# Brachial Artery Flow-mediated Dilatation and Carotid Intima-Media Thickness in Children With Idiopathic Nephrotic Syndrome

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**Keywords.** nephrotic syndrome, carotid intima-media thickness, brachial artery flow-mediated dilatation, atherosclerosis

**Introduction.** Disturbances of lipid metabolism has been reported in nephrotic syndrome (NS) and may predispose to atherosclerosis. This study aimed to investigate the correlation between cardiovascular risk factors and carotid intima-media thickness (CIMT) and brachial artery flow-mediated dilatation in patients with idiopathic NS.
**Materials and methods.** This case-control study included 31 patients with NS and 31 healthy individuals as the control group. All patients were subjected to full clinical examination; laboratory investigations in the form of lipid profile, kidney function tests, serum protein, serum albumin, C-reactive protein, and ferritin; carotid ultrasonography, and brachial artery flow-mediated dilatation.
**Results.** Serum cholesterol, low-density lipoprotein cholesterol, and triglyceride levels was significantly higher in the case group than the control group. High-density lipoprotein cholesterol and albumin levels were significantly lower in the case group. The absolute change in brachial artery diameter was significantly lower in the case group than that of the control group. Proportionate change in brachial artery diameter was significantly lower in the case group than that of the control group. Common carotid artery CIMT in the case group was significantly higher than that of the controls. Lastly, there were significant increases in weight and body mass index in the relapse group than the remission group.
**Conclusions.** Patients with NS are more prone to atherosclerosis and vascular changes; CIMT was thicker in nephrotic children compared to the controls. The significantly abnormal values of flow-mediated dilatation in children with NS suggests an ongoing process of endothelial dysfunction.

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## INTRODUCTION

Nephrotic syndrome (NS) is a chronic disorder in children characterized by selective proteinuria (primarily albumin) greater than 40 mg/m$^2$/h.[1] More than 90% of children respond to treatment with oral steroids, and about 60% have a frequently relapsing NS or steroid-dependent NS that requires a prolonged period of steroid therapy or treatment with other immunosuppressants.[2]

Disturbances of lipid metabolism found in NS have been reported to persist even during remission periods and may predispose

to endothelial dysfunction or structural atherosclerosis.[3] Endothelial dysfunction and structural atherosclerosis are commonly studied by 2 methods of disturbance in flow-mediated dilatation (FMD) and increase in the carotid intima-media thickness (CIMT), respectively.[4]

High-resolution ultrasonography is a reliable noninvasive method for detecting early structural and functional atherosclerotic changes in the arterial wall. Increased carotid intimal-media thickness, a structural marker of early atherosclerosis, relates to the severity and extent of coronary artery disease and predicts the likelihood of cardiovascular events in population groups. Flow-mediated dilation of the brachial artery is a marker of endothelial function that can be assessed by measuring arterial diameter responses to increased flow.[5] Studies on the evaluation of endothelial function and its predictive risk factors in children with NS are scarce. Such studies are important from the therapeutic point of view as well as planning preventive strategies.[6] The aim of this study was to investigate the correlation between CIMT and brachial artery FMD with cardiovascular risk factors in patients with idiopathic NS.

## MATERIALS AND METHODS

### Participants

The study was conducted in the Nephrology Unit and Radiology Department, Zagazig University Children's Hospital, from May 2016 till December 2016. This Case-control observational study was designed to compare patients with idiopathic NS and control subjects. The study protocol was approved by the local ethics committee, and a written informed consent was obtained from all patients' parents before starting the clinical study.

The Study included 31 patients with idiopathic NS with an age range between 3 and 10 years (19 males and 12 females) who were diagnosed clinically and proven by laboratory results and were classified according to their response to steroid treatment into steroid-sensitive, steroid-dependent, and steroid-resistant NS. These patients had been followed up at the nephrology unit of the Department of Pediatrics, Zagazig University Hospital. The control group consisted of 31 age- and sex-matched apparently healthy children selected from the general pediatric outpatient department.

