

## Evaluation of the Cardiovascular System in Children and Adolescents with Nephrotic Syndrome

Nahla Heshmat, Sawsan Moselhy, Mona El-Ganzoury and Dalia Mashaly

*Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt.*

### ABSTRACT

**Background:** Patients with nephrotic syndrome (NS) are assumed to be at increased risk for atherosclerosis and coronary heart disease (CHD), probably because of NS associated hyperlipidemia.

**Objectives:** This study was aimed at evaluation of the cardiovascular system in children and adolescents with nephrotic syndrome.

**Methods:** Forty-two children and adolescents attending the Pediatric Nephrology Unit of Ain Shams University Children's Hospital were enrolled in this study. They were 24 males and 18 females. Their ages ranged between 3 and 18 years with a mean of  $10.47 \pm 4.62$  years. They were subdivided into 2 subgroups; one included 21 patients (50%) having proteinuria and the other included 21 patients (50%) in remission. Ten healthy age and sex matched children 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 hemoglobin level, serum creatinine, albumin, triglycerides (TGs), cholesterol, low and high density lipoproteins (LDL and HDL), electrocardiogram (ECG) as well as echocardiography.

**Results:** Serum TGs, LDL and cholesterol were significantly higher in nephrotic patients than controls ( $p < 0.01$ ), whereas HDL levels were comparable. Serum albumin was inversely correlated to serum TGs, LDL and cholesterol ( $p < 0.05$  for each). ECG did not reveal any ischemic changes in nephrotic patients. Echocardiography showed normal systolic function in all patients. Diastolic dysfunction including abnormal relaxation or restrictive filling was detected in 30 patients (71%). Diastolic dysfunction was evidenced by abnormal isovolumic relaxation time (IVRT), deceleration time of the peak early filling velocity (DT) and/or decreased E/A ratio which is the ratio between peak early filling (peak E) velocity and peak late (peak A) velocity. Left ventricular mass (LVM) was increased and was positively correlated to disease duration and number of relapses ( $p < 0.05$ ).

**Conclusions:** Nephrotic patients did not have ischemic changes in the resting ECG, whereas their echocardiography revealed diastolic dysfunction and increased left ventricular mass. The duration of hypertension and hyperlipidemia make nephrotic patients more susceptible to myocardial ischemia, so they must be properly controlled. More sensitive diagnostic techniques and follow up of the nephrotic children for possible development of CHD in young adulthood is recommended.

### INTRODUCTION

Nephrotic syndrome (NS) is associated with hyperlipidemia. Increased total cholesterol is invariably found in patients with nephrotic-range proteinuria. Apolipoprotein B, the major protein in low-density lipoprotein (LDL) is particularly high. Hypertriglyceridemia is very common in patients with severe proteinuria. Although

the pathogenesis of hyperlipidemia in nephrotic syndrome is still not completely understood, it appears that both overproduction and decreased catabolism of lipoproteins play a role. In addition, the corticosteroids and cyclosporine often used to treat patients with nephrotic syndrome may also contribute to elevations of total and LDL cholesterol<sup>(1)</sup>.

There have been no controlled intervention trials to prove or disprove the hypothesis that abnormalities of lipoproteins in nephrotic syndrome contribute to cardiovascular disease. There have been few studies examining the incidence of cardiovascular disease in patients with nephrotic syndrome. Ordonez et al.<sup>(2)</sup> reported a 5.5 fold increase in the risk of cardiovascular disease, and a 2.8-fold increase in the risk of cardiovascular disease death in adult patients with nephrotic syndrome compared to control subjects. The increased risk was independent of hypertension. An autopsy study found a very high prevalence of coronary lesions in adults with nephrotic syndrome<sup>(3)</sup>. Kallen et al.<sup>(4)</sup> reported coronary artery disease occurring in a young child with nephrotic syndrome.

#### AIM OF THE WORK

The goal of the present study was to evaluate the cardiovascular system in children and adolescents with nephrotic syndrome. It is important to judge if these patients are in need of specific treatment for hyperlipidemia by dietary restriction or pharmacologic therapy.

#### SUBJECTS AND METHODS

##### *Subjects*

This study was conducted at the Pediatric Nephrology Unit of Ain Shams University Children's Hospital. It included 2 groups:

**Group I:** It comprised 42 children and adolescents with nephrotic syndrome (24 males and 18 females), their ages ranged between 3 and 18 years with a mean of

10.47 ± 4.62 years. They were subdivided into 2 subgroups:

**Group IA:** Included 21 patients (50%) having proteinuria (Albustix = 1+ or more up to 4+ with or without edema). Sixteen of them were in relapse. Relapse is defined as the occurrence of edema and not simply proteinuria as many children with this condition have intermittent proteinuria that resolves spontaneously<sup>(5)</sup>.

