

Original Article

Aortic Stiffening in Children with Nephrotic Syndrome

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Highlights

- Early aortic stiffening was detected in children with nephrotic syndrome, indicating subclinical cardiovascular risk even during remission.
- M-mode echocardiography proved to be a simple, reliable, and child-friendly method for assessing vascular stiffness in clinical settings.
- Vascular stiffness correlated with renal function and body indices, linking kidney health to early cardiovascular alterations in NS.

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ABSTRACT

Background: Nephrotic syndrome (NS) in children is a chronic glomerular disorder that, beyond its renal implications, poses a significant risk for cardiovascular complications. Early vascular alterations, such as increased aortic stiffness, may signal subclinical cardiovascular dysfunction with long-term consequences.

Objective: This study aimed to evaluate aortic stiffness in children with idiopathic NS compared with age and sex-matched healthy controls using noninvasive echocardiographic indices.

Methods: A case-control study was conducted at Ali Asghar Pediatric Hospital from 2023 through 2024. Eighty-seven children with idiopathic NS and 87 healthy controls underwent M-mode echocardiographic assessment of the ascending aorta. Aortic systolic and diastolic diameters, along with systolic and diastolic blood pressure (SBP and DBP, respectively), were used to calculate stiffness indices: aortic strain, distensibility, stiffness index β , and pressure-strain elastic modulus (PSEM). Data were analyzed using SPSS version 23 (IBM), and a P value below 0.05 was considered statistically significant for all analyses.

Results: Children with NS had significantly higher SBP and DBP, reduced aortic strain (9.62% vs 14.77%), decreased aortic distensibility (0.0050 vs 0.0085), and elevated stiffness index β and PSEM values ($P < 0.001$ for all). No significant sex distribution differences were noted. Responders to treatment showed better renal function and lower BP but did not differ significantly in vascular stiffness measures. Positive correlations were found between stiffness parameters and proteinuria, serum creatinine, and anthropometric indices.

Conclusion: Children with NS exhibited early signs of aortic stiffening, even during clinical remission. These findings support the incorporation of cardiovascular surveillance into the long-term management of NS to identify at-risk children and initiate early interventions.

Keywords: Aortic Stiffening; Nephrotic Syndrome; Children

Introduction

Nephrotic syndrome (NS) is among the most common glomerular disorders in childhood, defined by the classic triad of heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema.¹

Traditionally, research and clinical care have focused on the renal aspects of NS; however, growing evidence now points to its broader systemic implications, particularly the cardiovascular changes that may profoundly influence long-term health outcomes.^{1,2}

Cardiovascular dysfunction in NS extends beyond traditional risk factors such as dyslipidemia and hypertension.² One of the earliest and most subtle markers of cardiovascular compromise is aortic stiffness, which reflects both structural and functional alterations in the arterial wall.³ The elastic properties of the aorta are essential for cushioning the pulsatile flow of blood ejected from the heart and ensuring steady peripheral perfusion.⁴ In children, whose vascular systems are still developing, any reduction in aortic elasticity is especially concerning. It may indicate early vascular aging and signal an increased lifetime risk for cardiovascular disease.⁵

Children with NS are particularly vulnerable to cardiovascular complications due to factors such as persistent hyperlipidemia, increased thrombogenic potential, and endothelial dysfunction.^{6,7} These conditions can promote atherosclerotic vascular changes even at a young age.⁸ Emerging research suggests that even in the absence of overt cardiovascular symptoms, children with idiopathic NS may show early signs of vascular dysfunction.⁹ Such alterations can be quantified using noninvasive echocardiographic indices, including aortic strain (AS), distensibility, pressure-strain elastic modulus (PSEM), and the stiffness β -index.³⁻⁵

Moreover, NS coexisting with peripheral artery disease has been identified as a risk factor for myocardial infarction later in life.¹¹ Children with this comorbidity may, therefore, be at risk of developing cardiovascular events at an earlier age than their healthy peers. One of the strongest predictors for peripheral artery disease development is atherosclerosis,^{12,13} and given that hyperlipidemia—a hallmark feature of NS—is a major contributor to atherosclerosis,^{4,14} children with NS are at particular risk for vascular injury and subsequent peripheral

artery disease.¹⁵

The early detection of vascular stiffness in children with NS holds significant clinical value.¹⁰ Parameters such as AS and the arterial stiffness β index have been shown to change even before the onset of structural heart disease or sustained hypertension, suggesting their role as sensitive early biomarkers of cardiovascular risk.³ Recognizing subclinical vascular impairment at this stage allows for timely interventions that could improve long-term cardiovascular health.⁴ Importantly, the pediatric vascular system retains a high degree of elasticity and adaptability, meaning that early pharmacologic or lifestyle-based interventions can often mitigate or even reverse arterial stiffening.⁵