The inclusion criteria were both male and female children, age at start of study greater than 2 years, and normal kidney function in the control group. The exclusion criteria were a family history of premature cardiovascular diseases (ie, disease at or before age of 55 years in fathers and 65 years in mothers, elevated serum creatinine for age, acute infections and inflammatory disorders, current use of statins.

### Methods

All children included in this study were subjected to full history taking, thorough clinical examination, laboratory investigations in the form of fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDLC], low-density lipoprotein cholesterol [LDLC], and triglycerides), serum urea and creatinine, total protein and serum albumin, C reactive protein, ferritin, and urine protein-creatinine ratio. Serum ferritin was checked because it might cause vascular changes with higher levels.[7]

All children were also subjected to imaging techniques in the form of carotid ultrasonography for CIMT measurement and brachial artery FMD for assessment of endothelial function. Measurements were done by B-mode ultrasound in the common carotid and internal carotid and brachial arteries from the thickest area along the course by a Prosound Alfa 7 Aloka ultrasound machine that had a broad-band linear probe with a frequency of 1 MGz to 15 MGz.

### Statistical Analysis

Data were collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered, and analyzed using the Microsoft Excel software. Data were then imported into the SPSS software (Statistical Package for the Social Sciences, version 20.0, SPSS Inc, Chicago, IL, USA) for analysis. According to the type, qualitative data were presented as number and percentage and quantitative data as mean ± standard deviation. The following tests were used to examine differences for significance: frequencies were compared by the chi-square test between groups. Parametric quantitative independent groups were examined using the *t* test or the Mann-Whitney test. *P* value was set at less than .05 for significant results and less than .001 for highly significant result.

## RESULTS

Histopathological examination of kidney biopsies were done is 7 patients, 4 of which indicated focal segmental glomerulosclerosis (FSGS) and 3, minimal change disease. Sex distribution was comparable between the case and control groups. Body weight and body mass index (BMI) were significantly greater in the case group than the control group (Table 1). Serum cholesterol, LDLC, and spot urine protein-creatinine ratio were also significantly higher in the case group. Serum triglyceride was significantly higher in the case group, while HDLC, serum total protein, serum albumin were significantly lower than the control group (Table 1).

Brachial diameter was greater at rest in the case group than that of the control group but significantly lower regarding after release of the cuff (Figure 1). Velocity of blood in the brachial artery was significantly higher during rest and after release of the cuff in the control group than that of the case group (Figure 2).

The steroid-resistant NS cases had higher levels of cholesterol, triglyceride, and LDLC than the other clinical types of NS (Table 2). There was no significant difference in the common carotid artery CIMT among the clinical types of NS. The

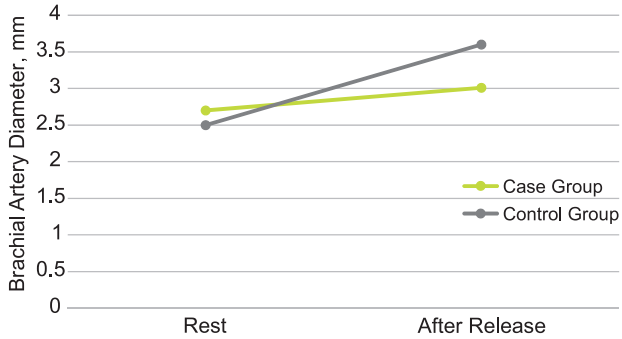


**Figure 1.** Comparison of brachial artery diameter between rest and after release of cuff in the case and control groups.
*P* < .001 for both groups

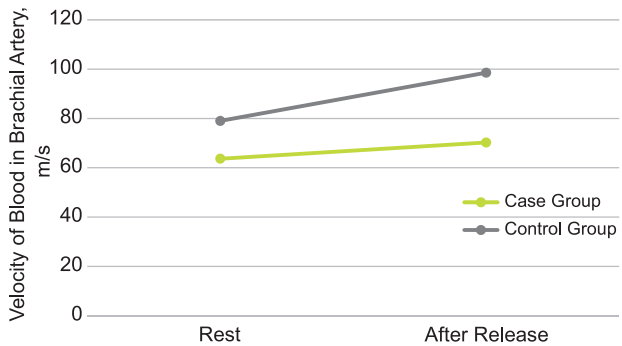


**Figure 2.** Comparison of velocity of blood in brachial artery between rest and after release of cuff in the case and control groups.
*P* < .001 for both groups