**Group IB:** Included 21 patients (50%) in remission. Remission is defined as urinary protein excretion < 4 mg/hr/m<sup>2</sup> or Albustix = negative or trace for 3 consecutive days<sup>(6)</sup>. Concerning the treatment of patients having proteinuria; all of them were receiving prednisone (dose ranging between 5 and 60 mg every day or every other day), 4 patients were receiving levamisole (dose: 2.5 mg/Kg on alternate days), 5 patients were receiving cyclophosphamide (dose: 3 mg/Kg/day following an 8 weeks course or 2 mg/Kg/day for 12 weeks) and 7 patients were receiving cyclosporine (dose: 5 mg/Kg/day).

As regards the treatment of patients in remission, 19 patients were receiving prednisone. In addition to prednisone, 2 patients were receiving levamisole, 5 patients were receiving cyclophosphamide and 7 patients were receiving cyclosporine. The doses were the same as the proteinuria group. Two patients in this group were off treatment.

Twenty-seven of the studied 42 nephrotic patients had hypertension. Their hypertension was treated by antihypertensives as captopril, amlodipine, nifedipine, atenolol and/or prazosin.

**Group II (control group):** It included 10 age and sex matched healthy children (7 males

and 3 females). Their ages ranged between 3-14 years with a mean of  $7.6 \pm 4.06$  years.

*Ain Shams University Children's 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.

### Methods

All the subjects in this study 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 included:
  - Hemoglobin level by Microdiff 18 Coulter counter.
  - Serum creatinine by Synchron CX7 autoanalyzer.
  - Serum albumin by colourimetric method using spectrophotometer.
  - Serum triglycerides (TGs), cholesterol, high-density lipoproteins (HDL) and low-density lipoproteins (LDL) by colourimetric method using Synchron CX 5.
4. Electrocardiogram (ECG):

Resting 12 lead surface ECG was done to all patients to detect evidence of: left ventricular hypertrophy, ischemic heart disease, pericarditis and pericardial effusion.

5. Echocardiography:

Standard transthoracic M-mode, two dimensional and Doppler colour flow mapping echocardiograms were performed to

every subject, Acuson 128/5xp USA apparatus computerized system.

- a) *M-mode* measurements were obtained according to The American Society of Echocardiography:

- Left ventricular end diastolic diameter (LVED)
- Interventricular septal wall thickness in diastole (IVST).
- Left ventricular posterior wall thickness in diastole (LVPWT).

- b) Systolic function indices:

- Ejection fraction (EF).
- Fractional shortening (FS).

Systolic dysfunction is present if the ejection fraction is below 50%<sup>(7)</sup>.

- c) Left ventricular diastolic function assessment:

- *Assessment of peak E, A velocities and E/A ratio:*

A pulsed wave Doppler examination of the left ventricular inflow was performed in the apical 4 chamber view, the mitral valve funnel was interrogated immediately on the left ventricular side of the mitral annulus and the position of the sample volume was adjusted until the highest peaks of diastolic flow velocity with optimal graphic wave forms was obtained<sup>(8)</sup>.

Peak early filling (peak E) velocity corresponds to rapid ventricular filling in early diastole. Peak late (peak A) velocity corresponds to atrial contraction in late diastole. In diastolic dysfunction due to left ventricular hypertrophy in hypertension, peak A velocity is increased and E/A ratio is decreased.

Normal values: peak E velocity  $0.91 \pm 0.11$  cm/sec.; peak A velocity  $0.49 \pm 0.08$  cm/sec.; E/A ratio  $2.0 \pm 0.5$ <sup>(9)</sup>.

- *Assessment of E-wave deceleration time (DT):*

Deceleration time of the peak early filling flow velocity, this is the time from peak early filling velocity to the end of the rapid filling wave measured in msec. Normal value ( $180 \pm 20$  msec)<sup>(9)</sup>.

- *Assessment of isovolumic relaxation time (IVRT):*

It was measured using a Doppler signal which intersect both the left ventricular outflow and the mitral valve motion, it is the time interval from aortic valve closure to mitral valve opening. Normal value ( $71 \pm 11$  msec)<sup>(9)</sup>.

Diastolic dysfunction was considered to be present if the patient had one of these parameters abnormal. Diastolic dysfunction could be abnormal relaxation or restriction to filling.

Abnormal relaxation can be identified by presence of prolonged IVRT, low E/A ratio and/or prolonged DT.

Restriction to filling can be identified by presence of short IVRT, high E/A ratio and/or short DT<sup>(9)</sup>.

### **Statistical Analysis**

The results were analyzed by commercially available software package (Stat View, Abacus Concepts, Inc, Berkley, CA, USA). The data were expressed as mean  $\pm$  standard deviation (SD). Pearson r

correlation coefficient was used to determine the relationship between different quantitative variables. Student t test was employed to compare mean values of different variables. Mann-Whitney U test was used to compare non parametric data. For all tests a probability of less than 0.05 was considered significant.

