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# Vascular and Lipid profile in Children with Chronic Kidney Disease

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## ABSTRACT

**Background:** Chronic kidney disease (CKD) is characterized by irreversible kidney damage and/or progressive loss of function. Patients with CKD have hypertension and dyslipidemia, which lead to carotid intima media thickness and early atherosclerosis.

**Objective:** This study aimed to evaluate the interrelationship between vascular and lipid profile abnormalities and the different stages of CKD in pediatric patients. **Methods:** This cross-sectional study was done on 99 patients: 33 with stage 5 CKD on regular hemodialysis & 33 pre-dialysis CKD stage 2-4 on conservative management & 33 age and sex matched controls. Anthropometric measures, blood pressure readings, and a lipid profile were done to all groups**.** Intima media thickness was measured using ultrasound Doppler in both the common and internal carotid arteries (CCA & ICA)

**Results:** The waist-to-hip ratio in CKD 2-4 patients was significantly higher than in CKD 5 patients, and both were higher than the controls, with means of 1.01 ± 0.19, 0.88 ± 0.10, and 0.86 ± 0.05 respectively. Except for high-density lipoproteins (HDL), the lipid profile, including triglycerides, cholesterol, and low-density lipoproteins (LDL), were all significantly increased when comparing CKD 2-4 with CKD 5, and both were higher than the controls: 170.45 ± 42.04, 166.00 ± 45.57, and 100.88 ± 26.19 for triglycerides (p 0.001). The right and left ICA and CCA showed a significant increase in the intimal thickness being higher in the CKD 5 group than in the CKD 2-4 and both were higher than the controls.

**Conclusion:** Patients with CKD had a higher waist to hip ratio with elevated lipid profile and carotid intimal thickness.

**Keywords:** CKD, Vascular, Lipid profile, Dyslipidemia, Carotid intima media thickness.

## INTRODUCTION

A condition known as chronic kidney disease (CKD) is characterised by permanent kidney damage and/or a steady loss in kidney function over time. Kidney Disease Improving Global Outcomes' clinical practise recommendations KDIGO established guidelines for paediatric CKD staging in 2012 [1].

Moderate to severe loss of glomerular filtration rate (GFR) (i.e., GFR <45 mL/min per 1.73 $m^2$ G3b to G5) may result in several complications due to kidney function impairment. These consequences include anaemia, uremic diseases, dyslipidemia, hypertension, endocrine abnormalities, fluid and electrolyte problems, mineral and bone disorders, and hypertension [1].

Children with CKD often have additional CVD risk factors, including hypertension and dyslipidemia. They may have myocardial abnormalities and early atherosclerosis evidence, such as coronary artery calcification, [2] abnormal flow-mediated dilation, increased carotid intima-medial thickness (CIMT), and increased aortic stiffness [3]. These abnormalities seem to be, in part, related to the degree of uremia [4].

According to earlier research, central obesity is more pathological than total fat. Body mass index (BMI) is commonly used to detect overall obesity, other anthropometric indices for obesity include waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR), which are regarded as accurate indicators of central obesity or abdominal fat [5].

Intimal media thickness (IMT) of the common carotid artery (CCA) can be assessed by B-mode ultrasound. This is a simple, non-invasive way for children receiving hemodialysis and CKD to measure the artery walls and track the early impacts of the atherosclerotic process [6].

This study aimed to evaluate the interrelationship between vascular and lipid profile abnormalities and the different stages of CKD in pediatric patients.

## SUBJECTS & METHODS

A cross-sectional study was accomplished in Ain Shams University Children's Hospital Nephrology Unit on 99 children and adolescents. Three groups were generated: 33 patients with stage 5 CKD on regular hemodialysis for almost four hours three times weekly, 33 pre-dialysis patients with stage 2-4 CKD on conservative management and 33 apparently healthy controls of the same age and sex (Table 1) [7].

**Table (1): Grading of CKD according to GFR**

| GFR Category | | GFR (mL/min/1.73m$^2$) | Terms |
|---|---|---|---|
| **G1** | | >90 | Normal or high |
| **G2** | | 60 to 89 | Mild decrease |
| **G3** | **G3a** | 45 to 59 | Mild to moderate |
| | **G3b** | 30 to 44 | Moderate to severe |
| **G4** | | 15 to 29 | Severe decrease |
| **G5** | | < 15 | Kidney Failure |



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**Exclusion criteria:** Patients with chronic debilitating conditions not primarily related to the kidney problem including diabetes, malignancy, liver, and heart disease.
Most of our CKD patients were treated with anti-hypertensive drugs and erythropoietin stimulating agents (ESA), L-carnitine, phosphate binders, calcium, and vitamin D supplementation, in addition to sodium bicarbonate in the pre-dialysis group.

