



## cIMT A MARKER OF ENDOTHELIAL DYSFUNCTION IN CHILDREN WITH NEPHROTIC SYNDROME: A CASE CONTROL STUDY

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### ABSTRACT

**Background:** In Nephrotic syndrome there is increased total plasma low-density lipoprotein (LDL). The children with nephrotic syndrome are chronically exposed to abnormal lipid levels. Carotid intima-media thickness (cIMT) is an indirect marker of atherosclerosis and target organ damage in adults. Thus cIMT was used as a tool for measuring endothelial thickness in children with nephrotic syndrome. This was a case control study conducted at a tertiary care hospital in children with NS who were more than 2 years and children had more than 1 relapses of NS 35 children with NS constituted the case material and equal number children were taken as control. The mean age in case and control cohort was  $6.11 \pm 2.93$  and  $8.26 \pm 3.16$  years, respectively. Thickness of cIMT was higher in NS children as compared to control group in all the ages, but this difference was statistically significant.

**Aim:** To study the endothelial dysfunction in children with nephrotic syndrome.

**Methodology:** This study was done in Assam Medical College and Hospital, Dibrugarh, Assam, in Paediatric Department, from the period of June 2020 to May 2021. All the diagnosed case of Nephrotic syndrome aged 2 to 12 years was included in cases and the others were controls.

**Results:** The mean age increases with increase in the mean triglyceride and serum cholesterol, and serum LDL and Serum VLDL. The serum cholesterol, serum triglyceride and the serum VLDL were found to be increases in the mean score of the school. Serum HDL and the serum albumin decreases. The carotid intima media thickness is  $0.47 \pm 0.14$  in cases and in control it is  $0.33 \pm 0.07$  found to be increased in the cases compared to control. There difference is found to be statistically significant ( $p < .0004$ ).

**Conclusion:** The thickness of cIMT was higher in Nephrotic syndrome children compared to the control group and their difference is found to be statistically significant.

**KEYWORDS :** Nephrotic syndrome, cIMT, Atherosclerosis, Dyslipidaemia

### INTRODUCTION:

About 1–3 per 100000 children less than 16 years are affected with nephrotic syndrome. Most of them get affected with the primary type. The primary type is also known as idiopathic type. The most common idiopathic type is Minimal change disease. 80-90% of children with idiopathic nephrotic syndrome respond to daily glucocorticoid therapy [1]. Based on the response to steroid therapy, Nephrotic syndrome can also be classified into: Steroid-sensitive nephrotic syndrome (SSNS), Steroid-resistant nephrotic syndrome (SRNS), Steroid-dependent nephrotic syndrome (SDNS), and Frequent (FRNS), and infrequent relapsing nephrotic syndrome (IFRNS) [2]. In Nephrotic syndrome there is increased total plasma low-density lipoprotein (LDL) [3, 4]. The children with nephrotic syndrome are chronically exposed to abnormal lipid levels which can leads to endothelial dysfunction. Also, high serum lipid level in adults is an established risk factor for atherosclerosis [5], cardiovascular diseases (CVDs), and even cardiac death [6]. These endothelial dysfunction and structural atherosclerosis are commonly studied by 2 methods: disturbance in flow-mediated dilatation (FMD) [7, 8] and Carotid artery intima media thickness (cIMT).

The Carotid intima-media thickness (cIMT) is an indirect marker of atherosclerosis and target organ damage in adults. Its value in children is still under debate but there are increasing numbers of studies among children with risk factor for vascular damage [9]. Hence in this study, we studied about the endothelial dysfunction in children with nephrotic syndrome in the form of carotid intima media thickening in the endothelial layer with the help of B-mode ultrasonogram,

using cIMT as the surrogate marker for future cardiovascular events such as myocardial infraction and coronary artery disease.

### Methodology:

#### Study Place:

Department of Pediatrics, Assam Medical College and hospital, Dibrugarh.

#### Study Design:

Case control study

#### Study Period:

June 2020 to May 2021

**Sample size:** The sample size was calculated based on Nakya Hooman et al [10], Sample size

$$n = (Z \cdot 1 - \alpha / 2 \cdot \sigma / E)^2$$

Where,

n	=	sample size
$\sigma$	=	population standard deviation
e	=	margin of error
Z	=	the value for the given confidence interval

Substituting the above values in the formula, 35 cases and 35 controls where recruited.

### Selection of Study population:

All the paediatric cases diagnosed of nephrotic syndrome and who fulfil the criteria of inclusion and exclusion during the study period will be recruited for the study.