### **RESULTS**

The characteristics of the studied nephrotic patients are shown in Table 1. Twenty-seven of the studied 42 NS patients had hypertension and their blood pressure was controlled by antihypertensive medications.

#### ***Lipid profile in nephrotic patients and controls***

Serum cholesterol, TGs, LDL were significantly higher in nephrotic patients whether having proteinuria or in remission than controls. They were higher in nephrotic patients having proteinuria than those in remission, however the difference did not reach statistical significance (Fig. 1).

HDL were comparable in nephrotic patients whether having proteinuria ( $57.9 \pm 22.5$  mg/dL) or in remission ( $56.57 \pm 21.9$  mg/dL) and controls ( $42.5 \pm 4.8$  mg/dL) ( $z = 1.67$ ,  $p > 0.05$ ;  $z = 2.4$ ,  $p > 0.05$  respectively).

Serum albumin was negatively correlated to serum TGs, cholesterol and LDL ( $r = -0.44$ ,  $p < 0.05$ ;  $r = -0.66$ ,  $p < 0.05$ ;  $r = -0.61$ ,  $p < 0.05$  respectively).

#### ***Cardiac Examination and ECG***

All of our patients were free from cardiovascular symptoms and none of them had any symptoms or signs of heart failure.

Resting ECG did not reveal any

ischemic changes in nephrotic patients. Two patients (4.8%) showed right bundle branch block (RBBB), four patients (9.4%) showed left ventricular hypertrophy and six patients (14.2%) showed right ventricular hypertrophy.

### *Echocardiographic parameters*

The results of echocardiography in nephrotic patients and controls are shown in Table 2 and Fig. 2.

Echocardiographic findings revealed that LVED and LVPWT were comparable in nephrotic patients whether having proteinuria or in remission and controls. Meanwhile when those in remission were compared to those having proteinuria it was found that LVED was significantly higher while LVPWT showed no statistical significance.

Nephrotic patients whether having proteinuria or in remission had higher peak A than the control group, whereas their E/A ratio, IVRT, AT and DT were lower than controls. IVST was higher in nephrotic patients having proteinuria than controls, meanwhile it was comparable in patients in remission and controls.

Nephrotic patients with proteinuria had higher LVED and IVST than those in remission, whereas both groups had comparable other echocardiographic parameters.

LVM was higher in nephrotic patients whether having proteinuria or in remission

than controls, however the difference reached statistical significance only in those with proteinuria.

LVM was positively correlated to AT, IVST, LVPWT, number of relapses and disease duration ( $p < 0.05$ ) (Fig. 3).

We found that IVST was positively correlated to the duration of the disease, number of relapses, triglycerides level and AT ( $p < 0.05$ ). LVPWT was positively correlated to number of relapses ( $p < 0.05$ ). LVED was positively correlated to the duration of the disease ( $p < 0.05$ ).

All of the studied patients and controls had normal systolic functions, their ejection fraction was above 50%, and their FS was within normal. (Tables 2 & 3).

Thirty of the studied 42 NS patients (71%) had diastolic dysfunctions; six patients (28.5%) with proteinuria and 2 patients (9.5%) in remission had abnormal relaxation of the myocardium. While 12 patients (57.1%) with proteinuria and 10 patients (47.6%) in remission had restriction to filling indicating stiff myocardium (Table 3). Abnormal relaxation was detected by the presence of prolonged IVRT, low E/A ratio and/or prolonged DT. Restriction of filling was detected by the presence of short IVRT, increased E/A ratio and/or short DT.

Segmental wall motion abnormality in echocardiography which suggests ischemia was not detected in our series.

**Table 1: Characteristics of nephrotic patients with proteinuria compared to those in remission.**

Data	Nephrotic patients with proteinuria (n = 21)	Nephrotic patient in remission (n = 21)	Z/t	p
Age (years)	10.4 ± 4.62	9.61 ± 4.6	1.39	> 0.05
Duration (months)	86.19 ± 58.03	57.3 ± 57.7	1.91	< 0.05*
No of relapses	6.8 ± 6.6	2.23 ± 3.28	3.51	< 0.05*
Wt percentile	60.5 ± 29.6	38.2 ± 32.4	2.45	< 0.05*
Ht percentile	23.9 ± 29.2	14.04 ± 21.57	1.83	> 0.05
BMI percentile	72.04 ± 32.7	65.76 ± 32.5	1.02	> 0.05
SBP percentile	57.09 ± 14.56	62.6 ± 15.4	1.64	> 0.05
DBP percentile	71.14 ± 17.87	67.4 ± 18.2	0.29	> 0.05
Hb (gm/dl)	12.6 ± 1.56	12.5 ± 1.19	0.15	> 0.05
S. creatinine (mg/dl)	0.63 ± 0.37	0.58 ± 0.16	0.13	> 0.05
S. albumin (g/dl)	2.93 ± 1.05	3.39 ± 0.96	0.28†	> 0.05

Wt = weight; Ht = height; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; S = serum, \* = significant; † = value of t-test.