In one study, Hooman et al¹⁰ examined carotid artery function in children with idiopathic NS and found that arterial stiffness indices were significantly higher in the NS group than in healthy controls. Furthermore, when NS patients were categorized into steroid-sensitive, steroid-dependent, and steroid-resistant subgroups, carotid parameters did not differ significantly among them. These findings underscore the pervasive vascular involvement in NS, independent of treatment response or disease subtype. Considering these insights, evaluating aortic stiffness in children with NS is not only valuable for early detection of cardiovascular risk but also represents a vital opportunity for preventive care.

The present study sought to address a key gap in the existing literature by providing a detailed assessment of aortic stiffness parameters in a pediatric NS population compared with age- and sex-matched healthy controls. By identifying early vascular changes, we aim to emphasize the importance of cardiovascular monitoring in children with NS and to promote a more comprehensive approach to disease management, one that extends beyond renal outcomes to include long-term vascular health.

Methods

Study Design and Setting

This case-control study was conducted from 2023 through 2024 in collaboration between the Pediatric Nephrology and Cardiology Departments at Ali Asghar Pediatric Hospital (affiliated with

Zahedan University of Medical Sciences, Zahedan, Iran). The study included 174 participants, equally divided between children with NS and healthy controls. The study aimed to evaluate vascular stiffening in children diagnosed with idiopathic NS compared with age- and sex-matched healthy controls.

Definition and Diagnostic Criteria of NS

Children were diagnosed with NS according to standard clinical criteria, including proteinuria greater than 40 mg/m²/h, hypoalbuminemia less than 3 g/dL, hypoproteinemia below 5.5 g/dL, hypercholesterolemia exceeding 250 mg/dL, and the presence of peripheral edema. Only idiopathic cases of NS were included, and patients with congenital renal anomalies or secondary causes of NS were excluded to ensure diagnostic consistency and population homogeneity. The inclusion criteria for the NS group were children younger than 18 years with a confirmed diagnosis of idiopathic NS, no evidence of congenital renal abnormalities, and documented informed consent. Exclusion criteria for both the NS and control groups included severe cardiac, hepatic, or renal disease; any form of secondary NS; or incomplete clinical or echocardiographic data.

Definition of Responders and Nonresponders

In this study, children with NS were further categorized according to their clinical response to corticosteroid therapy. Responders were defined as patients who achieved complete remission after standard corticosteroid treatment, evidenced by the resolution of edema and a reduction in urinary protein excretion to less than 4 mg/m²/h or negative to trace protein on urine dipstick testing for at least 3 consecutive days. Nonresponders were defined as patients who did not achieve remission after 4 weeks of daily corticosteroid therapy and were

considered to have steroid-resistant NS. These definitions followed the International Study of Kidney Disease in Children (ISKDC) guidelines and were applied consistently in the analysis of clinical and echocardiographic findings.

Data Collection Procedure

Laboratory Parameters

For both groups, a 5-mL sample of venous blood was collected into a plain tube, allowed to clot, and centrifuged to obtain serum. Biochemical analyses, including serum albumin, total cholesterol, urea, and creatinine, were performed using the Architect C-8000 system (Abbott Diagnostics, Santa Clara, California) based on spectrophotometric methods.

Blood Pressure (BP)

After at least 5 minutes of supine rest, BP was measured from the brachial artery using a sphygmomanometer. Three measurements were taken at least 2 minutes apart, and the mean value was recorded. Korotkoff phases I and V were used to determine systolic and diastolic blood pressure (SBP and DBP), respectively.

Echocardiographic Measurements

Each child underwent a physical examination, medical history review, chest radiography, and echocardiography using 3- and 8-MHz transducers (MyLab 60, Italy). Measurements were repeated across three cardiac cycles to improve accuracy, and the mean was used for analysis. The echocardiographic parameters assessed included the aortic diastolic diameter (AOD) and aortic systolic diameter (AOS). AOD was measured as the distance between the inner edges of the anterior and posterior aortic walls during diastole. AOS was recorded when the aortic wall was fully open, and the QRS peak on the ECG was recorded simultaneously with AOD (Figure 1).

