

# Ankle Brachial Index in Children with Steroid-Resistant Nephrotic Syndrome

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## مؤشر الكاحل العضدي في الأطفال الذين يعانون متلازمة الكلوية مقاومة الستيرويد

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**الملخص:** الهدف: تهدف هذه الدراسة إلى تقييم مؤشر الكاحل العضدي كمؤشر لأمراض الشرايين الطرفية في الأطفال المصابين بمتلازمة الكلوية المضادة الستيرويد. الطريقة: اشتملت هذه الدراسة على عشرين طفلاً من الذين يحضرون العيادة الخارجية لأمراض الكلى للأطفال بمستشفى المنيا الجامعي، مصر. في هذه الدراسة كان 11 من الذكور و 9 من الإناث تراوحت أعمارهم بين 5 و 15 عام وكان بهم زلال بالبول و يخضعون للعلاج بالستيرويد. تم أخذ 20 طفلاً صحيح مطابق للجنس و السن كمجموعة ضابطة. تعرض جميع المرضى و الأصحاء لأخذ التاريخ المرضي و للفحص السريري. خضع جميع المرضى في هذه الدراسة للاختبارات المعملية مثل تحليل البول، نسبة البروتينات في بول 24 ساعة، اليوريا والكرياتينين في مصل الدم، نسبة الألبومين و الكالسيوم و الفسفور و الفوسفات القلوي في مصل الدم، و كذلك نسبة الدهون الثلاثية و الكوليستيرول. تم أخذ خزعة من الكلى لتشخيص نوع المرض في متلازمة الكلوية وكذلك عمل دراسة دوبلر لتحديد مؤشر الكاحل العضدي. النتائج: أظهرت النتائج أن مؤشر الكاحل العضدي كان أعلى بكثير في مجموعة المرضى عن المجموعة الضابطة، و كان هناك ارتباط إيجابي بين مؤشر الكاحل العضدي و جرعة الستيرويد و مدة العلاج. الخلاصة: انتهت الدراسة إلى أن مؤشر الكاحل العضدي طريقة بسيطة للتنبؤ بتصلب الشرايين في الأطفال المصابين بمتلازمة الكلوية المضادة الستيرويد لفترة طويلة.

**مفتاح الكلمات:** مؤشر الكاحل العضدي، الأطفال، مقاومة الستيرويد، متلازمة الكلوية، مصر.

**ABSTRACT: Objectives:** This study aimed to assess the ankle brachial index (ABI) as a predictor of peripheral arterial diseases (PAD) in children with steroid-resistant nephrotic syndrome (NS). **Methods:** Twenty children (11 males and 9 females) attending the Pediatric Nephrology Outpatient Clinic of El-Minia University Hospital, Egypt, were enrolled in this study. Their age ranged between 5 and 15 years with a mean of  $10.75 \pm 3.31$  years. They had proteinuria and were dependent on steroid therapy. Twenty healthy age- and sex-matched children served as a control group. All patients and controls underwent a thorough history-taking and clinical examination. All subjects in the study underwent laboratory investigations, including a urine analysis (24-hour test for protein in urine, and levels of serum urea and creatinine, triglycerides, and cholesterol). A renal biopsy was done to diagnose the children's histopathological type of NS. A Doppler study was done to determine patients' ABI. **Results:** ABI was significantly higher in the patient group than in the control group ( $P < 0.0001$ ). There was a negative correlation between ABI and duration of treatment ( $r$  value = 0.77 and  $P < 0.001$ ). **Conclusion:** ABI is simple non-invasive manoeuvre that can reliably assess arterial stiffness as an early predictor of atherosclerosis in nephrotic patients with long duration of both illness and steroid therapy.

**Keywords:** Ankle brachial index; Children; Steroid resistant; Nephrotic syndrome; Egypt.

### ADVANCES IN KNOWLEDGE

- An increased risk of cardiovascular disease exists in patients with nephrotic syndrome (NS) because of hyperlipidaemia, increased thrombogenesis, and endothelial dysfunction.
- Hypercholesterolaemia is strongly associated with severity of hypoalbuminemia, and persistent proteinuria or renal insufficiency also contributes to cardiovascular disease.
- The risk of premature atherosclerosis is increased due to hyperlipidaemia.
- The duration of nephrotic hyperlipidaemia appears to be critical to initiating vascular damage.
- Endothelial damage from hyperlipidaemia may favor influx of lipoprotein into the mesangium, leading to proliferation and sclerosis.
- Lipoproteins are elevated in children with long-standing and frequently relapsing NS.
- They are at increased risk for developing atherosclerosis, glomerular and interstitial renal disease.