**Table 2: Comparison of echocardiographic findings among nephrotic patients and controls.**

Data	Nephrotic patients in remission (n = 21)	Nephrotic patients with proteinuria (n = 21)	Controls (n = 10)	Remission vs control p	Proteinuria vs control p	Proteinuria vs remission p
<b>Measurements</b>						
LVED (cm)	3.68 ± 0.52	4.1 ± 0.61	3.92 ± 0.45	> 0.05	> 0.05	< 0.05*
IVST (cm)	0.63 ± 0.14	0.73 ± 0.16	0.63 ± 0.1	> 0.05	< 0.05*	< 0.05*
LVPW (cm)	0.52 ± 0.16	0.53 ± 0.18	0.56 ± 0.09	> 0.05	> 0.05	> 0.05
LVM (gm/m <sup>2</sup> )	59.84 ± 32.72	77.6 ± 26.06	53.76 ± 29.76	> 0.05	< 0.01**	> 0.05
<b>Diastolic functions</b>						
Peak E (cm/sec)	88.5 ± 18.25	88.8 ± 15.93	75 ± 12	< 0.01**	< 0.01**	> 0.05
Peak A (cm/sec)	55.25 ± 12.99	53.75 ± 14.17	36 ± 9	< 0.05*	< 0.05*	> 0.05
E/A ratio	1.65 ± 0.40	1.73 ± 0.46	2.2 ± 0.7	< 0.01**	< 0.01**	> 0.05
IVRT (msec)	59.5 ± 15.72	45.5 ± 16.45	71 ± 11	< 0.05*	< 0.01**	> 0.05
AT (msec)	99.09 ± 20.48	91.1 ± 25.7	112 ± 21	< 0.05*	< 0.01**	> 0.05
DT (msec)	142.38 ± 58.45	138.7 ± 45.9	182 ± 19	< 0.01**	< 0.001**	> 0.05
<b>Systolic functions</b>						
EF%	67.19 ± 7.08	65.8 ± 6.56	72.17 ± 6.01	< 0.05*	< 0.05*	> 0.05
FS%	36.90 ± 5.42	35.5 ± 5.72	41.89 ± 4.92	< 0.05*	< 0.05*	> 0.05

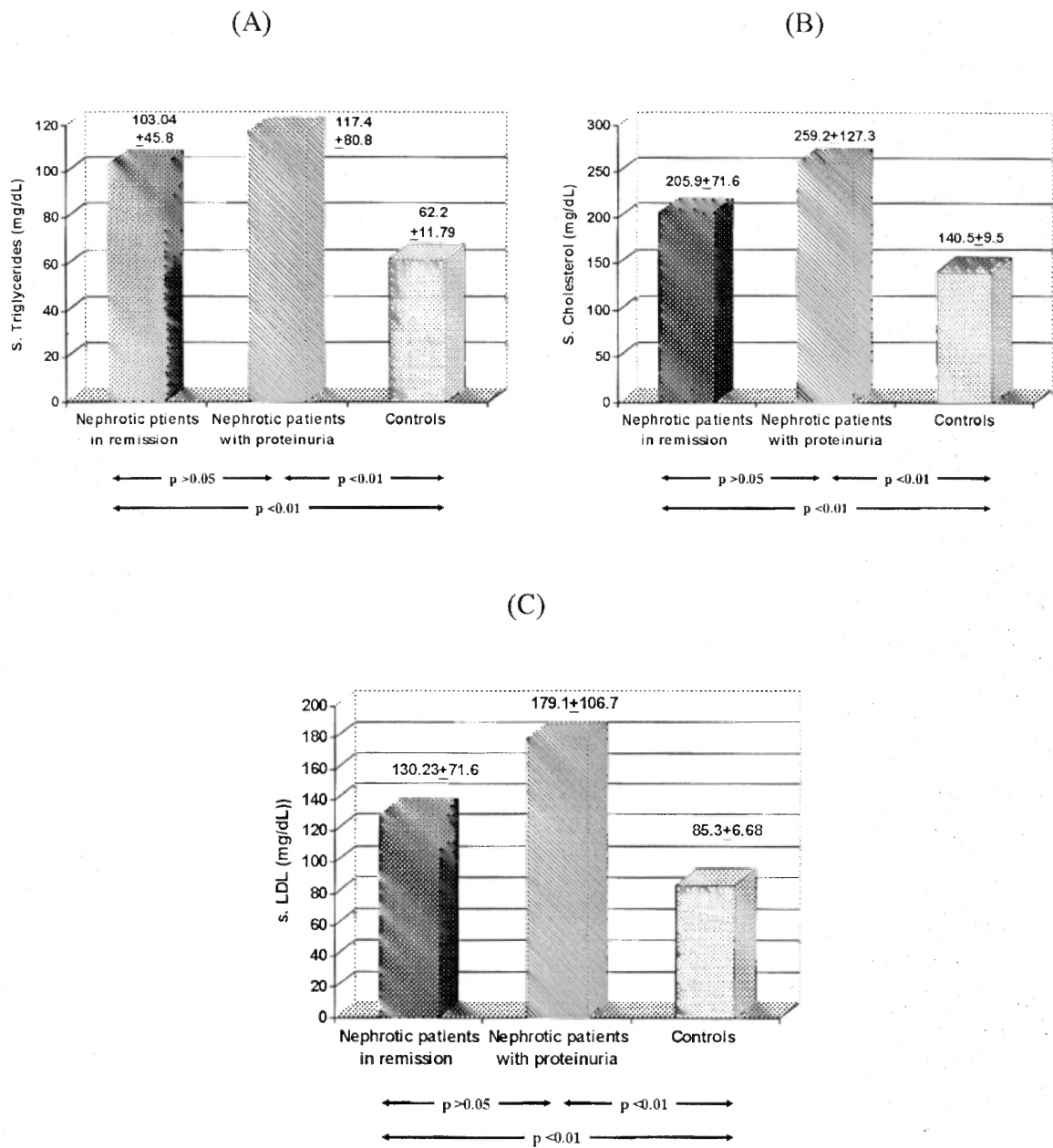
\* = Significant, \*\* = Highly significant; LVED = Left ventricular end diastolic diameter; IVST = Inter ventricular septal thickness; LVPW = Left ventricular posterior wall thickness; LVM = Left ventricular mass; peak E = peak velocity of early diastolic filling wave; peak A = peak velocity of late diastolic filling wave; E/A ratio = peak E/peak A ratio; IVRT = Isovolumic relaxation time; AT = E-wave acceleration time; DT = E-wave deceleration time; EF = Ejection fraction; FS = Fractional shortening.