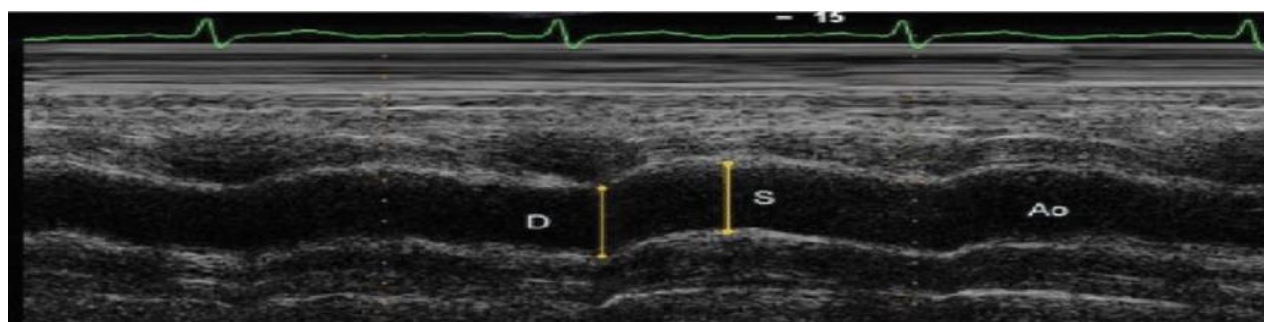


Figure 1. The image depicts the systolic (S) and diastolic (D) diameters of the ascending aorta in the M-mode echocardiographic tracing obtained 3 cm above the aortic valve.

Arterial Stiffness Parameters

Vascular stiffness was assessed to explore the impact of idiopathic NS on large artery compliance and hemodynamic function. Arterial stiffness parameters were measured using noninvasive M-mode echocardiography, which has been validated for assessing aortic elasticity in pediatric populations.¹ All assessments were performed by the same pediatric cardiologist using a standard echocardiographic system equipped with high-resolution probes and integrated software for vascular measurements. The following aortic elasticity parameters were calculated from direct measurements of AOD, AOS, SBP, and DBP:

- AS, % = $(\text{AOS}-\text{AOD}) \times 100 / \text{AOD}$
- Aortic stiffness β index ($\text{AS}\beta$) = $\ln (\text{SBP} / \text{DBP}) / ([\text{AOS}-\text{AOD}] / \text{AOD})$
- Aortic distensibility (AD), $10^{-6} \text{ cm}^2/\text{dyn} = 2 \times ([\text{AOS}-\text{AOD}] / \text{AOD}) / (\text{SBP}-\text{DBP})$
- PSEM = $(\text{SBP}-\text{DBP}) / ([\text{AOS}-\text{AOD}] / \text{AOD})^{3-5}$

Ethical Considerations

This study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all parents or legal guardians. The study protocol was reviewed and approved by the Ethics Committee of Zahedan University of Medical Sciences, under the Children and Adolescents Health Research Center (Approval ID: IR.ZAUMS.REC.1402.007).

Statistical Analysis

Data were entered into SPSS, version 23 (IBM Corp), for analysis. Continuous variables were expressed as means and standard deviations, and categorical variables were summarized as frequencies and percentages. The normality of data distribution was assessed using appropriate statistical tests. Depending on the distribution, independent-samples *t* tests (for normally distributed data) or Mann–Whitney *U* tests (for nonparametric data) were applied to compare the NS and control groups. The χ^2 test was used for categorical variables. A *P* value below 0.05 was considered statistically significant for all analyses.

Results

The sex distribution for the 87 children with NS

(case group) and the 87 healthy children (control group) is shown in (Table 1). In the case group, 39 (44.8%) were girls and 48 (55.2%) were boys. In the control group, 49 (56.3%) were girls and 38 (43.7%) were boys. A χ^2 test indicated no statistically significant difference in sex distribution between the two groups ($\chi^2=0.299$; $P=0.129$), suggesting sex is unlikely to be a confounding factor in this study.

The mean age of children with NS was 9.22 (SD, 3.68) years compared with 9.86 (SD, 3.00) years in the control group. An independent-samples *t* test showed no significant difference in age between the groups ($t=-1.264$; $P=0.208$), indicating successful age matching. The calculated Cohen *d* of -0.192 (95% CI, -0.489 to 0.106) suggested a small and negligible effect size, reinforcing that the age distribution was comparable.