**APPLICATION TO PATIENT CARE**

- Peripheral artery disease (PAD) can be accurately diagnosed with the ankle brachial index (ABI).
- Low values of the ABI are predictive of incident cardiovascular disease (CVD), as well as total mortality. These associations hold true in both sexes and are independent of traditional CVD risk factors.
- ABI is an independent newer biomarker for standard CVD risk factors.
- ABI measurement can provide a simple and early prediction of patient with high risk of CVD and lead to better protection.

**P**ATIENTS WITH NEPHROTIC SYNDROME (NS) are assumed to be at increased risk for peripheral arterial diseases (PAD) and coronary heart diseases, probably because NS is associated with hyperlipidaemia, hypertension and steroid therapy. NS is defined by the presence of a nephrotic range of proteinuria, oedema, hyperlipidaemia, and hypoalbuminemia. Primary or idiopathic nephrotic syndrome (INS) is divided into steroid-sensitive NS and steroid-resistant NS because a patient's response to steroids has a high correlation with histological subtype and prognosis.<sup>1</sup> INS is accompanied by a disordered lipid metabolism. Apolipoprotein-B (apo-B)-containing lipoproteins are elevated with resultant increases in total cholesterol and low-density lipoprotein (LDL) cholesterol. Elevations in triglyceride levels occur with severe hypoalbuminaemia. The traditional explanation for hyperlipidaemia in INS was the increased synthesis of lipoproteins that accompany increased hepatic albumin synthesis due to hypoalbuminaemia.<sup>2</sup> High mortality from chronic kidney disease (CKD)—due to cardiovascular complications, vascular calcification induced by excess calcium and phosphate, and uremia—is a major risk factor and is independently associated with cardiovascular events and death. CKD-induced vascular disease causes stiffness of the arterial tree causing, in turn, systolic hypertension and left ventricular hypertrophy.<sup>3</sup> Management of CKD is difficult but early detection and treatment are crucial to reducing cardiovascular mortality.

This study therefore aimed to assess ankle brachial index as a predictor of developing atherosclerosis in children with steroid-resistant nephrotic syndrome.

## Methods

Twenty patients from the Pediatric Nephrology Clinic of El-Minia University Hospital, Egypt, participated in the study, which took place between

April and December 2010. The study was comprised of 11 males and 9 females with a mean of age  $10.75 \pm 3.31$  years who had been diagnosed with steroid-resistant NS. Their diagnosis was made according to the following criteria set forth by the International Study of Kidney Disease in Children (ISKDC): no urinary remission within 4 weeks of a prednisone therapy course of 60 mg/m<sup>2</sup>/day.<sup>4</sup>

Twenty apparently healthy children with no history of cardiovascular or renal diseases and matched by age and sex served as a control group. Their ages ranged between 8 and 14 years with a mean age of  $11 \pm 2.1$  years. The study was approved by the Local Ethical Committee of El-Minia University in Egypt and was sponsored by Dr. Manal Ismail. Written informed consent was obtained from the parents for all participating children.

All patients' medical histories were taken, and their clinical examinations included an accurate and thorough measurement of arterial pressure, an examination of oedema, and a cardiac examination. None of our patients had congenital or rheumatic heart disease.

Laboratory investigations included: 1) urine analysis and urinary protein measurement; 2) blood tests during which about 3 ml of venous blood was obtained by sterile vein puncture after the patients had fasted for 12–14 hours (the separated serum was then used for assessment of serum albumin, urea, creatinine, alkaline phosphatase, calcium, phosphorus, cholesterol, and triglycerides [TG]); and 3) renal ultrasonography and biopsy.