**Table 3: Affection of cardiac functions in the studied patients.**

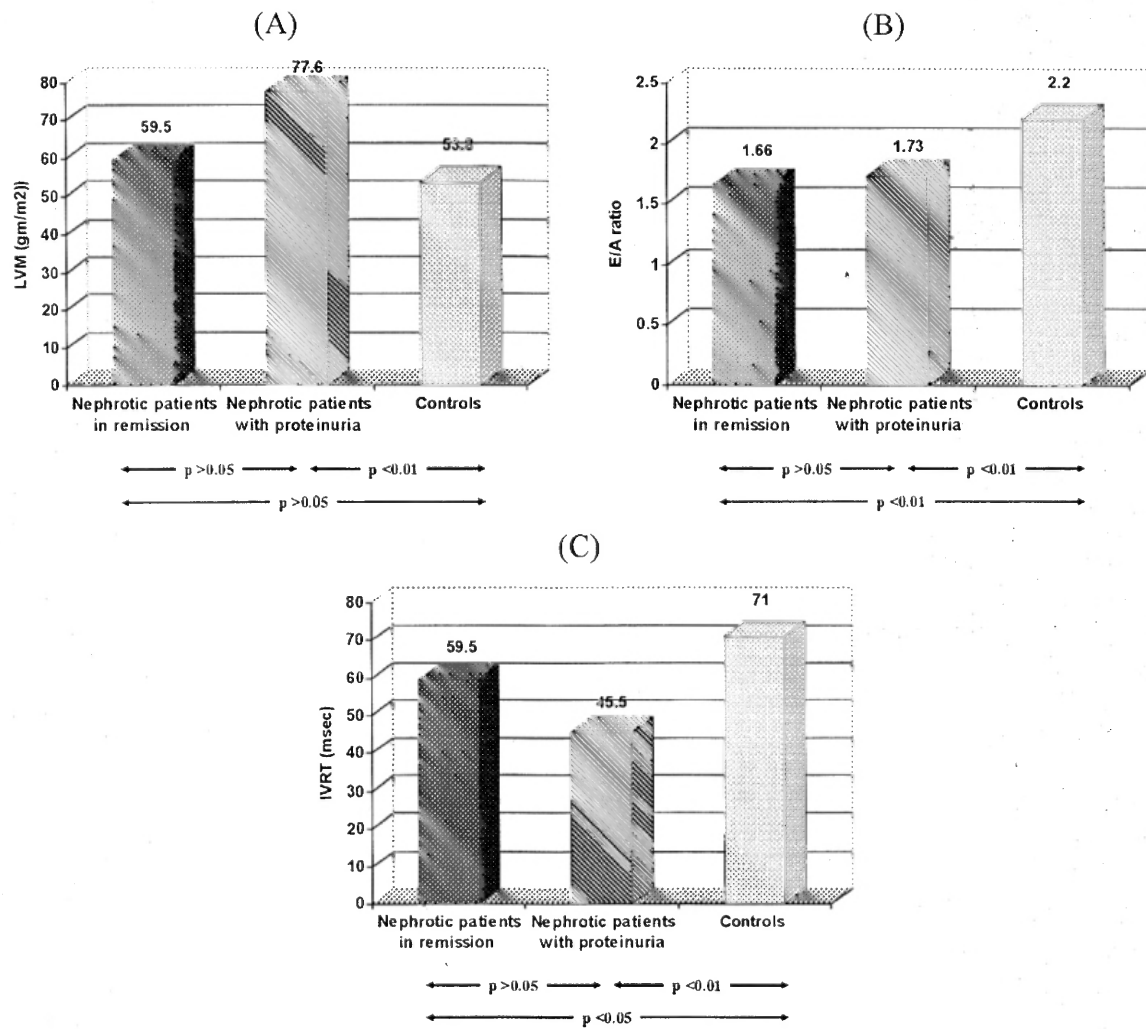
Data	Nephrotic patients with proteinuria		Nephrotic patients in remission		All nephrotic patients	
	Number	%	Number	%	Number	%
<b>Systolic functions</b>						
Normal EF %	21	100	21	100	42	100
Normal FS %	21	100	21	100	42	100
<b>Diastolic dysfunctions</b>						
<b>Abnormal relaxation</b>						
↑ IVRT	1	4.8	1	4.8	2	4.8
↓ E/A ratio	6	28.5	2	9.5	8	19
↑ DT	2	9.5	1	4.8	3	7.1
Total: ↑ IVRT, ↓ E/A ratio and/or ↑ DT	6	28.5	2	9.5	8	19
<b>Restriction to filling</b>						
↓ IVRT	4	19	4	19	8	19
↑ E/A ratio	1	4.8	0	0	1	2.4
↓ DT	12	57.1	10	47.6	22	52
Total: ↓ IVRT, ↑ E/A ratio and/or ↓ DT	12	57.1	10	47.6	22	52