**Table 1.** Demographics, Clinical Characteristics, and Biochemical Parameters of Patients

| Characteristic | Patients | | *P* |
|---|---|---|---|
| | Case | Control | |
| Number of patients | 31 | 31 | |
| Sex | | | |
| Male | 19 | 19 | |
| Female | 12 | 12 | > .99 |
| Age, y | 6.13 ± 0.76 | 6.03 ± 0.83 | .64 |
| Weight, kg | 26.54 ± 5.66 | 21.87 ± 2.70 | < .001 |
| Height, m | 1.16 ± 0.063 | 1.16 ± 0.071 | .77 |
| Body mass index, kg/m$^2$ | 19.28 ± 2.88 | 16.14 ± 1.31 | < .001 |
| Systolic blood pressure, mm Hg | 106.45 ± 7.97 | 105.16 ± 8.89 | .55 |
| Diastolic blood pressure, mm Hg | 64.51 ± 5.67 | 71.29 ± 7.18 | .66 |
| Serum cholesterol, mg/dL | 419.21 ± 164.81 | 147.87 ± 10.63 | < .001 |
| Serum triglycerides, mg/dL | 374.55 ± 176.66 | 81.69 ± 16.42 | .003 |
| High-density lipoprotein cholesterol, mg/dL | 34.98 ± 10.49 | 57.20 ± 3.23 | < .001 |
| Low-density lipoprotein cholesterol, mg/dL | 363.36 ± 159.57 | 83.75 ± 7.04 | < .001 |
| Serum urea, mg/dL | 8.95 ± 1.20 | 8.57 ± 1.12 | .21 |
| Serum creatinine, mg/dL | 0.15 ± 0.033 | 0.21 ± 0.108 | .004 |
| Serum total protein, g/dL | 4.62 ± 1.70 | 7.00 ± 0.39 | < .001 |
| Serum albumin, g/dL | 2.31 ± 1.16 | 4.21 ± 0.44 | < .001 |
| Spot urine protein-creatinine ratio, mg/mg | 1.58 ± 0.86 | 0.11 ± 0.026 | < .001 |
| C-reactive protein, mg/dL | 0.26 ± 0.190 | 0.19 ± 0.072 | .18 |
| Ferritin, ng/mL | 88.98 ± 9.08 | 89.35 ± 8.17 | .87 |

**Table 2.** Clinical Types of Nephrotic Syndrome by Lipid Profile*

| Parameter | Patients With Nephrotic Syndrome | | | | *P* |
|---|---|---|---|---|---|
| | FRNS | IFRNS | SDNS | SRNS | |
| Serum cholesterol, mg/dL | 405 ± 174.55 (155.6 to 583.6) | 390.8 ± 172.83 (160.8 to 610.6) | 392.5 ± 183.64 (145.8 to 617.4) | 535.6 ± 49.6 (490.3 to 620.3) | .41 |
| Serum triglycerides, mg/dL | 370.4 ± 196.17 (79.8 to 454.9) | 376.6 ± 203.5 (80.5 to 544.7) | 337.2 ± 194.99 (74.3 to 530.7) | 446.6 ± 14.03 (429.7 to 464.8) | .61 |
| High-density lipoprotein cholesterol, mg/dL | 33.9 ± 13.71 (22.5 to 56.9) | 35.8 ± 5.59 (30.1 to 44.6) | 37.9 ± 12.48 (23.9 to 60.1) | 30.9 ± 1.02 (29.6 to 32.2) | .68 |
| Low-density lipoprotein cholesterol, mg/dL | 352.7 ± 175.5 (99.6 to 524) | 338.3 ± 158.62 (98.9 to 447.6) | 350.4 ± 192.27 (88.8 to 510.6) | 443.2 ± 16.34 (422 to 460.5) | .70 |

*FRNS indicates frequent-relapsing nephrotic syndrome; IFRN, infrequent-relapsing nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome; and SRNS, steroid resistant nephrotic syndrome.