All study participants were given a history that included their age, gender, diagnosis, duration of CKD, and duration of hemodialysis. Anthropometric measures were taken. Blood pressure readings were taken and plotted on percentiles. Laboratory tests were done by withdrawing 3 ml of venous blood after 12 hours of fasting for the lipid profile, including triglycerides, cholesterol, LDL, and HDL**.** In dialysis patients, sampling was done before the mid-week dialysis session. Then all subjects were referred to undergo echocardiography for ultrasound assessment of intimal thickness in the right and left common carotids (CCA) and internal carotid arteries (ICA).

**Ethical consideration:**

**Approval from the Pediatric Department and Ethics Committee, Faculty of Medicine, Ain Shams University were obtained. Signed informed consents before enrollment in the study were obtained from the patients' legal guardians. This work was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

***Statistical analysis***

Statistical Package for Social Science (SPSS) version 25 was used to code, and tabulate the obtained data. Using the proper tests, descriptive and analytical statistics were both carried out including Chi-square test, One Way ANOVA test and Spearman correlation coefficients.

## RESULTS

This study included 66 CKD paediatric patients (33 with CKD 2-4 on pre-dialysis and 33 with CKD 5 on regular dialysis) and 33 seemingly healthy age- and gender-matched children as controls, with mean ages of 9.48 ± 3.75, 10.48 ± 2.65, and 8.97 ± 2.19 years (p = 0.109). The male to female ratio showed a highly significant difference (p = 0.006) between all three groups, in which controls were 1:1, CKD 2-4 was 1:2, and CKD 5 was 2.7:1 (Table 2).

As regards blood pressure percentiles, lipid profiles, and carotid intima thickness in the three groups (Control, CKD 4, and CKD 5), all showed a highly statistically significant difference between all three groups with a p value < 0.001 (Table 3).

The CKD 5 group had a significantly higher hip circumference than the CKD 2-4 and control groups, with means of 72.85 ± 10.37), 63.76 ± 18.51, and 69.27 ± 3.43, respectively, with a p value of 0.014.

The waist-to-hip ratio was significantly higher in CKD 2-4 patients than in CKD 5, and both were higher than in the control group, with mean of 1.01 ± 0.19, 0.88 ± 0.10, and 0.86 ± 0.05, respectively. But there was no difference in the waist circumference between the studied groups.When observing the lipid profile values, including triglycerides, cholesterol, and LDL except for HDL, all were significantly higher in the CDK 2-4 group than the CKD-5 group, and both were higher than the control group.

In terms of the right and left ICA and CCA IMT, the CKD-5 group outperformed the CKD-2 group, and both were higher than the control group.

As for hypertension in the form of blood pressure percentiles, in table (3), an obvious increase in the percentiles is recognised in all CKD patients in relation to controls. On one hand, almost half of our CKD patients (48.5%) reported high systolic blood pressure percentiles, and on the other hand, more than half of the patients (54.5% in CKD 2-4) and up to 63% in CKD 5 reported high diastolic blood pressures. (Table 4)

On studying the correlation between the duration of CKD in years and other variables, we found a positive correlation with triglycerides (r = 0.409 & p = 0.001) and right CCA IMT (r = 0.271 & p = 0.028). However, the HDL (r = -0.326 & p = 0.007) revealed a negative correlation in all CKD patients (Table 5).

The HDL level showed an inverse correlation with right CCA and ICA, with a Pearson correlation and p value of -0.314 and 0.017, respectively, for right CCA and -0.291 and 0.026, respectively and for right ICA. The correlation with the rest of the lipid profile did not have statistical significance. (Table 6)

**Table (2):** Relation between CKD grading and demographic data of the studied patients

| | | Control group | CKD 2 - 4 | CKD5 | Test value | P-value | Sig. |
|---|---|---|---|---|---|---|---|
| | | No. = 33 | No. = 33 | No. = 33 | | | |
| Age (years) | Mean ± SD<br>Range | 8.97 ± 2.19<br>5 – 13 | 9.48 ± 3.75<br>4 – 15 | 10.48 ± 2.65<br>4 – 14 | 2.272• | 0.109 | NS |
| Gender | Female<br>Male | 16 (48.5%)<br>17 (51.5%) | 22 (66.7%)<br>11 (33.3%) | 9 (27.3%)<br>24 (72.7%) | 10.289* | 0.006 | HS |