EF = Ejection fraction; FS = Fractional shortening; IVRT = Isovolumic relaxation time; E/A ratio = the ratio between peak velocity of early diastolic filling wave (peak E)/peak velocity of late diastolic filling wave (peak A); DT = E-wave deceleration time; ↑ = increased; ↓ = decreased.

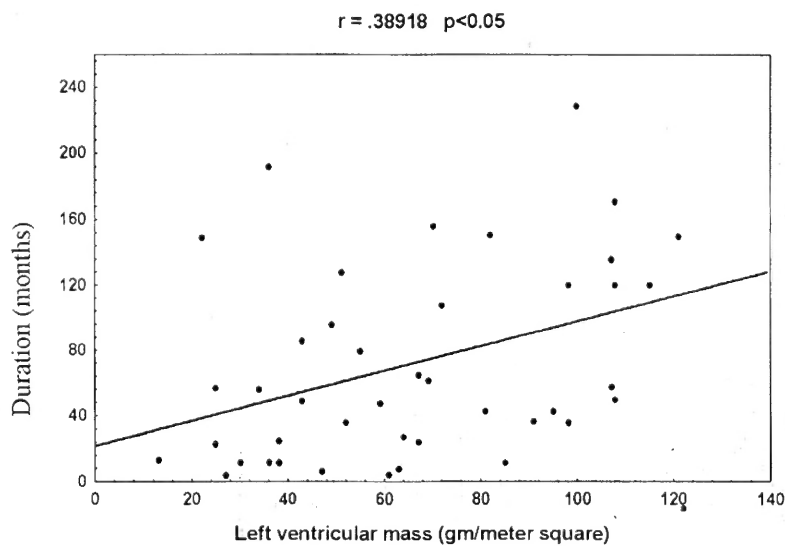




**Fig. 1: Comparison of serum triglycerides (A), cholesterol (B) and low density lipoprotein (LDL) (C) among the studied groups.**



**Fig. 2: Comparison of some echocardiographic parameters among the studied groups: left ventricular mass (LVM) (A), E/A ratio (B) and isovolumic relaxation time (IVRT) (C).**



**Fig. 3: Correlation between left ventricular mass and disease duration.**

## DISCUSSION

Our results showed that serum TGs, cholesterol and LDL were significantly increased in nephrotic patients. Similarly, previous investigators reported hyperlipidemia in many patients with nephrotic syndrome<sup>(2,10-14)</sup>. Whether atherosclerosis was more common in such patients than in healthy people had never been clearly established<sup>(15-17)</sup>.