The ankle brachial index (ABI) is a clinical tool used for the detection of peripheral arterial disease, which in turn predicts cardiovascular morbidity and mortality.<sup>5</sup> In this study, patients were placed supine for at least 5 minutes. The systolic blood pressure of the brachial artery of both arms and the posterior tibial artery of both ankles were then measured using a blood pressure cuff and a Parks Model 841-A pocket Doppler probe (Parks Medical

**Table 1:** Demographic and laboratory variables in patients and control groups

Data	Patients	Controls	P value
	Mean ± SD	Mean ± SD	
Age (years)	10.75 ± 3.31	11 ± 4.24	0.08
Sex (M/F)	9/11	9/11	
Disease duration (years)	3.42 ± 1.73		
Urea (mg/dl)	49.0 ± 34.17	21 ± 1.4	0.009 *
Creatinine (mg/dl)	1.13 ± 0.7	0.47 ± 0.1	0.001**
Calcium (mg/dl)	0.96 ± 0.17	1.09 ± 0.01	0.01*
Phosphorus (mg/dl)	5.06 ± 1.27	4.05 ± 0.78	0.03*
Albumin (g/dl)	2.85 ± 0.7	4.75 ± 0.35	0.0001**
Alkaline phosphates (u/l)	178.16 ± 109.0	81.67 ± 19.8	0.006*
Cholesterol (mg/dl)	248.18 ± 101.7	104.7 ± 26.2	0.0001**
TG (mg/dl)	259.4 ± 152.09	173.7 ± 22.6	0.06

SD = standard deviation; M = male; F = female; TG = triglycerides; \* = significant; \*\* = highly significant.

Electronics, Aloha, Oregon, USA). The highest arm pressure was then used to calculate ABI. The ratio of ankle to arm systolic blood pressure was calculated for each leg, and the lowest ratio was recorded as

**Table 3:** Correlation between mean ankle brachial index scores and different parameters in the patient group

Parameter	r-Value	P Value
Disease duration (years)	-0.77	<0.001*
Urea (mg/dl)	-0.74	<0.001 **
Creatinine (mg/dl)	-0.66	<0.001**
Calcium (mg/dl)	-0.06	<0.7#
Albumin (g/dl)	0.35	<0.02*
Alkaline phosphates (u/l)	-0.21	<0.2#
Cholesterol (mg/dl)	-0.59	<0.0001**
TG (mg/dl)	-0.45	<0.02*

TG = triglycerides; \* = significant; \*\* = highly significant; # = non-significant.

**Table 2:** Comparison between patients and controls in regards to mean score on the ankle brachial index

	Patients	Controls	P value
	Mean ± SD	Mean ± SD	
ABI score	0.89 ± 0.02	1.04 ± 0.08	0.0001**

SD = standard deviation; ABI = ankle brachial index; \*\* = highly significant.

the ABI. ABIs were classified as low ( $\leq 0.9$ ), normal (0.91–1.3), or high ( $> 1.3$ ).<sup>5</sup>

Collected data were then tabulated. Numerical data were expressed by the mean ± standard deviation (SD) and categorical data were expressed by a number and a percentage. Statistical analysis was conducted by means of Statistical Package for Social Science (SPSS), Version 15.0 (IBM, Inc., Chicago, Illinois, USA) using an unpaired t-test for comparison of numerical data of both groups. A correlation-coefficient study between ABI and laboratory data was done, with a *P* value considered significant at  $< 0.05$ .

## Results

Table 1 shows a significant increase in renal function markers in the patient group in contrast to the control group, including increases in serum urea and creatinine (*P* values 0.009 and 0.001, respectively). Also, serum phosphorus and alkaline phosphatase were significantly higher in patients *versus* controls, (*P* values 0.03 and 0.006, respectively). Serum albumin and serum calcium were significantly decreased in the patient group as compared with controls (*P* value 0.0001–0.01). For lipid markers, serum cholesterol was significantly higher in the patients than in the controls (*P* value 0.0001) but there was no significant difference in TG levels. The ABI in the patient group was significantly lower ( $0.89 \pm 0.02$ ) than in the control group ( $1.04 \pm 0.08$ ) (*P* value 0.0001) [Table 2]. Also, there was a highly significant negative correlation between patients' mean ABI scores and their disease duration, serum urea, serum creatinine, and cholesterol levels (*P* value  $< 0.001$ ). Additionally, there was a significant negative correlation between patients' mean ABI score and serum TG (*P* value  $< 0.02$ ). On the other hand, there was a significant positive correlation between patients' mean ABI scores and their serum albumin (*P* value  $< 0.02$ )

[Table 3]. According to renal biopsy, 17 patients had membranoproliferative glomerulonephritis, two patients had focal segmental glomerulosclerosis, and only one patient had diffuse mesangial proliferation.