**Table 3.** Clinical Types of Nephrotic Syndrome by Imaging Parameters*

| Parameter | Patients With Nephrotic Syndrome | | | | *P* |
|---|---|---|---|---|---|
| | FRNS | IFRNS | SDNS | SRNS | |
| Common carotid artery intimal medial thickness, cm | 0.49 ± 0.09 (0.4 to 0.7) | 0.42 ± 0.06 (0.3 to 0.5) | 0.46 ± 0.06 (0.4 to 0.6) | 0.47 ± 0.08 (0.4 to 0.6) | .23 |
| Resting brachial artery diameter, mm | 2.94 ± 0.32 (2.4 to 3.2) | 2.76 ± 0.25 (2.5 to 3.2) | 2.59 ± 0.24 (2.3 to 3.1) | 2.64 ± 0.34 (2.3 to 3.1) | .07 |
| Post flow-mediated dilatation, mm | 3.13 ± 0.29 (2.6 to 3.4) | 3.10 ± 0.21 (2.8 to 3.4) | 2.92 ± 0.29 (2.5 to 3.4) | 2.84 ± 0.34 (2.5 to 3.3) | .19 |
| Absolute change in brachial artery diameter, mm | 0.19 ± 0.09 (0.1 to 0.4) | 0.34 ± 0.17 (0.2 to 0.7) | 0.33 ± 0.14 (0.2 to 0.6) | 0.19 ± 0.01 (0.2 to 0.2) | .47 |
| Proportionate change in brachial artery diameter, % | 6.46 ± 3.83 (3.12 to 14.8) | 12.43 ± 7.26 (6.25 to 28) | 12.87 ± 5.55 (7.69 to 23) | 7.41 ± 0.88 (6.45 to 8.69) | .24 |
| Resting brachial artery blood flow velocity, mm | 61.81 ± 7.43 (53.1 to 74.3) | 68.80 ± 11.71 (55.5 to 82.4) | 64.59 ± 13.84 (51.7 to 96.5) | 59.12 ± 6.35 (53.2 to 66.5) | .42 |
| Velocity after release cuff, m/s | 69.02 ± 9.18 (60.3 to 85.7) | 76.84 ± 10.44 (67.1 to 90.2) | 70.84 ± 16.21 (56 to 108.6) | 63.22 ± 5.88 (57.7 to 72.2) | .26 |

proportionate change in the brachial artery diameter in the frequently relapsing–steroid-resistant NS cases was less than the proportionate change in the infrequently relapsing–steroid-dependent NS cases (Table 3).

Serum cholesterol, LDLC and spot protein-creatinine ratio was significantly higher in the relapse group than the remission group. Serum triglyceride was significantly higher in the relapse group. Serum HDLC and albumin was significantly lower in the relapse group than the remission group (Table 4). There was no significant changes between the relapse and remission groups regarding imaging (Table 5). There was a significance correlation between disease duration and resting brachial artery diameter and post-FMD (Table 6). There was a significant correlation between serum triglyceride and the right common carotid artery CIMT (Table 7).

## DISCUSSION

Idiopathic nephrotic syndrome is the most common glomerulopathy of childhood. It is defined by nephrotic-range proteinuria, generalized edema, hypoalbuminemia, and hyperlipidemia with normal kidney function.[9] Childhood NS typically follows a relapsing-remitting course, often requiring recurrent courses of glucocorticoids, but with low systemic inflammation during remission.[10]

Disturbances of lipid metabolism found in NS have been reported to persist even during remission periods and may predispose to endothelial dysfunction or structural atherosclerosis.[11] Nephrotic patients are prone to myocardial infarction and coronary artery disease secondary to hypoalbuminemia, dyslipidemia, and hypercoagulopathy state.[12]