To compare key variables between children with NS and healthy children, we employed the Kolmogorov-Smirnov test. Most variables, except for weight ($P=0.200$), deviated significantly from a normal distribution ($P<0.05$). Variables such as SBP and DBP, aortic diameter (AD), AS, height, and stiffness indices (AS, β index, AD, and PSEM) showed significant non-normality.

As shown in (Table 1), significant differences were observed in vascular stiffening parameters between the groups. Children with NS had higher SBP (111.13 [13.47] mm Hg) and DBP (69.79 [12.92] mm Hg) than controls (101.68 [9.75] mm Hg and 64.94 [6.62] mm Hg, respectively; both $P < 0.01$). Aortic diameter was larger in the NS group (18.76 [3.42] mm vs 17.11 [2.11] mm; $P=0.001$), although the difference in AOS was not statistically significant ($P=0.136$). Children with NS had significantly lower weight (29.87 [14.10] kg) and height (125.66 [21.34] cm) than controls (44.75 [12.93] kg and 153.83 [12.91] cm; both $P<0.001$). Measures of vascular stiffness indicated more rigidity in the NS group, with significantly lower AS (9.62% [5.99%] vs 14.77% [4.22%]), higher stiffness β index (6.20 [0.68] vs 5.53 [0.38]), increased PSEM (6.41 [5.98] vs 2.70 [0.97]), and reduced AD (0.0050 [0.0032] vs 0.0085 [0.0035]; all $P<0.001$).

The normality of distribution for various clinical and laboratory variables was assessed in children with NS using the Kolmogorov-Smirnov test. The test results revealed that only total cholesterol ($P=0.200$), height ($P=0.200$), and $\text{As}\beta$ ($P=0.136$) did not show significant deviations from normality.

As shown in (Table 2), among children with NS, those who responded to treatment had significantly lower serum creatinine levels (0.61 [0.20] mg/dL) than nonresponders (1.05 [1.34] mg/dL; $P=0.002$), indicating better renal function. Responders also had significantly lower serum sodium levels (137.02 [4.21] mEq/L) than nonresponders (138.52 [5.82] mEq/L; $P=0.027$). Further, SBP was significantly lower in the response group (108.59 [13.15] mm Hg) than in the nonresponse group (115.27 [13.13] mm Hg; $P=0.039$). In addition, 24-hour urinary protein and creatinine excretion were both lower in responders and reached borderline significance ($P=0.050$), suggesting reduced proteinuria and renal strain. In contrast, no statistically significant differences were observed between responders and nonresponders for other parameters, including white blood cell count, hemoglobin, platelet count, mean platelet volume, blood urea nitrogen, potassium, calcium, triglycerides, cholesterol, albumin, protein-to-creatinine ratio, DBP, aortic dimensions (AOD and AOS), anthropometric measures (weight and height), and vascular stiffness indices (AS, stiffness β index, AD, and PSEM).

Table 3 presents the correlations between various blood and biochemical parameters and arterial stiffness indices in children with NS. Several significant relationships were identified. Hemoglobin levels showed a positive correlation with AOD ($r=0.262$; $P=0.014$) and AOS ($r=0.240$; $P=0.025$), indicating that higher hemoglobin may be

associated with larger aortic dimensions. Blood urea nitrogen demonstrated a positive correlation with AS ($r=0.244$; $P=0.023$) and AD ($r=0.345$; $P=0.001$) and a negative correlation with the stiffness β index ($r=-0.306$; $P=0.004$), suggesting a relationship between renal function and arterial stiffness. Furthermore, serum creatinine was positively correlated with AS ($r=0.218$; $P=0.043$), while serum sodium showed a positive association with the stiffness β index ($r=0.230$; $P=0.032$) and PSEM ($r=0.225$; $P=0.036$). The protein-to-creatinine ratio was positively correlated with AS ($r=0.230$; $P=0.032$), implying a link between proteinuria severity and aortic stiffness. Additionally, 24-hour protein excretion was positively correlated with AOS ($r=0.237$; $P=0.027$), and 24-hour creatinine excretion showed significant correlations with AOD ($r=0.344$; $P=0.001$), AOS ($r=0.291$; $P=0.006$), and PSEM ($r=0.215$; $P=.046$), but was inversely correlated with AS ($r=-0.218$; $P=0.043$).