**Inclusion Criteria:**

- Diagnosed cases of frequent relapse, steroid dependent and steroid resistance nephrotic syndrome between 2 to 12 years of age.
- Attenders of children ready to take part in the study

**Exclusion Criteria:**

- First attack of nephrotic syndrome.
- Infrequent relapse nephrotic syndrome.
- All cases of hyperlipidemia other than nephrotic syndrome.
- Attenders of children those who did not give consent.

**cIMT Measurement:**

It was measured by an experienced radiologist. Ultrasound measurement was obtained using a single ultrasound machine. The patient was asked to lie in supine position and head is turned to the contralateral side with slight overextended neck. In longitudinal view the arterial wall is measured after minutes of rest perpendicular to the ultrasound beam with both the wall clearly visualized in order to achieve diameter measurements. The measurement is obtained from the far wall of both common carotid arteries mm proximal to bifurcation. Measurements were made on each side and the mean of left and the right common carotid artery was used in our study.

**Data Collection:**

The study was started after getting ethical clearance from the Institutional Committee (H) of Assam Medical College and Hospital. The baseline characteristics like Name, Age, and Sex was collected from the attender. Systolic and diastolic blood pressure was measured and cIMT was measured using ultra sonogram.

**Consent:**

Informed consent was got from all the patients and any cost incur during the study will be borne by the researcher.

**Statistical Analysis:**

After data was collected it was entered in Microsoft Excel. The data was exported to Statistical Package for Social Sciences software version 16 for analysis. Descriptive statistics such as Mean, Standard deviation range was calculated as appropriate for continuous variables. Categorical data was presented in the form of proportions and Chi Square test and Fischer exact test was used as test of significance. For continuous variables student t test was used as test of significance. p value of less than 0.05 has been considered to be statistically significant.

**RESULTS:**

In our study 35 cases and 35 controls were recruited.

**Table 1: Baseline characteristics of the cases and controls:**

Baseline characteristics	Cases (n=35)	Control (n=35)	p value
Age			
<10 years	29(82.8%)	22(62%)	<0.02
>10 years	6(17.2%)	13(37.2%)	
Sex			
Male	28(80%)	21(60%)	<0.03
Female	7(20%)	14(40%)	
Blood pressure			
Normotensive	23(65.7%)	26(73%)	0.22
Prehypertensive	7(20.1%)	5(14%)	
Hypertensive	5(14.2%)	4(13%)	

The baseline features of the study participants. The mean ages of the cases are  $6.11 \pm 2.93$  and the control is  $8.26 \pm 3.16$  and the minimum age is 2 and the maximum age is 12 in both cases and controls. Male preponderance is observed in our

study. 7 (20.1%) were prehypertensive in cases and 5 (14.2%) were hypertensive in Cases and were more compared to control group.

**Table 2: Number of relapses of cases and controls:**

	Cases	Controls	P value
Number of relapses (Mean $\pm$ SD)	$6.09 \pm 5.98$	$1.28 \pm 0.71$	<0.0001

The number of relapses in cases was  $6.09 \pm 5.98$  and controls was  $1.28 \pm 0.71$ . There is a difference between the groups and the difference is statistically significant.

**Table 3: Lipid profile and serum albumin of the cases and controls:**

Lipid profile	Cases (n=35)	Control (n=35)	p value
Serum cholesterol	$411.55 \pm 124.81$	$124.8 \pm 15.1$	<.0001
Serum triglycerides	$348.83 \pm 129.03$	$74.38 \pm 13.38$	<.0001
Serum LDL	$320.23 \pm 86.07$	$82.09 \pm 14.89$	<.0001
Serum HDL	$49.27 \pm 17.39$	$60.78 \pm 8.73$	<.0001
Serum VLDL	$62.31 \pm 32.00$	$26.95 \pm 11.66$	<.0001
Serum albumin	$2.03 \pm 0.28$	$3.61 \pm 1.01$	<.0001

In our study the mean serum cholesterol in cases is  $411.55 \pm 124.81$  which is higher than the controls and the difference is statistically significant. The mean serum triglycerides and the serum LDL were found to be increased by threefold. Serum HDL is found to be decreased in cases compared to the controls. The difference between them was found to be statistically significant.

**Table 4: Average Carotid intima thickness of the cases and controls:**

	Cases (n=35)	Control (n=35)	p value
Carotid intima thickness	$0.47 \pm 0.14$	$0.33 \pm 0.07$	<.0004

The mean carotid intima thickness of cases is  $0.47 \pm 0.14$  and the control is  $0.33 \pm 0.07$  and their difference is found to be statistically significant.