Endothelial dysfunction, reflecting functional change in the arterial elasticity and hemodynamics, is an early reversible stage in the development of atherosclerosis and has predictive value for future cardiovascular events.[13] Endothelial dysfunction and structural atherosclerosis are commonly studied by 2 methods: disturbance in FMD and increase in the CIMT, respectively.[14] Carotid intima-media thickness is an indirect marker of atherosclerosis and target organ damage in adults. Its value in children is still under debate but there are increasing numbers of studies among children with risk factors for vascular damage.[13]

Hemodynamic, metabolic, and inflammatory factors change reversibly the arterial wall thickness. Impaired function of endothelium has been shown in acute phase of idiopathic NS. Few studies of CIMT in nephrotic children show correlations with duration of disease and unresponsiveness

**Table 4.** Laboratory Results in Patients With Relapse and Remission

| Parameter | Relapse | Remission | *P* |
|---|---|---|---|
| Serum cholesterol, mg/dL | 507.18 ± 75.10 | 166.30 ± 12.55 | < .001 |
| Serum triglycerides, mg/dL | 476.02 ± 40.70 | 85.21 ± 12.19 | < .001 |
| High-density lipoprotein cholesterol, mg/dL | 29.46 ± 3.73 | 50.86 ± 6.33 | < .001 |
| Low-density lipoprotein cholesterol, mg/dL | 454.35 ± 34.13 | 101.77 ± 7.87 | < .001 |
| Serum Urea, mg/dL | 9.03 ± 1.22 | 8.71 ± 1.21 | .52 |
| Serum Creatinine, mg/dL | 0.14 ± 0.02 | 0.17 ± 0.04 | .04 |
| Serum total Protein, g/dL | 3.65 ± 0.37 | 7.36 ± 0.48 | < .001 |
| Serum Albumin, g/dL | 1.67 ± 0.31 | 4.17 ± 0.39 | < .001 |
| Spot urine protein-creatinine ratio, mg/mg | 2.08 ± 0.08 | 0.13 ± 0.017 | < .001 |
| C-reactive protein, mg/dL | 0.18 ± 0.08 | 0.50 ± 0.29 | .005 |
| Ferritin, ng/dL | 88.88 ± 9.93 | 89.27 ± 6.58 | .92 |

**Table 5.** Imaging Results in Patients With Relapse and Remission

| Parameter | Relapse | Remission | *P* |
|---|---|---|---|
| Right common carotid artery intimal medial thickness, cm | 0.45 ± 0.07 | 0.43 ± 0.05 | 0.531 |
| Left common carotid artery intimal medial thickness, cm | 0.46 ± 0.08 | 0.47 ± 0.07 | 0.876 |
| Resting brachial artery diameter, mm | 2.72 ± 0.30 | 2.81 ± 0.33 | 0.507 |
| Post flow-mediated dilatation, mm | 2.98 ± 0.29 | 3.10 ± 0.28 | 0.358 |
| Resting brachial artery blood flow velocity, mm | 62.35 ± 10.58 | 67.81 ± 10.00 | 0.213 |
| Velocity after release of cuff | 69.51 ± 12.45 | 72.87 ± 10.29 | 0.499 |

**Table 6.** Correlations Between Patient Characteristics and Imaging Results*

| Patient Characteristics | Right Common Carotid Artery Intimal Medial Thickness | Left Common Carotid Artery Intimal Medial Thickness | Resting Brachial Artery Diameter | Post Flow-mediated Dilatation | Resting Brachial Artery Blood Flow Velocity | Velocity After Release Of Cuff |
|---|---|---|---|---|---|---|
| Age | 0.117 (.53) | 0.326 (.07) | -0.154 (.41) | -0.187 (.31) | -0.023 (.90) | 0.053 (.78) |
| Onset | 0.228 (.22) | 0.120 (.52) | -0.475 (.007) | -0.510 (.003) | 0.087 (.64) | 0.234 (.21) |
| Disease duration | -0.137 (.46) | 0.215 (.25) | 0.383 (.03) | 0.387 (.03) | -0.126 (.50) | -0.213 (.25) |
| Body mass index | 0.015 (.94) | 0.136 (.47) | -0.012 (.95) | 0.117 (.53) | -0.179 (.33) | -0.061 (.75) |
| Systolic blood pressure, mm Hg | -0.192 (.30) | 0.041 (.83) | -0.130 (.49) | 0.054 (.78) | -0.178 (.34) | -0.223 (.23) |
| Diastolic blood pressure, mm Hg | -0.099 (.60) | -0.423 (.02) | -0.147 (.43) | 0.035 (.85) | 0.192 (.30) | 0.198 (.29) |

*Values indicate correlation coefficient (*P* value).