Strong positive correlations were observed between anthropometric indices and arterial measurements. Weight and height were significantly and positively correlated with SBD and DBP, aortic dimensions (AOD and AOS), and PSEM (all $P<0.001$). Height was also correlated with the stiffness β index ($r=0.244$; $P=0.023$) and PSEM ($r=0.214$; $P=0.047$). These findings suggest that both renal function markers and body size play important roles in vascular stiffness among children with nephrotic syndrome.

Table 1. Vascular stiffness variables in children with nephrotic syndrome (NS) and healthy controls

Variables	Groups	Mean	SD	Mean Rank	Sum of Ranks	Test value	P
Systolic blood pressure (mmHg)	NS	111.13	13.47	106.03	9224.5	2172.5	<0.001
	Control	101.68	9.75	68.97	6000.5		
Diastolic blood pressure (mmHg)	NS	69.79	12.92	97.71	8501	2896	0.007
	Control	64.94	6.62	77.29	6724		
Aortic diameter in diastole (mm)	NS	18.76	3.42	100.63	8754.5	2642.5	0.001
	Control	17.11	2.11	74.37	6470.5		
Aortic diameter in systole (mm)	NS	20.49	3.42	93.19	8107.5	3289.5	0.136
	Control	19.6	2.2	81.81	7117.5		
Weight (kg)	NS	29.87	14.1			3.21	<0.001
	Control	44.75	12.93				
Height (cm)	NS	125.66	21.34	56.12	4882.5	1054.5	<0.001
	Control	153.83	12.91	118.88	10342.5		
Aortic strain	NS	9.62	5.99	59.56	5181.5	1353.5	<0.001
	Control	14.77	4.22	115.44	10043.5		
Aortic stiffness β index	NS	6.2	0.68	114.95	10001	1396	<0.001
	Control	5.53	0.38	60.05	5224		
Pressure-strain elastic modulus (kPa)	NS	6.41	5.98	114.95	10001	1396	<0.001
	Control	2.7	0.97	60.05	5224		
Aortic distensibility (10 ⁻⁶ cm ² /dyn)	NS	0.005	0.0032	60.05	5224	1396	<0.001
	Control	0.0085	0.0035	114.95	10001		

Table 2. Biochemical and vascular stiffness parameters in children with nephrotic syndrome by treatment response