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS),
*:Chi-square test; •: One Way ANOVA test

**Table (3):** Blood pressure percentile, lipid profile, carotid intimal thickness and anthropometric measures in CKD vs. controls

| | | Control group | CKD 2 - 4 | CKD5 | Test value• | P-value | Sig. |
|---|---|---|---|---|---|---|---|
| | | No. = 33 | No. = 33 | No. = 33 | | | |
| **Systolic BP percentile %** | **Mean ± SD** | 49.24 ± 11.67 | 89.06 ± 15.22 | 88.30 ± 16.96 | 78.35 | 0.001 | HS |
| | **Range** | 25 – 75 | 50 – 99 | 50 – 99 | | | |
| **Diastolic BP percentile %** | **Mean ± SD** | 49.24 ± 7.62 | 88.97 ± 15.12 | 90.15 ± 15.58 | 101.40 | 0.001 | HS |
| | **Range** | 25 – 75 | 50 – 99 | 50 – 99 | | | |
| **Triglycerides** | **Mean ± SD** | 100.88 ± 6.19 | 170.45 ± 4.04 | 166.00 ± 5.57 | 33.14 | 0.001 | HS |
| **Cholesterol** | **Mean ± SD** | 104.58 ± 25.32 | 169.67 ± 32.92 | 165.15 ± 27.25 | 53.00 | 0.001 | HS |
| **LDL** | **Mean ± SD** | 89.10 ± 15.82 | 108.70 ± 21.02 | 99.25 ± 21.21 | 8.32 | 0.001 | HS |
| **HDL** | **Mean ± SD** | 48.64 ± 6.35 | 46.85 ± 8.00 | 42.00 ± 7.35 | 7.37 | 0.001 | HS |
| **Right CCA intima media Thickness** | **Mean ± SD** | 0.31 ± 0.04 | 0.41 ± 0.09 | 0.49 ± 0.09 | 49.40 | 0.001 | HS |
| | **Range** | 0.26 – 0.39 | 0.27 – 0.62 | 0.35 – 0.72 | | | |
| **Right ICA intima media Thickness** | **Mean ± SD** | 0.23 ± 0.06 | 0.33 ± 0.07 | 0.43 ± 0.11 | 47.52 | 0.001 | HS |
| | **Range** | 0.15 – 0.37 | 0.2 – 0.45 | 0.27 – 0.66 | | | |
| **Left CCA intima media Thickness** | **Mean ± SD** | 0.28 ± 0.04 | 0.39 ± 0.08 | 0.49 ± 0.13 | 42.97 | 0.001 | HS |
| | **Range** | 0.21 – 0.34 | 0.14 – 0.56 | 0.3 – 0.78 | | | |
| **Left ICA intima media Thickness** | **Mean ± SD** | 0.25 ± 0.07 | 0.33 ± 0.09 | 0.43 ± 0.13 | 29.61 | 0.001 | HS |
| | **Range** | 0.14 – 0.34 | 0.17 – 0.57 | 0.2 – 0.69 | | | |
| **Waist circumference** | **Mean ± SD** | 59.15 ± 4.40 | 62.39 ± 16.49 | 63.67 ± 8.93 | 1.446 | 0.241 | NS |
| | **Range** | 53 – 65 | 30 – 88 | 40 – 82 | | | |
| **Hip circumference** | **Mean ± SD** | 69.27 ± 3.43 | 63.76 ± 18.51 | 72.85 ± 10.37 | 4.495 | 0.014 | S |
| | **Range** | 64 – 78 | 32 – 108 | 50 – 95 | | | |
| **Waist/hip ratio** | **Mean ± SD** | 0.86 ± 0.05 | 1.01 ± 0.19 | 0.88 ± 0.10 | 13.840 | <0.001 | HS |
| | **Range** | 0.77 – 0.93 | 0.6 – 1.37 | 0.71 – 1.1 | | | |