Berlyne and Mallick<sup>(10)</sup> were the first to record increased frequency of ischemic heart disease in NS compared with the frequency in the general population. In our study neither ECG nor echocardiography revealed ischemic changes in children and adolescents with nephrotic syndrome. Kallen et al.<sup>(4)</sup> were the only investigators who reported premature atherosclerosis in a 5-year-old child with corticosteroid refractory nephrotic syndrome. All the other studies concerning coronary heart disease (CHD) associated with nephrotic syndrome were conducted on adults.

The previous attempts to describe how NS and CHD were related in adult nephrotic patients produced inconsistent results and generated disagreement among authorities about whether NS increases CHD risk. Two published reports by Hopper et al.<sup>(18)</sup>, Wass et al.<sup>(17)</sup> and data presented in two letters by Vosnides and Cameron<sup>(19)</sup>, and Gilboa<sup>(20)</sup>, found no increased risk of CHD. However, Berlyne and Mallick<sup>(10)</sup>, Alexander et al.<sup>(11)</sup>, Ordonez et al.<sup>(2)</sup> found an increased risk of CHD.

The estimates from Berlyne and Mallick<sup>(10)</sup> that risk is increased 85 times and from Alexander et al.<sup>(11)</sup> that CHD will develop in 53% of NS were very high. The

results of these two studies were substantially less reliable than the study of Ordonez et al.<sup>(2)</sup> because they depended on a small number of subjects (15 and 17). The study of Ordonez and his colleagues<sup>(2)</sup> included 149 NS patients and the mean follow-up for non fatal CHD events was 5.6 years for NS subjects and 11.2 years for controls. It showed modestly elevated estimate.

Ordonez and his colleagues<sup>(2)</sup> found that NS was associated with an increased risk of CHD. They estimated that the risk of myocardial infarction was between five and six times higher for persons with NS than for those without NS and that all CHD events and deaths from CHD were between two and three times higher than they were in the general population of the same age and sex.

The studies that showed no increased risk done by Hopper et al.<sup>(18)</sup>, Vosnides and Cameron<sup>(19)</sup>, Gilboa<sup>(20)</sup> and Wass et al.<sup>(17)</sup> included slightly more cases (N = 18-49 for the first 3 studies and N = 159 for the last one). However, they had insufficient follow up and reflected the possible blunting effect of including a high proportion of patients with minimal change disease. Moreover, these studies either had no control group or failed to control for the potential confounding effects of smoking and hypertension.

The single large study which showed no increased risk done by Wass et al.<sup>(17)</sup>, 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 the deaths from

CHD was not significantly above normal. However, they found that 27% of subjects had minimal change disease and they used large and relatively undefined population for comparison.

In the absence of firm epidemiologic evidence, those who believe that the association exists had relied on the biologic plausibility of an increased risk of CHD in NS patients. Fifty percent or more NS patients were known to have elevated serum cholesterol or LDL levels or both<sup>(13)</sup>, and hypercholesterolemia was recognized as a major risk factor for myocardial ischemia and other forms of cardiovascular disease<sup>(21)</sup>.

In patients with NS, hyperlipidemia could accelerate progression of atherosclerosis and increase platelet aggregation. Frequent hypertension and use of steroids in therapy could further increase CHD risk. Given this line of evidence, reinforced by increased safety and effectiveness of antihyperlipidemic medications, authorities advocated pharmacologic treatment of the hyperlipidemia of NS<sup>(11,12,22-24)</sup>.

Berlyne and Mallick<sup>(10)</sup> reported that CHD had been the second most common cause of death in NS, the commonest being uremia. They recommended that the frequency of myocardial infarction should be borne in mind in the differential diagnosis of obscure chest pain in young adult nephrotic patients. However, Wass et al.<sup>(17)</sup> found that despite the high mortality rate of their series of adults with nephrotic syndrome at a mean follow up of 5 years, CHD made only a small statistical non significant contribution to the total causes of death.

Wass and Coworkers<sup>(17)</sup> found no

increased risk of CHD among adults, similar to what we have found in children. They also did not find significant difference in the incidence of CHD in patients who had persistent compared to those who had intermittent episodes. They postulated that, because of the fluctuant nature of nephrotic syndrome and the significant correlation of hyperlipidemia with severity of nephrotic syndrome, hyperlipidemia may therefore be present for only a relatively short time. So, the duration of exposure to lipid abnormalities induced by the nephrotic syndrome must be taken into account, since atherosclerosis evolved over an extended time<sup>(25)</sup>.

Ordonez and his colleagues<sup>(2)</sup> did not determine which specific aspect of NS (that was hypercholesterolemia, hypertriglyceridemia or hypertension) conferred the most risk for CHD. In patients with NS, hyperlipidemia could accelerate progression of atherosclerosis and increase platelet aggregation. Frequent hypertension and use of steroids in therapy can further increase CHD risk<sup>(11,12)</sup>.