Variable	Response	N	Mean	SD	Mean Rank	Sum of Ranks	Mann–Whitney U Statistic	P
White blood cells ($\times 10^3/\mu\text{L}$)	Yes	54	11974.07	10439.05	46.49	2510.5	756.5	0.239
	No	33	10196.97	5316.39	39.92	1317.5		
Hemoglobin (gr/dl)	Yes	54	12.08	1.37	42.35	2287	802	0.434
	No	33	12.17	1.96	46.7	1541		
Platelet ($\times 10^3/\mu\text{L}$)	Yes	54	407.65	138.19	47.2	2549	718	0.13
	No	33	367.97	135.37	38.76	1279		
Mean platelet volume (fl)	Yes	54	7.49	1.03	41.43	2237	752	0.223
	No	33	9.70	10.39	48.21	1591		
Blood urea nitrogen (mg/dL)	Yes	54	15.92	9.55	40.42	2182.5	697.5	0.09
	No	33	19.18	11.44	49.86	1645.5		
Serum creatinine (mg/dL)	Yes	54	0.61	0.20	37.51	2025.5	540.5	0.002
	No	33	1.05	1.34	54.62	1802.5		
Sodium (mEq/L)	Yes	54	137.02	4.21	39.34	2124.5	639.5	0.027
	No	33	138.52	5.82	51.62	1703.5		
Potassium (mEq/L)	Yes	54	4.29	0.47	43.03	2323.5	838.5	0.638
	No	33	4.33	0.39	45.59	1504.5		
Calcium (mg/dL)	Yes	54	8.02	0.77	43.66	2357.5	872.5	0.869
	No	33	8.05	0.70	44.56	1470.5		
Triglycerides (mg/dL)	Yes	54	229.70	112.53	43.33	2340	855	0.753
	No	33	245.70	129.92	45.09	1488		
Total cholesterol (mg/dL)	Yes	54	333.67	114.85			0.78	0.343
	No	33	308.52	89.50				
Albumin (gr/L)	Yes	54	2.19	0.49	44.74	2416	851	0.726
	No	33	2.20	0.65	42.79	1412		
Protein in urine (mg/dL)	Yes	54	429.93	349.73	39.84	2151.5	666.5	0.05
	No	33	603.61	486.95	50.8	1676.5		
Creatinine in urine (mg/dL)	Yes	54	115.44	102.84	39.85	2152	667	0.05
	No	33	143.00	92.22	50.79	1676		
Protein/creatinine in urine	Yes	54	4.64	3.88	42.53	2296.5	811.5	0.487
	No	33	5.82	5.08	46.41	1531.5		
Systolic blood pressure (mmHg)	Yes	54	108.59	13.15	39.66	2141.5	656.5	0.039
	No	33	115.27	13.13	51.11	1686.5		
Diastolic blood pressure (mmHg)	Yes	54	68.00	11.50	40.53	2188.5	703.5	0.099
	No	33	72.73	14.67	49.68	1639.5		
Aortic diameter in diastole (mm)	Yes	54	18.37	3.21	40.62	2193.5	708.5	0.11
	No	33	19.39	3.69	49.53	1634.5		
Aortic diameter in systole (mm)	Yes	54	20.14	3.33	40.59	2192	707	0.107
	No	33	21.05	3.55	49.58	1636		
Weight (kg)	Yes	54	27.82	13.09	40.49	2186.5	701.5	0.097
	No	33	33.21	15.24	49.74	1641.5		
Height (cm)	Yes	54	123.31	20.06			0.91	0.137
	No	33	129.48	23.10				
Aortic strain	Yes	54	9.94	6.41	44.18	2385.5	881.5	0.934
	No	33	9.11	5.28	43.71	1442.5		
Aortic stiffness β index	Yes	54	6.13	0.58			0.83	0.597
	No	33	6.32	0.81				
Aortic distensibility (10 ⁻⁶ cm ² /dyn)	Yes	54	0.01	0.00	45.12	2436.5	830.5	0.597
	No	33	0.00	0.00	42.17	1391.5		
Pressure–strain Elastic modulus (kPa)	Yes	54	5.42	3.32	42.88	2315.5	830.5	0.597
	No	33	8.01	8.58	45.83	1512.5		

Table 3. Correlation between laboratory measures and arterial stiffness parameters in children with nephrotic syndrome