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) •: One Way ANOVA test

**Table (4):** Percentage of patients with systolic and diastolic blood pressure equal or more than 95 and 99 percentiles

| | CKD 2-4 (no 33) | | | | CKD5 (no 33) | | | |
|---|---|---|---|---|---|---|---|---|
| | Systolic B.p. | | Diastolic B.p. | | Systolic B.p. | | Diastolic B.p. | |
| | no. | % | no. | % | no. | % | no. | % |
| **≥ 95 Percentile** | 16 | 48.5 | 18 | 54.5 | 16 | 48.5 | 21 | 63.6 |

**Table (5):** Correlation between duration of CKD with the other studied parameters

| | Duration of CKD (years) | |
|---|---|---|
| | All CKD patients no.66 | |
| | r | P-value |
| **Systolic BP percentile %** | -0.069 | 0.581 |
| **Diastolic BP percentile %** | -0.108 | 0.389 |
| **Triglycerides** | 0.409** | 0.001 |
| **Cholesterol** | 0.170 | 0.171 |
| **LDL** | 0.159 | 0.202 |
| **HDL** | -0.326** | 0.007 |
| **Right CCA** | 0.271* | 0.028 |
| **Right ICA** | 0.209 | 0.093 |
| **Left CCA** | 0.186 | 0.135 |
| **Left ICA** | 0.078 | 0.535 |

P-value >0.05: Non significant; P-value <0.05: Significant (*); P-value< 0.01: highly significant (**) Spearman correlation coefficients

**Table (6):** Correlation between lipid profile and carotid intimal thickness

| | | Triglycerides | Cholesterol | LDL | HDL |
|---|---|---|---|---|---|
| **Right CCA** | **Pearson Correlation** | -0.183 | -0.004 | -0.055 | -0.314 |
| | **p-Value** | 0.168 | 0.979 | 0.679 | 0.017 |
| | **Sig.** | NS | NS | NS | S |
| **Right ICA** | **Pearson Correlation** | -0.252 | -0.095 | -0.122 | -0.291 |
| | **p-Value** | 0.057 | 0.479 | 0.361 | 0.026 |
| | Sig. | NS | NS | NS | S |
| **Left CCA** | **Pearson Correlation** | -0.165 | 0.034 | 0.070 | -0.225 |
| | **p-Value** | 0.215 | 0.801 | 0.600 | 0.089 |
| | **Sig.** | NS | NS | NS | NS |
| **Left ICA** | **Pearson Correlation** | -0.227 | -0.037 | -0.064 | -0.123 |
| | **p-Value** | 0.086 | 0.782 | 0.631 | 0.357 |
| | **Sig.** | NS | NS | NS | NS |

P-value >0.05: Non significant; P-value <0.05: Significant (*); P-value< 0.01: highly significant (**)

## DISCUSSION

CKD patients have a variety of different characteristics, some related to the cause of the disease and others related to the disease itself. In our study, we explored the different characteristics seen, with special emphasis on the lipid and vascular systems. In our cohort of 99 patients and controls (33 CKD5, 33 CKD2-4, and 33 healthy controls), we found that there was an increased risk of CKD5 in males (72.7%) in relation to females (27.3%) because they are more likely to have congenital kidney and urinary tract abnormalities (CAKUT), such as obstructive uropathy and kidney dysplasia and hypoplasia, that is the same as previously stated by **Wong *et al.*** [8].

As regards the age of our patients, almost all of them ranged from 4 to 15 years old, which is wider than the NAPRTCS annual report 2008, which revealed the 6-13 age group is the commonest age group for CKDs, representing 32.1% [9].

One of the most important factors influencing the development of paediatric renal illness and a significant risk factor for cardiovascular problems is systemic arterial hypertension. High systolic blood pressure (SBP) (> 95 percentile) was seen in 48% of patients, while high diastolic blood pressure (DBP) was recorded in 54% of CKD2-4 and 63% of CKD5. These numbers coincide with those of **Peralta and Shlipak** [10] who stated that the prevalence of hypertension in their cohort was 54% in 540 CKD patients. Also, **Lee *et al.*** **(11)** reported that the SBP and DBP were ≥ 130 mmHg and ≥80 mmHg in 48.52% and 51.99% of the participants in their study, respectively. The clear increase in blood pressure rate from CKD 2-4 to CKD 5 can be explained by the rationale of progressive decline in GFR leading to volume expansion and/or activation of the renin-angiotensin system. Moreover, concurrent medications like corticosteroids or calcineurin inhibitors that are used to treat the underlying kidney disease can induce hypertension. Among the most significant, modifiable risk factors for cardiovascular disorders in CKD patients is blood pressure. According to research in the literature, children's high blood pressure and symptoms of atherosclerosis or arteriosclerosis are related [12].

