Carotid Intimal Medial Thickness in Children and Young Adolescents with Nephrotic Syndrome

Sawsan M. El-Bana,[1] Mohamed A. Sharawe ,[2] and Adel H. Mahmoud[3]

From the Departments of Pediatric Medicine, [1] Internal Medicine, [2] and Cardiology, [3] Faculty of Medicine, El-Minia University, Egypt.

Abstract:

Patients with nephrotic syndrome (NS) are assumed to be at increased risk for atherosclerosis and coronary heart diseases (CHD), probably because of NS associated with hyperlipidemia, hypertension and steroid therapy. This study was aimed at evaluation of the carotid intimal thickness as a predictor of developing atherosclerosis in children and young adolescents with nephrotic syndrome. Twenty-five children and young adolescents attending the Pediatric Nephrology outpatient clinic of El- Minia University Hospital were enrolled in this study. They were 16 males and 9 females. Their age ranged between 8 and 14 years with a mean of 11 ± 2.1 years. They were subdivided into 2 subgroups; one included 15 patients (60%) having proteinuria and not responding to steroid therapy and the other included 10 patients (40%) having proteinuria and responding to steroid therapy. Fifteen healthy age and sex matched young adolescent served as a control group. All patients were subjected to thorough history taking and clinical examination. All subjects in the study underwent laboratory investigations including urinalysis, 24-hour protein in urine, serum creatinine, triglycerides (TGs), cholesterol, low and high density lipoproteins (LDL and HDL), as well as carotid duplex.

The results showed that carotid intimal thickness was significantly higher in nephrotic patients than controls ($p < 0.001$). Serum LDL and cholesterol were significantly higher in nephrotic patients than controls ($p < 0.01$, $p < 0.02$ respectively). Carotid intimal thickness was directly correlated to relapse rates and serum HDL, LDL and cholesterol ($p < 0.001$ for each).

Conclusions: *Nephrotic patients with long duration of illness, resistant to steroid therapy, have a history of hypertension and hyperlipidemia are more susceptible to early development of atherosclerosis and subsequent cardiovascular complications so they must be properly controlled especially early use of statins in children and young adolescent in those with high risk factors. Follow up of the high-risk nephrotic adolescent for possible development of CHD in young adulthood is recommended.*

Introduction:

Nephrotic syndrome (NS) may be defined as heavy proteinuria that is severe enough to cause hypoalbuminemia, hypercholesterolemia and usually edema.

Proteinuria of any magnitude has been identified as a risk factor for cardiovascular diseases in adults.[1] Severe persistent proteinuria may also be a long-term risk factor for atherosclerosis in children.[2] As severity of proteinuria increases; it is associated with a variety of metabolic disturbances that contribute to cardiovascular disease, e.g. hypercholesterolemia, hypertriglyceridemia, and hypercoagulability. In some patients, factors as hypertension, renal insufficiency, and steroid therapy may also contribute to the risk for cardiovascular diseases.[2] Severe disorder of lipid metabolism is associated with an enhanced risk to develop cardiovascular risk factors later in life with atherosclerotic lesions beginning already in childhood.[3]

The thickness of the carotid artery wall, as measured by ultrasound, is a good predictor of heart attack and stroke in asymptotic, elderly individuals, according to a new report (New England Journal of Medicine 1999). Ultrasound examination of the carotid arteries has emerged as an alternative noninvasive method to study the evolution of cardiovascular disease.[4] In adults, increased intimal-medial thickness of the carotid artery (cIMT) has gained acceptance as a reliable marker for generalized atherosclerosis on the basis of the positive association between cIMT and the severity of several different cardiovascular disease risk factors, coronary artery disease, myocardial infarction, and stroke.[5,6]

Increased cIMT has also been demonstrated in children with cardiovascular risk factors such as diabetes, familial hypercholesterolemia, and growth hormone deficiency, as well as in children with arteriopathic diseases such as Williams syndrome and Kawasaki disease.[7] To determine whether atherosclerosis and cardiac hypertrophy are co-

morbid conditions in hypertensive children, Jonathan M. Sorof,[8] in 1999, investigated the relationship between cIMT and LVMI in newly referred patients to a pediatric hypertension clinic. Direct relation between carotid arterial wall thickness and cardiovascular event risk has been investigated. A nearly fivefold increase in stroke or heart attack rates occurred in people with the thickest carotid arteries compared with those with the thinnest.[8] The results from the current study demonstrated for the first time in children with elevated blood pressure that early arterial wall changes related to atherosclerosis and increases in LVM occur in concert. This relationship is evidenced both by the positive correlation between LVMI and cIMT and the association between LVH and increased cIMT. Specifically, a compelling finding of the study is the high percentage of LVH in children with increased cIMT.