**DISCUSSION:**

The mean age of the cases in our group is  $6.11 \pm 2.93$  in controls it is  $8.26 \pm 3.16$ . In Anita Mehta *et al* [11] study it was found that their mean age was  $4.32 \pm 2.25$  which is comparatively lesser than our study. In our study a male predominance was seen, 28 (80%) males in cases and 21 (60%) in controls, similarly in a study done by Chaubey *et al* [12]. The blood pressure tend to increase in the cases like prehypertensives 7 (20.1%) and hypertensives 5 (14.2%) which is more than controls. Tkaczyk *et al* [13] and Nakysa *et al* [10] stated that blood pressure is indirectly related to the thickness of cIMT. The number of relapses was  $6.09 \pm 5.98$  which is more than in controls which are  $1.28 \pm 0.71$ . These results are more compared to the results of Anita Mehta *et al* [11] where the relapses were  $3.46 \pm 1.34$ . There is an increase in Serum total cholesterol, Low density lipid, VLDL and Serum triglycerides. This is seen to be increased in the cases group compared to the control group. Also there low level of HDL which also increases the risk for the cases. In our study both hypoalbuminemia and hypercholesterolemia is observed similar results also seen in Bhatia A *et al* [14]. In our study the carotid intima thickness is  $0.47 \pm 0.14$  in cases and in control it is  $0.33 \pm 0.07$  found similar to Chaubey *et al* [12] study.

**CONCLUSION:**

cIMT thickness increases with advancing age and increase cIMT is considered as an important marker for atherosclerosis in children. Thus assessment of the cIMT will help in early diagnosis of the evolving disease and will benefit on long term management of nephrotic syndrome children.

**Limitation:**

The small size of the sample and low power is the main

limitation. There is no long term follow up to observe the changes in cIMT over a period of time especially in the phase of remission.

#### REFERENCES:

1. EPSTEIN A. The nature and treatment of chronic parenchymatous nephritis (nephrosis). *J Am Med.* 1917;69 (6):444-9.
2. Lane J. Pediatric Nephrotic Syndrome Clinical Presentation: History, Physical Examination [Internet]. *Emedicine.medscape.com.* 2020 [cited 30 August 2021]. Available from: <https://emedicine.medscape.com/article/982920-clinical>.
3. Hu P, Lu L, Hu B, Du PF. Characteristics of lipid metabolism under different urinary protein excretion in children with primary nephrotic syndrome. *Scand J Clin Lab Invest.* 2009;69 (6):680-6.
4. Doucet C, Mooser V, Gonbert S, Raymond F, Chapman J, Jacobs C, et al. Lipoprotein (a) in the nephrotic syndrome: molecular analysis of lipoprotein (a) and apolipoprotein (a) fragments in plasma and urine. *Am Soc Nephrol.* 2000;11:507-13.
5. Watts G, Burnett J. HDL revisited: new opportunities for managing dyslipoproteinaemia and cardiovascular disease. *Clin Biochem.* 2004;25 (1):2.
6. Ordoñez J, Hiatt R, Killebrew E, Fireman B. The increased risk of coronary heart disease associated with nephrotic syndrome. *Kidney Int.* 1993;44 (3):638-42.
7. Celermajer D, Sorensen K, Gooch V, Spiegelhalter D, Miller O, Sullivan I, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet.* 1992;340 (8828):1111-5.
8. Spence J. Technology insight: ultrasound measurement of carotid plaque—patient management, genetic research, and therapy evaluation. *Nat Clin Pract Neurol.* 2006;2 (11):611-9.
9. Litwin M, Niemirska A. Intima-media thickness measurements in children with cardiovascular risk factors. *Pediatr Nephrol.* 2009;24 (4):707-19.
10. Hooman N, Isa-Tafreshi R, Otukesh H, Mostafaei SH, Hallaji F. Carotid artery function in children with idiopathic nephrotic syndrome. *Nefrol (English Ed.)* 2013;33 (5):650-6.
11. Mehta A, Mishra S, Ahmad K, et al. Carotid intima media thickness in children with nephrotic syndrome : an observational case control study. *Sudan J Paediatr.* 2019;19(2):110-6.
12. Chaubey S, K SV, Singh P, Mittal M, K SA, Kushwaha KP. A study on intima-media thickness of carotid artery in children with nephrotic syndrome : a cross sectional study. *J Pediatr Rev.* 2017;4 (02):89-99.
13. Tkaczyk M, Czupryniak A, Owczarek D, Lukamowicz J, Nowicki M. Markers of endothelial dysfunction in children with idiopathic nephrotic syndrome. *Am J Nephrol.* 2008;28 (2):197-202.
14. Bhatia A, Saha A, Deepthi B, et al. Endothelial Dysfunction in Children with Frequently Relapsing and Steroid - Resistant Nephrotic Syndrome. *Asian J Pediatr Nephrol.* 2020;3(1):4-9.