Variables	Statistics	Systolic Blood Pressure	Diastolic Blood Pressure	Aortic Diameter in Diastole	Aortic Diameter in Systole	Aortic Strain	Aortic Stiffness β Index	Aortic Distensibility	Pressure-Strain Elastic Modulus
White blood cells ($\times 10^3/\mu\text{L}$)	Pearson Correlation	0.05	-0.044	0.072	0.053	-0.072	0.139	-0.105	0.102
	P	0.646	0.684	0.505	0.624	0.507	0.198	0.331	0.349
Hemoglobin (gr/dl)	Pearson Correlation	0.093	0.056	0.262*	0.240	-0.139	0.197	-0.121	0.2
	P	0.39	0.607	0.014	0.025	0.199	0.068	0.263	0.063
Platelet ($\times 10^3/\mu\text{L}$)	Pearson Correlation	-0.109	-0.071	-0.149	-0.146	0.027	-0.124	0.073	-0.14
	P	0.316	0.511	0.169	0.178	0.805	0.251	0.504	0.197
Mean platelet volume (fl)	Pearson Correlation	0.037	-0.032	-0.043	-0.067	-0.074	0.131	-0.093	0.103
	P	0.736	0.769	0.693	0.536	0.494	0.225	0.39	0.34
Blood urea nitrogen (mg/dl)	Pearson Correlation	-0.113	0.058	-0.081	-0.01	0.244*	-0.306	0.345	-0.217
	P	0.296	0.591	0.454	0.926	0.023	0.004	0.001	0.044
Serum creatinine (mg/dl)	Pearson Correlation	0.097	-0.021	-0.077	-0.026	0.218	-0.112	0.096	-0.078
	P	0.373	0.846	0.476	0.814	0.043	0.302	0.376	0.471
Sodium (mEq/L)	Pearson Correlation	0.085	0.018	0.088	0.029	-0.183	0.230	-0.171	0.225*
	P	0.433	0.868	0.417	0.793	0.091	0.032	0.113	0.036
Potassium (mEq/L)	Pearson Correlation	-0.009	0.106	0.105	0.065	-0.11	0.078	-0.032	0.044
	P	0.931	0.328	0.334	0.552	0.309	0.471	0.766	0.683
Calcium (mg/dl)	Pearson Correlation	-0.011	-0.018	0.083	0.043	-0.144	0.104	-0.147	0.02
	P	0.917	0.865	0.447	0.69	0.182	0.336	0.173	0.853
Triglycerides (mg/dL)	Pearson Correlation	-0.032	0.021	-0.011	-0.014	0.022	-0.064	0.103	-0.031
	P	0.771	0.847	0.917	0.897	0.839	0.558	0.343	0.774
Total cholesterol (mg/dL)	Pearson Correlation	-0.188	-0.08	0.026	-0.013	-0.137	0.015	-0.083	-0.07
	P	0.081	0.461	0.809	0.902	0.205	0.892	0.447	0.521
Albumin (gr/L)	Pearson Correlation	0.033	-0.004	-0.097	-0.107	-0.024	0.098	-0.031	0.192
	P	0.763	0.97	0.374	0.322	0.827	0.366	0.778	0.075
Protein in urine (mg/dL)	Pearson Correlation	-0.004	-0.02	0.21	0.237	0.048	-0.045	0.079	-0.046
	P	0.971	0.855	0.05	0.027	0.658	0.68	0.465	0.673
Creatinine in urine (mg/dL)	Pearson Correlation	0.095	0.114	0.344	0.291	-0.218	0.209	-0.123	0.215
	P	0.381	0.295	0.001	0.006	0.043	0.052	0.258	0.046
Protein/creatinine in urine	Pearson Correlation	0.06	0.007	-0.034	0.043	0.230*	-0.186	0.171	-0.183
	P	0.583	0.952	0.752	0.693	0.032	0.084	0.112	0.09
Weight (kg)	Pearson Correlation	0.598	0.431	0.731	0.730	-0.16	0.307	-0.211	0.297
	P	<0.001	<0.001	<0.001	<0.001	0.139	0.004	0.05	0.005
Height (cm)	Pearson Correlation	0.523	0.424	0.755	0.765	-0.148	0.244	-0.193	0.214
	P	<0.001	<0.001	<0.001	<0.001	0.171	0.023	0.073	0.047

Discussion

The collective evidence from recent studies indicates that children with NS exhibit early vascular alterations suggestive of increased arterial stiffness and endothelial dysfunction, both of which are important precursors of premature atherosclerosis and cardiovascular morbidity. Several studies have

reported persistent dyslipidemia in children with NS, even during remission, which represents a critical risk factor for vascular stiffness. By way of example, one study found that more than 50% of children with NS had dyslipidemia, with high rates of hypercholesterolemia and elevated low-density lipoprotein cholesterol despite being in remission. This dyslipidemic profile contributes to endothelial

dysfunction and heightened cardiovascular risk in these patients.¹⁶ Similar findings have been reported by other authors, emphasizing the contribution of lipid abnormalities to the pathogenesis of vascular changes in NS.^{10,16}

A focused review of recent literature confirms that although vascular stiffness and endothelial dysfunction are increasingly investigated in children with NS, the most frequently used measures are pulse wave velocity (PWV), carotid intima-media thickness (cIMT), augmentation index (AIx), and flow-mediated dilation (FMD). Parameters such as AS (%) and AD, which provide direct and sensitive measures of local aortic elasticity, are notably underreported in this population. For instance, recent studies have emphasized the utility of PWV, RHI, and cIMT in identifying early vascular changes in NS but did not assess AS or AD.^{16,17} In this regard, Filip et al¹⁷ concluded that PWV values indicated increased arterial stiffness and might represent an important parameter for identifying children with kidney diseases and children at high risk for major cardiovascular events.

With respect to direct measures of arterial stiffness, findings are somewhat mixed but generally indicate increased stiffness in children with NS, particularly among those with steroid-resistant forms. PWV, the gold standard measure of arterial stiffness, has been reported to be elevated in pediatric patients with steroid-resistant NS, accompanied by increased cIMT and left ventricular mass index, suggesting early subclinical cardiovascular disease.¹⁸ Another study found significantly greater cIMT in children with NS than in healthy controls, supporting the presence of early vascular remodeling.¹⁹

Nonetheless, some studies did not find statistically significant differences in carotid intima-media thickness or FMD, possibly due to small sample sizes or heterogeneity in patient populations.^{16,18} FMD, an indicator of endothelial function, was reported to be lower in children with longer disease duration and in those with steroid-resistant NS, suggesting impaired endothelial-dependent vasodilation.¹⁸ Although one study found no significant difference in FMD between patients with NS and controls, it did note a trend toward a lower reactive hyperemia index, which also reflects endothelial dysfunction.¹⁶ These subtle changes in endothelial function may precede overt arterial

stiffness and provide an early window for intervention.