The goal of the present study was to evaluate the carotid intimal thickness in children and young adolescents with nephrotic syndrome. It is important to judge if these patients with high risk factors are in need of specific treatment for hyperlipidemia by dietary restriction or pharmacological therapy.

Subjects and Methods:

This study was conducted at the Outpatient Pediatric Nephrology Unit of El-Minia University Hospital. It included 2 groups.

Group I comprised 25 children and young adolescents with nephrotic syndrome (16 males and 9 females). Their age ranged between 8 and 14 years, with a mean of (11±2.1) years. They were subdivided into 2 subgroups:

Group IA: Included 15 patients in relapse with a mean age(9.4±1.5)years .

group IB: Included 10 patients were in remission with a mean age(11.5±0.9). Relapse is defined as the occurrence of edema and not simply proteinuria as many children with this condition have intermittent proteinuria that resolves spontaneously .

Group II (control group) included 15 age and sex matched healthy children (10 males and 5 females) with a mean age of 10.5 ± 1.9) years.

El-Minia University Hospital Ethics Committee approved the study, Informed consent was obtained from patients or caregivers of each patient or control subject before enrollment in the study.

All the subjects in this study fulfilled the following exclusion criteria:

1. No symptoms or signs of heart diseases either congenital or rheumatic.
2. No ECG abnormalities.
3. Non diabetic.
4. Non obese.
5. No primary hyperlipidemia.

All the subjects underwent the following:

1. *History* analysis.
2. *Clinical examination* laying stress on measurement of weight and height, calculation of body mass index, measurement of arterial blood pressure, examination for edema and cardiac examination. None of our patients had congenital or rheumatic heart disease.
3. *Laboratory investigations* including serum creatinine, serum albumin, serum triglycerides (TGs), cholesterol, high-density lipoproteins (LDL) and low-density lipoproteins (LDL.
4. *Electrocardiogram (ECG):* Resting 12 lead surface ECG was done to all patients.
5. *Carotid artery ultrasound* was performed by experienced vascular sonographers. Briefly, subjects were examined in a supine position. A longitudinal view of the distal common carotid artery (CCA) was obtained using a linear 8-MHz transducer. The gain and focus settings were optimized to contrast the vessel lumen and IMT appearance. The IMT measurements were made on both CCAs on the far wall of the distal CCA at least 2 cm below the flow divider. A longitudinal B-mode image of the CCA with sharp edges of the far wall IMT complex was used to place 2 measurements with digital calipers at 1 cm apart. The measurements were carried on frozen images demonstrating the thickest IMT complex with calipers placed on a zoomed CCA image.

Statistical Analysis:

Descriptive statistics are presented as percentages, means, and standard deviations. Univariate analyses for group comparisons of continuous variables were performed using Student t test. Multivariate analyses for group comparisons were performed using analysis of covariance. The correlations were determined using the Pearson correlation coefficient. Multiple regression analysis was used to determine the strength of association among cIMT, and multiple independent variables. $P < .05$ indicated statistical significance.

Results:

The results of our study were demonstrated in tables I to IV and figure 1 and 2:

Table I: Clinical data of patients versus control group

Variables	Patients	Control	P- Value	Significance
Age (years)	11±2.1	10.5±1.9	<0.2	#
Sex (M/F)	16/9	10/5		
Duration of illness (years)	2.5 ± 2.1	0		
Systolic B.P. (mmHg)	103±10.4	98.5±8.7	<0.25	#
Diastolic B.P. (mmHg)	70.6±7.1	64.3±4.6	<0.05	*

Table II: Clinical data of patients with relapse versus those with remission

Variables	Relapse (A1)	Remission (A2)	P-Value	Significance
Age (years)	9.4±1.5	11.5±0.9	<0.12	#
Sex (M/F)	10/5	5/5		
Duration of illness (years)	5.6 ± 1.7	1.7±1.2	<0.13	#
Number of relapses	6.4 ± 2.9	1.5±0.5	<0.001	**
Systolic B.P. (mmHg)	120.7±7.1	98.8±5.6	<0.22	#
Diastolic B.P. (mmHg)	78±10.9	68.8±4.8	<0.009	*