Neaton et al.<sup>(26)</sup> and Wilson et al.<sup>(27)</sup> stated that hypertension is a major risk factor for myocardial ischemia and infarction. In the present study, there was an increase in both systolic and diastolic blood pressure levels in nephrotic patients. Left ventricular mass (LVM) was higher in nephrotic patients whether having proteinuria or in remission than controls, however the difference reached statistical significance only in those with proteinuria. LVM was also positively correlated to disease duration and number of relapses in patients with NS. The increase in LVM is considered one of the risk factors for

development of myocardial ischemia and coronary heart diseases in those patients. This is supported by Frohlich et al.<sup>(28)</sup> who stated that increased left ventricular mass may contribute to the increased cardiovascular risk because left ventricular hypertrophy is an ominous prognostic sign and independent risk factor for sudden death, myocardial ischemia, coronary heart disease and heart failure.

Diastolic dysfunction with abnormal relaxation and restrictive filling was evident in our series. Abnormal relaxation of the myocardium was detected in 28.5% of patients with proteinuria and 9.5% of patients in remission. Abnormal relaxation was indicated by the presence of prolonged isovolumic relaxation time (IVRT), low E/A ratio and/or prolonged DT<sup>(29)</sup>. Fifty-seven percent of patients with proteinuria and 47.6% of patients in remission had restriction to filling indicating stiff myocardium.

Ren et al.<sup>(30)</sup> stated that the earliest functional cardiac changes in hypertension are in left ventricular diastolic functions with prolongation and incoordination of isovolumic relaxation time, reduced rate of rapid filling and an increase in the relative amplitude of the Q wave, probably caused by increased passive stiffness. Up to our knowledge no previous studies were done on diastolic dysfunction in nephrotic patients.

ECG manifestations of left ventricular hypertrophy (LVH) were found only in 9.4% of our studied patients while LVH was diagnosed in almost all our patients by echocardiography, this was in agreement with Braunwald<sup>(31)</sup> who stated the ECG is

not a sensitive predictor for the presence of left ventricular hypertrophy and with Ganau et al.<sup>(32)</sup> who stated that echocardiography is widely used to determine human left ventricular mass as it's non-invasive device, broadly applicable, sensitive and lack ionizing radiation.

Our measurements indicate that left ventricular hypertrophy was more evident in the group with proteinuria than in the group with remission. So, this may indicate that those with proteinuria are more susceptible to develop ischemia and myocardial infarction than those in remission. We found that interventricular septal thickness (IVST) was positively correlated to the duration of the disease, number of relapses and triglycerides level. Left ventricular mass (LVM) and left ventricular posterior wall thickness (LVPWT) were positively correlated to number of relapses. LVM and left ventricular end diastolic diameter (LVED) were positively correlated to the duration of the disease. These results indicate how much the duration of hypertension and hyperlipidemia affect the cardiac state of our patients making them more susceptible to myocardial ischemia. It was stated by Pringle et al.<sup>(33)</sup> that symptomatic and silent myocardial ischemia are common in hypertensive patients with left ventricular hypertrophy.

Proper control of hypertension in NS patients is of great importance as hypertension leads to increased tension on the left ventricular myocardium, causing it to stiffen and hypertrophy affecting diastolic function. Also, it accelerates the development of atherosclerosis with the coronary vessels. So, hypertension is a major risk factor for myocardial ischemia and infarction<sup>(30,34)</sup>.

Also, every effort should be made to lower the plasma-lipid values to normal rapidly in nephrotic syndrome, and the measures should include vigorous use of steroids and immunosuppressive drugs to induce complete remission. If remission is not likely, consideration should be given to reduce proteinuria. Dietary modification with low fat and protein is the best initial intervention for hyperlipidemia, in addition to exercise. Drug therapy with HMG-CoA reductase inhibitors (statins) may be considered in children aged 10 years or older, if after adequate trial (6 m - 1 y) dietary therapy failed<sup>(35-37)</sup>.

In conclusion, the resting ECG did not reveal any ischemic changes in nephrotic patients. Echocardiography showed left ventricular hypertrophy and diastolic dysfunction

evidenced by abnormal relaxation of the myocardium and restrictive filling in nephrotic patients. Further studies to correlate this with levels of cholesterol and triglycerides and degree of hypertension in nephrotic patients is needed.

The current assumption about increased coronary heart disease risk among adults can not be excluded in nephrotic children and adolescents. More sensitive diagnostic techniques are recommended like exercise ECG and exercise treadmill cardiac scintigraphy. Moreover, follow up of these children and adolescents during adulthood is recommended since we could not exclude early subclinical coronary atheromas that may progress by time leading to myocardial infarction at young age during adulthood.

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