Hypertension, frequently observed in children with NS, further exacerbates vascular stiffness. The prevalence of hypertension varies widely due to the dynamic nature of NS and treatment regimens, but elevated blood pressure correlates with increased arterial stiffness in these children.^{18,20} This relationship underscores the importance of blood pressure control in mitigating arterial stiffness. Longitudinal studies and those assessing the impact of kidney transplantation indicate potential reversibility of vascular stiffness changes. For instance, arterial stiffness indices improved after living-donor kidney transplantation in children, suggesting that early vascular changes associated with NS-related kidney damage can be at least partially reversed with restoration of kidney function.^{18,21} The pathophysiology underlying these vascular changes in NS is multifactorial, involving chronic inflammation, oxidative stress, and exposure to steroids and immunosuppressive drugs.^{1,16,18} These factors collectively promote endothelial dysfunction, vascular remodeling, and increased arterial stiffness, which may progress to premature atherosclerosis if unaddressed. The absence of such assessments highlights a methodological gap in pediatric NS research, as aortic-based indices may better capture early central vascular remodeling. The present study contributes to the field by applying these underutilized yet physiologically relevant parameters—namely, AS and AD—to evaluate vascular stiffness in children with NS, thereby offering insights into early cardiovascular involvement that may not be detected by conventional peripheral stiffness metrics alone. Building on collective evidence that highlights the widespread use of peripheral arterial stiffness markers such as PWV, it is important to consider the complementary role of central aortic stiffness measures—namely, AS and AD—in evaluating early vascular changes in children with NS. Although PWV remains a widely accepted and validated marker of arterial stiffness, particularly for reflecting conduit artery properties and central-to-peripheral arterial dynamics, it primarily provides a global estimate of arterial compliance that may not fully capture localized central vascular changes occurring in the aorta.²² In contrast, AS and AD directly assess the mechanical properties of the

aortic wall and are considered sensitive indices of central vascular elasticity. These parameters provide a more physiologically targeted assessment of vascular stiffness at the aortic root or ascending aorta, regions often affected early in disease progression.^{3,4} By integrating aortic stiffness indices into clinical research and practice, this study addresses a significant methodological gap and proposes a complementary approach to conventional vascular stiffness assessments. The application of these parameters offers a valuable addition to the cardiovascular risk stratification toolbox in pediatric NS and may ultimately support earlier identification and intervention for subclinical vascular disease in this vulnerable population.

Study Limitations

Despite the strengths of the study design and the novelty of using aortic-based stiffness parameters in pediatric NS, several limitations should be acknowledged. The study was conducted at a single pediatric hospital, which may limit the generalizability of the findings to broader or more diverse pediatric populations. Further, all aortic stiffness parameters were calculated manually based on M-mode measurements, which, while feasible, may introduce minor computational or observational errors compared with automated or software-assisted systems used in advanced vascular laboratories.

Conclusion

Our study highlights an underrecognized but important concern in children with NS: early vascular changes that may increase the risk of future cardiovascular disease. By focusing on the aorta—the body's main artery—and its response to each heartbeat, we employed a simple, child-friendly echocardiographic method to assess arterial elasticity and vascular health. Even when children were in remission and clinically well, their aortic elasticity was significantly lower than that of healthy controls, indicating increased arterial stiffness and potential predisposition to cardiovascular complications. Unlike previous studies that relied on more complex or less accessible assessments such as pulse wave velocity, we demonstrated that clinically useful information about vascular health can be obtained using equipment commonly available in most hospitals. This approach is both

practical and impactful, particularly in resource-limited settings. Collectively, these findings underscore the importance of considering cardiovascular health in the long-term care of children with NS, beyond the evaluation of renal function alone.

Declarations:

Ethical Approval

This investigation was approved by the Research Ethics Committee of Zahedan University of Medical Sciences under number IR.ZAUMS.REC.1402.007.

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Conflict of Interest

The authors affirm that there are no financial or personal relationships that could have influenced the work reported in this paper.

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