## Discussion

Overall, approximately 10% of patients with INS do not respond to an initial trial of steroids. Additionally, about 1–3% of patients who initially do respond to steroids later become non-responders, or resistant to treatment.<sup>6</sup> Most patients who do not achieve remission of proteinuria with steroids have kidney biopsy findings other than minimal change NS. Most cases fail to achieve remission with any treatment and progress to end-stage kidney disease.<sup>7,8</sup>

Chronic hyperlipidaemia has been linked to an increased risk of atherosclerosis and coronary artery disease, and has also been associated with the progression of renal disease.<sup>9</sup> However, small studies that have been done of the effects of lipid-lowering agents in paediatric INS have not shown an improvement in proteinuria or the progression of renal disease.<sup>2</sup> The ABI test is a popular tool for the non-invasive assessment of PAD. Studies have shown the sensitivity of ABI is 90% with a corresponding 98% specificity for detecting haemodynamically significant stenosis of >50% in major leg arteries as defined by angiogram.<sup>3</sup>

Our study on steroid-resistant NS proved that ABI scores in the patient group were significantly lower ( $0.89 \pm 0.02$ ) than in the control group ( $1.04 \pm 0.08$ ) ( $P < 0.0001$ ). This is related either to the nature of the disease and hyperlipidaemia, or to drugs used in treatment, such as corticosteroids. They both cause arterial stiffness and increase the risk of cardiovascular morbidity and mortality. They also predispose patients to rapid progression to end-stage kidney disease. Our results were in agreement with De Vinuesa *et al.* who investigated the prevalence of PAD using the ABI in 102 patients who had been referred for the first time to a nephrology clinic with CKD. The study found a high prevalence of PAD (considered an ABI score of <0.9) in non-dialysed patients with CKD.<sup>10</sup> Another study by Willenberg *et al.* focused on children with a history of longterm (>5 years) corticosteroid use (group A) and a matched control group without a

history of corticosteroid use (group B). ABI scores showed that 80% in group A as compared to 9% in group B ( $P = 0.0009$ ) were at risk of atherosclerosis. The results suggested that long-term corticosteroid therapy is associated with a distally accentuated calcifying atherosclerosis.<sup>11</sup> In our study, ABI scores correlated well with the renal function of patients ( $P < 0.001$ ) so ABI could be a very easy way to predict early complications in these patients; for example, when renal markers (urea and creatinine) start to be affected, peripheral arterial assessment must be done. Our findings also agree with those of Kshirsagar *et al.* who found that the presence of an ABI score <0.90 was associated with an estimated glomerular filtration rate (GFR) of <90 when compared to the reference group.<sup>12</sup> In our study, serum phosphorus and alkaline phosphatase were significantly higher in the patient group versus the control group, ( $P$  value 0.01–0.03 and 0.006, respectively) This finding agrees with that of Toussaint and Kerr who postulated that vascular calcification induced by calcium and phosphate excesses and uremia is a major risk factor and is independently associated with cardiovascular events and death.<sup>13</sup> They also recommended that both vascular calcification and arterial stiffness can be measured through non-invasive techniques involving computed tomography (CT), ultrasound, echocardiography, and pulse wave velocity. Also in our study, there was a highly significant negative correlation between mean ABI score and cholesterol levels ( $P < 0.001$ ). There was also a significant negative correlation between mean ABI score and serum TG ( $P < 0.02$ ). These results were in agreement with those of An *et al.* who studied the relation between PAD and renal insufficiency in high risk cardiovascular patients and concluded that a high prevalence of PAD (defined as an ABI  $\leq 0.9$ ) was associated with hypercholesterolaemia, CAD, and cerebrovascular diseases.<sup>14</sup>

## Conclusion

The ABI is a simple, non-invasive bedside test for early detection of PAD, which is a marker of cardiovascular morbidity. Steroid-resistant NS patients are at high risk of developing cardiovascular complications, so early screening for PAD would be useful to prevent morbid complications.

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