**Table 7.** Correlations Between Patient Characteristics and Lipid Profile*

| Patient Characteristics | Right Common Carotid Artery Intimal Medial Thickness | Left Common Carotid Artery Intimal Medial Thickness | Resting Brachial Artery Diameter | Post Flow-mediated Dilatation | Resting Brachial Artery Blood Flow Velocity | Velocity After Release Of Cuff |
|---|---|---|---|---|---|---|
| Serum cholesterol, mg/dL | 0.057 (.76) | -0.126 (.50) | -0.060 (.75) | -0.114 (.54) | -0.206 (.27) | -0.107 (.57) |
| Serum triglycerides, mg/dL | 0.386 (.03) | -0.162 (.38) | 0.177 (.34) | 0.071 (.71) | -0.017 (.93) | -0.053 (.78) |
| High-density lipoprotein cholesterol, mg/dL | -0.145 (.46) | -0.104 (.58) | -0.055 (.77) | 0.037 (.84) | 0.152 (.42) | 0.024 (.90) |
| Low-density lipoprotein cholesterol, mg/dL | 0.059 (.75) | -0.037 (.84) | -0.105 (.57) | -0.139 (.46) | -0.228 (.22) | -0.124 (.51) |

*Values indicate correlation coefficient (*P* value).

to steroid.[3]

This study was designed to investigate the correlation between CIMT and brachial artery FMD with cardiovascular risk factors in patients with idiopathic NS. Similar to our study, many authors studied the carotid intimal thickness and brachial artery FMD in vascular disease, like early rheumatoid arthritis,[14,15] childhood-onset systemic lupus erythematosus,[16] and presence of cardiovascular risk factors.[13]

There was a significant increase in weight and BMI in the case group than control group. Similar to our results, Kuźma-Mroczkowska and colleagues[11] found that mean BMI Z-score was significantly higher in children with idiopathic NS compared to the control group ($P$ = .049). They concluded that glucocorticoid therapy might result in body mass increase in children with idiopathic NS. Also, El-Mashad and coworkers[9] found that patients with NS had significantly higher weight and BMI Z-scores than the controls. Similar results were reported by Rahul and colleagues[6] found that BMI of NS cases was significantly higher than the controls. Increase weight and BMI in patients with NS can be explained by the fact that retention of excess weight during the period following glucocorticoid therapy is related to the dose and duration of glucocorticoid exposure and usually associated with hyperlipidemia, which might enhance cardiovascular risk.[17]

Regarding histopathology of renal biopsy, 12.9% of our patients had FSGS and 9.7% had minimal change disease. Renal biopsy is useful for determining the prognosis and for choosing the most appropriate treatment, although the invasiveness of this technique may lead to serious complications.[18] The diagnosis of FSGS is established by the finding of at least a single abnormal glomerulus and it has been stated that the probability of misdiagnosis is statistically relevant when fewer than 8 glomeruli are found in biopsy samples.[19] The histopathological patterns of NS varies widely from one paper to another.[20]

Hodgson and colleagues[21] have reported an increasing prevalence of FSGS. On the other hand, Adedoyin and Asinobi[22] reported higher incidence rates of membranoproliferative glomerulonephritis, with much lower figures for minimal change disease. Obiagwu and coworkers[23] performed renal biopsy for histopathology for 20 patients with NS and

found that the most common histopathological diagnosis was focal glomerulosclerosis in 9 (45%) children (segmental, 8; global, 1). Minimal change disease was found in 4 children (20%), membranoproliferative glomerulonephritis in 3 (15%), membranous nephropathy in 3 (15%), and diffuse mesangial hypercellularity in 1 (5%). In our study, we only do biopsy for resistant cases only and some cases of frequent relapsing nephrotic syndrome so most of our cases biopsy have not been done.