Table III: Laboratory data of patients versus control group

Variables	Patients	Control	P- Value	Significance
Cholesterol	158.6±29	131.4±17.4	<0.02	*
Triglyceride	113±22.2	83.7±15.4	<0.08	#
LDL	117.6±14.1	82.1±23.6	<0.01	*
HDL	43±7	54±8.5	<0.21	#
Urea	30.5±8.5	31.2±8.3	<0.2	#
Creatinine	0.5±0.243	0.6±0.2	<0.2	#
Carotid intimal thickness	42.5±13	35.1±3.4	<0.001	**

Table IV: Laboratory data of relapse group versus remission group

	Relapse (A1)	Remission (A2)	P-Value	Significance
Cholesterol	211.2±7.7	145.5±14.4	<0.13	#
Triglyceride	150±6.1	103.8±12.8	<0.8	#
LDL	135.2±19.5	113.3±8.3	<0.004	*
HDL	32.6±6.9	45.6±5.2	<0.04	*
Urea	34.5±8.5	30.2±8.3	<0.52	#
Creatinine	0.5±0.3	0.56±0.24	<0.32	#
Carotid intimal thickness	65.6±8.4	36.7±4.8	<0.04	*

** = Significant, ** = Highly significant, # Not significant*

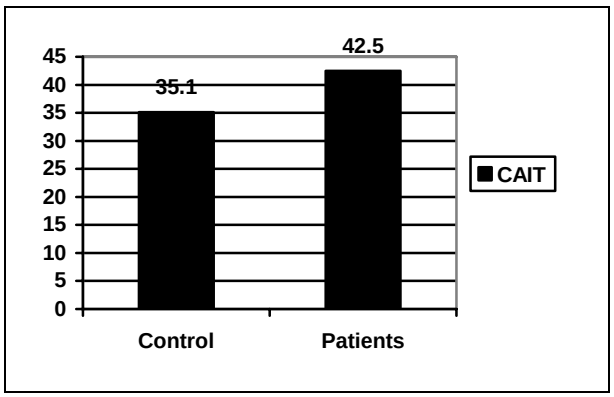

Figure 1: Carotid Intimal Thickness in Patients Versus Control Group

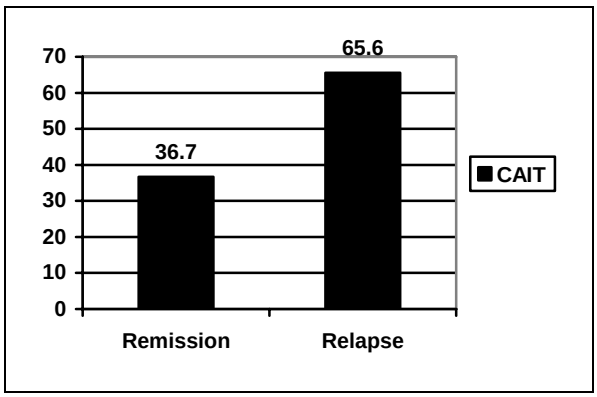

Figure (2): Carotid Intimal Thickness in Patients with remission Versus Relapse Group

Multiple regression analysis of carotid artery intimal thickness versus systolic, diastolic, cholesterol, LDL, duration of illness and number of relapses R-square was 0.91 with highly significant P- value (<0.001). This low P-value suggests that carotid intimal thickness may be linearly related to these independent risk variables.

Discussion:

Cardiac diseases are the major cause of morbidity and mortality among patients with chronic renal diseases regardless of their age. Coronary cardiovascular diseases account for approximately 23 % of deaths in children and young adults <30 years old who started treatment to end stage renal diseases

as children.[9] The uremic patients are exposed to a multitude of atherogenic risk factors mainly hypertension and abnormal lipid metabolism, in addition to diabetes mellitus and hyperparathyroidism.[10]

Children with hypercholesterolemia have endothelial dysfunction and increased carotid intimal-media thickness (cIMT), which herald the premature atherosclerotic disease they develop later in life.[11] This faster progression led to a significant deviation in terms of intimal- media thickness from the age of 12 years and onwards.[12]

In patients with nephritic syndrome the pathogenesis of hypercholesterolemia is still not completely understood but overproduction and decreased catabolism of lipoproteins may play a role.

