 years and 52% of children with CKD were boys. These findings were different from the findings of Mudi et al. The median CIMT observed in our study's case group was 0.48 mm, which was slightly lower than that of the study by Mudi et al (13).

We discovered that the disease duration and hemoglobin had no significant correlation with CIMT in children with CKD but with increasing the grade of CKD, the median CIMT increased. However, as the severity and grade of CKD increased, the median CIMT also increased. This finding emphasizes the significance of cardiovascular evaluation in children with advanced stages of CKD.

Brady et al found that the median CIMT in children with CKD was 0.43 mm compared to 0.41 mm in healthy controls. Dyslipidemia and hypertension were associated with higher median CIMT. Gender, GFR, body mass index, pubertal status, birth weight, calcium, and phosphorus were not associated with CIMT (4). These findings were similar to our study but based on our findings, dyslipidemia did not correlate with CIMT. Additionally, hypertension was not assessed in our study.

Kamel et al revealed that patients with nephrotic syndrome have higher CIMT. They mentioned that CIMT was positively correlated to disease duration and BMI (14). In the current study, we found that CKD was correlated to higher CIMT but we did not find any correlation between CIMT and disease duration or BMI. Moreover, Paripović et al conducted a study on children with nephrotic syndrome to evaluate CIMT in these patients. They found that children with nephrotic syndrome had higher CIMT in comparison to healthy children and CIMT had a positive correlation with BMI and disease duration (15). These findings were similar to the study by Kamel et al (14). Maybe the difference between our study with these two mentioned studies (14,15) about the associated factors between CIMT and renal failure comes from the different understudied populations because their population had nephrotic syndrome. Although the population of our study was different, all of these three studies confirmed that CIMT was correlated to renal function.

Likewise, Khandelwal et al evaluated the correlated factors between CIMT and CKD in children. They found that mean CIMT was higher in children with CKD than in normal children and also dyslipidemia was correlated to elevated CIMT (11). We did not find any correlation between higher CIMT and dyslipidemia in children with CKD. We found that higher CIMT was correlated to the presence of CKD. We should note that the correlated factors between CIMT and CKD were different in studies. Then, more studies should be performed in the future about the assessment of these factors.

Conclusion

It is concluded that CIMT is a good method for assessing and predicting cardiovascular events in children with CKD. This method correlates with age, weight, MCV, vitamin D level, uric acid level, and blood glucose level in patients with CKD, and children with CKD had a higher amount of CIMT than in children without CKD. Periodic CIMT should be performed in children with CKD.

Limitations of the study

One of the limitations of the current study was the limited statistical population as a case group. Another limitation of the study was the lack of parental consent to participate in the study.

Authors' contribution

Conceptualization: Nasrin Esfandiar.
Data curation: Golsa Tajziehchi.
Formal analysis: All authors.

Investigation: Nasrin Esfandiar.
Methodology: Mahmood Hajipour.
Project administration: Nasrin Esfandiar.
Resources: All authors.
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Writing–original draft: Nasrin Esfandiar, Mitra Khalili, Masoumeh Mohkam, Golsa Tajziehchi, Sara Rashki Ghalenoo.
Writing–review & editing: All authors.

Conflicts of interest

The authors report no biomedical financial interests or potential conflicts of interest.

Ethical issues

The research adhered to the principles of the Declaration of Helsinki. This study received approval from the ethics committee of Shahid Beheshti University of Medical Sciences (Ethical code: IR.SBMU.MSP.REC.1401.318). For this study, the parents of the children provide the consent for participation in this research. Additionally, the authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

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