Serum cholesterol, LDLC and spot protein-creatinine ratio in the case group was significantly higher than control group. Serum triglyceride was significantly higher in the case group and HDLC and serum albumin were significantly lower in the case group than the control group.

Similar to our results, Kniazewska and colleagues[3] found that the levels of total cholesterol, LDLC, homocysteine, apoprotein B, and A1 were significantly higher in children with history of idiopathic NS being off treatment for 4 to 15 years.

Patients with NS have a 5.5-fold increased relative risk of myocardial infarction and a 2.8-fold increased relative risk of coronary death. Possible etiological factors include hyperlipidemia, hypoalbuminemia, and a hypercoagulable state. The role of hyperlipidemia, in particular increased LDLC, as a cardiovascular risk factor in the general population is well established. It is pertinent to note that scientific literature opines that LDLC could be involved in the pathogenesis of increased oxidative stress in children with NS through synthesis of atherogenic factors such as malondialdehyde.[25,26]

The absolute change in brachial artery diameter in the case group was significantly lower than that of the control group. Proportionate change in brachial artery diameter (baseline diameter-diameter after cuff release by baseline diameter multiplied by 100) in the case group was significantly lower than that of the control group. Similar to our results, Rahul and colleagues[6] found that the brachial artery FMD after 5 minutes of induced ischemia was significantly lower in the cases. Also, Kocyigit and colleagues[27] found that the FMD values were lower in the NS patients than in the healthy controls.

Dogra and colleagues,[26] in a study of 38 adult patients (19 cases and 19 controls) with NS, reported that NS cases had significantly lower FMDs (NS, 5.1 ± 0.7% versus control, 7.3 ± 0.7%, $P$ = .02) than the control group. Caraba and Romos[28] evaluated 10 NS adults and matched controls. Their observations (FMD in cases, 4 ± 1.4 % versus controls, 11 ± 0.24%) were also consistent with the results of our study.

Common carotid artery CIMT in the case group was higher than that of the control group. There are few published studies about the value of CIMT in nephrotic children; CIMT is a surrogate marker for evaluation of diffuse thickening and stiffening of large and medium sized vessels. It is secondary to hypertension and atherosclerosis that is focal lesion secondary to hyperlipidemia and metabolic disorder. Cardiovascular disease preceded by endothelial dysfunction and CIMT changes.[29]

Taylor and colleagues[30] measured CIMT and atherosclerosis promoting risk factors in 70 children with obesity or familial dyslipidemia. They studied the prevalence of advance vascular age and its correlation with multiple risk factors including hyperlipidemia, insulin resistant statues, smoking, and hypertension. They used subclinical atherosclerosis definition for classifying advanced vascular age in children (maximum CIMT, ≥ 25%; sex-matched 45-year-old adults). The prevalence of advanced vascular age was about 73% to 75% in both groups. Nephrotic children have a trend towards hyperlipidemia, obesity, hypertension, or thromboembolic events.

However, unlike to our results, Rahul and colleagues[6] found that there were no significant differences in the mean CIMT between cases and controls. Also, Kniazewska and colleagues[3] found no differences in CIMT between 30 cases formerly treated for NS versus 30 controls. It is probable that the development of a structural change such as CIMT may require a longer duration of the underlying pathophysiology.

Regarding relapse and remission, there were significant increases in weight and BMI in the relapse group than the remission group. Similar to our results, Merritt and colleagues[31] evaluated the persistence of corticosteroid-induced obesity in 23 children aged 1 to 14 years requiring more than 60 days of therapy with prednisone for idiopathic NS, and they found that there is significant reduction of gained weight after cessation of corticosteroids in remission.