Obesity has been strongly associated with higher cardiovascular risk. It is well established that central fat distribution, rather than total body weight or BMI, is more strongly associated with obesity-related morbidities.[13, 14]. Abdominal circumference and waist-to-hip ratio are markers for central obesity, which are sensitive indicators for cardiovascular risk and are associated with an increased risk of developing atherosclerosis in children and adolescents [15] . The waist-to-hip ratio was significantly higher in CKD2-4 than in CKD 5, and both were higher than in the control group, indicating that CKD patients have central adiposity and a higher risk of developing cardiovascular diseases, but there was no difference in waist circumference between the studied groups. Notably, CKD2-4 patients had a higher waist-to-hip ratio and a higher lipid profile. This can be attributed to the need for diet control and a strict nutritional management plan for these patients even before the disease evolves and they start dialysis.

Atherosclerosis can occur as a result of lipid changes, which have been identified as a risk factor. When comparing the lipid profile of all CKD patients with healthy controls, our outcome showed a highly statistically significant increase in CKD patients (p =

0.001), which is in concurrence with **Saland *et al.*** [16] who has shown that dyslipidemia is a typical, enduring problem in CKD children and that it gets worse in line with a decreasing GFR.

In our study, we demonstrated the significant elevation of triglycerides, cholesterol, and LDL in CKD 2-4 patients. This is in concurrence with **Brady *et al.*** [17] who proved the presence of dyslipidemia in CKD 2-4 patients as well.

Both CKD groups had an increase in carotid intimal thickness in comparison to controls. It should be noted that CKD 5 patients had the highest thickness. Additionally, other researchers have shown that children with various degrees of renal disease have thicker carotid intima than the general population, with CKD5 patients having the highest measures.[18, 19] . Also, this is concomitant with the study done by **Lawal *et al.*** [20] that confirmed the increase in carotid intimal thickness in pre-dialysis patients.

Studies involving children have shown a link between dyslipidemia and increased carotid intima-media thickness. Children with CKD stages 2-4 were studied by **Brady *et al.*** [17] who established this connection.

High-density lipoproteins (HDL) are known to be protective against the development of atherosclerosis [21]. In our study, we demonstrated that HDL was significantly lower in CKD patients than in the control group. Also, there was an inverse correlation between the HDL level and the right CCA and ICA IMT. CKD 5 patients have malnutrition due to anorexia, drugs, and the effects of hemodialysis. Nausea and vomiting contribute to decreased feeding, low energy, and protein intake with loss of amino acids, which lead to increased production and impaired removal of triglycerides, and low apoprotein (A1 and A2), which leads to decreased HDL [22]. This indicates the importance of a nutritional rehabilitation and management plan to try to improve the lipid profile status, decrease triglycerides, cholesterol, and LDL, and increase HDL. This challenge in management is important to protect against the development of atherosclerosis.

Malnutrition, anemia, inflammation, oxidative stress, vascular calcification (caused by alterations in calcium and phosphorus metabolism), and endothelial dysfunction are additional variables in CKD-5 patients that contribute to the development of dyslipidemia. Efforts should be directed to try and treat these conditions and postpone the development of atherosclerosis [23, 24].

**Khandelwal *et al.*** [25] also discovered that children with CKD at various stages had increased carotid media-intima thickness, triglycerides, total cholesterol, and LDL cholesterol. In this study, the univariate analysis revealed an association between LDL cholesterol and altered carotid thickness, however the multivariate analysis failed to support this association.

There was a direct correlation between disease duration and right CCA intimal thickness, indicating that not only disease severity but also disease duration can play a role in the development of a cardiovascular risk. This correlation has not been studied before. Another study compared patients on hemodialysis for one year with those on it for more than one year and discovered no difference in triglyceride or HDL levels between the two groups [26].

## CONCLUSION

Patients with CKD have an increased waist-to-hip ratio, dyslipidemia, and increased carotid IMT, which are factors that lead to the early development of atherosclerosis. Special care should be directed to CKD patients, especially those in stages 2-4, to control their lipid profile and postpone the development of atherosclerosis as much as possible.

## Conflicts of Interest And Funding

The authors declared that there were no conflicts of interest. There was no funding for the study from any source.

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