Our results showed that serum cholesterol, LDL, diastolic blood pressure, and cIMT were significantly increased in nephrotic patient (NS) than in control and this was in agreement with Rodenburg et al.[12] in 2004, who found that LDL cholesterol was a strong and independent predictor of carotid artery intimal-medial thickness in these children, which confirms the pivotal role of LDL cholesterol for the development of atherosclerosis, and Berson et al.[13] in 2001, who reported that primary pediatric hypertension has become increasingly common in association with other cardiovascular risk factors such as obesity, hyperlipidemia, and diabetes. Also, the Expert panel III found that dyslipidemia is one of the most important modifiable risk factors for the coronary heart diseases (CHD) and many patient with CHD or who are at risk for CHD have more than one lipid abnormality, each of which increases cardiovascular risk.[14] In agreement with us, Heshmat et al.,[15] in 2004 found that serum triglyceride cholesterol and LDL were significantly increased in nephrotic patients but whether atherosclerosis was more common in such patients than in healthy people had never been clearly established because most of these studies concerning CHD associated with NS conducted on adults.[15]

Hopper et al.,[16] Wass et al.,[17] and Vonsnides and Cameron,[18] found that there is no increased risk of CHD in patient with NS. Theses difference in our results and theirs can be explained by lack of more sensitive diagnostic techniques at the past because these studies are old and were done 30 years ago.

The single large study which showed no increased risk was done by Wass et al.,[17] and included 159 adult NS patients. It showed that the prevalence of cardiovascular morbidity was not so much higher than controls and CHD made only a small statistically non significant contribution to the total causes of death and deaths from CHD was not significantly above normal.

The presence of preclinical atherosclerosis in children with cardiovascular risk factors has been documented in previous studies.[17]

In this study the measurement of cIMT was directly correlated to the duration of illness, relapse rates, and serum LDL in patients with NS ($p<0.001$ for each) .

Our results were in agreement with Portman et al.,[19] who found that atherosclerosis may develop at a relatively young age in children with persistent nephritic range proteinuria.

These results indicated that those with proteinuria are more susceptible to develop ischemia and myocardial infarction than those in remission, and the duration of hypertension and hyperlipidemia affect the cardiac state of our patients making them more susceptible to myocardial ischemia. Also, studies using carotid ultrasound to measure cIMT in children at risk for atherosclerotic diseases are consistent with these autopsy findings, and it has been reported in children with diabetes[20] and in children with familial hypercholesterolemia,[21] as compared with normal controls. Furthermore, prospective community-based studies have shown that total serum cholesterol measured in childhood predicts cIMT measured in the same subjects in adulthood,[22] and specific studies of adults have reported that cIMT -1mm is associated with a 2- to 5- fold greater risk of coronary events[23] and cIMT greater than or equal to 1.18 is associated with a 4- fold greater risk of combined acute myocardial infarction and stroke.[24]

The principal cause of hypertriglyceridemia can be explained by the increased production of apoprotein B and marked decrease in the metabolism of VLDL rich in triglycerides as a result of decreased endothelial cell delipidation of VLDL, decreased lipoprotein lipase activity, and hepatic triglyceride lipase.[25] In addition, loss of carnitine which plays an important role in facilitating the transport of fatty acids across the inner mitochondrial membrane prior to B oxidation[26] and decrease antioxidant activity might be an additional factor.[27]

Conclusion:

Endothelial dysfunction represents one of the earliest stages of atherogenesis and has been shown to have a predictive value for future CVD. In order to achieve normalization of endothelial function in atherogenic vascular bed, such as coronary arteries, therapy should be initiated at an early stage, before the onset of sever macrovascular structural abnormalities. So, proper control of hyperlipidemia and hypertension in nephrotic patients is of great importance because it might be of protective value to the cardiovascular system. Additional studies of carotid ultrasound in NS will help determine the extent to which increased cIMT

may be used as a marker for this risk. This might assist in the decision of when to start lipid- lowering medication in children with NS, because in children the lipid-lowering effect of diet is modest and moreover that long-term compliance is poor.

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