Unlike our results, Bakkaloglu and colleagues[32] found that there were no differences in body weight, height, and BMI among the steroid-resistant NS

relapse and steroid-resistant NS-remission groups. This difference can be explained as genetic factors may predispose children to weight gain during glucocorticoid exposure and persistent obesity following termination of glucocorticoid therapy during remission.[33]

Serum cholesterol, LDLC, and spot protein-creatinine ratio in the relapse group was significantly higher than the remission group. Also, serum triglyceride was significantly higher in the relapse group. Serum HDLC and albumin levels were significantly lower in the relapse group than the remission group. Similar to our results, Rahul and colleagues[6] found that NS cases with relapse (n = 7) had more deranged lipid profile than those in remission (n = 25). However unlike our results, Nakamura and colleagues[17] failed to demonstrate a correlation between glucocorticoid exposure and total cholesterol in relapses and remissions. This difference than our results can be explained by that hypercholesteremia following cessation of glucocorticoid therapy might be independent from the cumulative dose and duration of glucocorticoid exposure.

Serious complications can occur during the course of active disease including thrombotic events due to the hypercoagulable state and vasculotoxic effects of biochemical alterations resulting from the nephrotic state.[34] In addition, some patients may be at increased risk of developing premature atherosclerosis, since some nephrotic children have prolonged periods of hyperlipidemia and significantly decreased HDL/LDL ratio even after clinical remission.[32]

There is no significant changes regarding CIMT between the relapse and the remission groups. Similar to our results, Rahul and colleagues[6] found that there were no significant differences in brachial FMD or CIMT between NS cases in remission (n = 25) versus those having proteinuria (n = 7; FMD, 5.53 ± 6.64 versus 6.04 ± 3.72 %, respectively; $P$ = .06; and CIMT, 0.62 ± 0.06 versus 0.64 ± 0.08 mm, respectively; $P$ = .45).

Unlike our results, Pelkowska and colleagues[35] recruited 41 NS children having a mean age of 15.4 years and compared 24 children with NS on cyclosporine treatment (in remission) versus 17 NS children having relapse, and reported that 50% to 60 % of children in both groups had 'deranged' FMD of brachial artery. However, since healthy non-nephrotic controls were not recruited, interpretation of data was difficult.

Sharma and colleagues[36] found that children with idiopathic nephrotic syndrome had endothelial dysfunction which is largely dependent upon disease activity. They found that children with steroid-resistant NS had higher levels of thrombomodulin, plasminogen activator antigen ,von Willebrand factor as compared to infrequent relapses,

There is no significant difference between patients with remission or relapses regarding disease frequency. Similar to our results, Hooman and colleagues[10] found that nephrotic children were classified to steroid sensitive, dependent, and resistant. Mean CIMT and carotid parameters were not statistically different in three groups.

Kniazewska and colleagues[3] found that there was no correlation between CIMT and treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists.

There was statistically significant negative correlation between CIMT and diastolic blood pressure. Our results showed a significantly positive correlation between disease duration and each of resting brachial artery diameter and post-FMD. Similar to our results, Hooman and colleagues[10] found that CIMT was correlated with duration of disease more than 2 years ($P$ = .04, 95% confidence interval, 0.002 to 0.12). Even after excluding children with a glomerular filtration rate less than 90 mL/min/1.73m$^2$, this correlation remained significant ($P$ = .03).

Limitations of the study were as follows: duration of the study was short and number of cases was limited. Also, we did not have biopsy for all cases and did not have cases from all histopathological types in addition. Thus, we recommend a study with longer duration on larger number of patients

## CONCLUSIONS

Carotid intima-media thickness was thicker in nephrotic children. The other carotid parameters were correlated with longer duration of disease. The significantly deranged values of FMD in children with NS in contrast to matched controls suggest an ongoing process of endothelial dysfunction. It would be a major concern in children with NS as they might be more prone to atherosclerosis and vascular changes. Accordingly, longer follow-up

even during adulthood, close observation, change of life style, and modifying atherosclerosis risk factors might be considered seriously. From results of our study we recommend that NS patients should be examined carefully and undergo regular lipid profile measurement. Also, CIMT and FMD in children with NS should be considered as routine workup. Close observation, change of life style, and modifying atherosclerosis risk factors might be considered seriously in children with NS.

## CONFLICT OF INTEREST

None declared.

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