DOI: 10.7860/JCDR/2023/64029.18607

Original Article

Paediatrics Section

Assessment of Indices of Vascular Involvement in Children with Idiopathic Nephrotic Syndrome: A Case-control Study

ALOK KHANNA[1], MUKESH SAINI[2], ASHUMA SACHDEVA[3], JYOTSNA SEN[4], KAPIL BHALLA[5], ANIMESH DEBBARMA[6], YOGESH VERMA[7], PREET LAMBA[8]

ABSTRACT

Introduction: Nephrotic Syndrome (NS) is characterised by proteinuria, oedema, hypoalbuminaemia, and hypercholesterolemia. The latter is a risk factor for atherosclerosis, suggesting a higher risk of cardiovascular disease in children with NS. Atherosclerosis is proposed to be caused by vascular endothelial dysfunction, reflecting the inflammatory response to tissue damage.

Aim: To investigate indices of early vascular involvement in children with Idiopathic Nephrotic Syndrome (INS).

Materials and Methods: This case-control study was conducted at a tertiary-care hospital, Pt. BD Sharma PGIMS Rohtak, Haryana, India, over a period of two years and two months. The study included 50 children aged <14 years with NS. Vascular indices, including Carotid Intima Media Thickness (CIMT), high-sensitive C Reactive Protein (hs-CRP), and Atherogenic Index of Plasma (AIP), were evaluated. Analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. The correlation of cardiovascular risk in children with NS was calculated by measuring CIMT, AIP, and CRP levels, and the relationship was analysed using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results: The study found that the thickness of CIMT in group 1 was 0.67±1.39 mm, while in group 2, it was 0.31±0.04 mm. The calculated p-value was <0.001, which was statistically significant. The hs-CRP level in group 1 was 4.64±5.87 mg/L, higher than the control group (0.85±0.10 mg/L), with p-value of <0.001. Furthermore, AIP was higher in children with NS (0.80±0.19) compared to the control group (0.02±0.16). There was a statistically significant difference between both groups (p<0.001).

Conclusion: Early assessment of indices of vascular involvement, such as CIMT, hs-CRP, and AIP, in children with INS can aid in the early identification and prevention of cardiovascular complications.

Keywords: Atherogenic index of plasma, Carotid intima-media thickness, High-sensitive C-reactive protein

INTRODUCTION

Nephrotic Syndrome (NS) is a common chronic kidney disease in children characterised by the leakage of protein through a pathologically altered glomerular filtration membrane, associated with heavy (nephrotic-range) proteinuria. This is defined as a first morning or 24-hour urine protein creatinine ratio of ≥2 mg/mg or 200 mg/mmol, or 3+ proteinuria on a dipstick [1]. The clinical findings associated with NS include a triad of hypoalbuminaemia (≤2.5 g/dL), oedema, and hyperlipidaemia (cholesterol >200 mg/dL) [2].

NS is one of the most common paediatric renal disorders, with an annual incidence of 2-7 per 100,000 children in Western countries and an even higher incidence in South Asia [3]. INS accounts for more than 90% of NS cases in children between the ages of 1 and 10, and 50% of cases in children over 10 years of age [4]. According to the International Study of Kidney Disease in Childhood (ISKDC), 84.5% of children with INS have Minimal Change Nephrotic Syndrome (MCNS), 9.5% have Focal Segmental Glomerulosclerosis (FSGS), 2.5% have mesangial proliferative glomerulonephritis, and 3.5% have membranous nephropathy or other diseases leading to nephrotic-range proteinuria [5].

The risk of cardiovascular disease increases in NS due to hyperlipidaemia, increased thrombogenesis, and endothelial dysfunction [6]. Hypercholesterolemia is strongly associated with the severity of decreased albumin levels in patients with NS [7]. NS children exhibit increased levels of Intermediate-Density Lipoprotein (IDL), Very Low-Density Lipoprotein (VLDL), and Low-Density Lipoprotein (LDL), resulting in elevated serum cholesterol and Triglyceride (TG) levels [8]. In clinical practice, hyperlipidaemia is usually assessed by calculating the ratio of TG to High-Density Lipoprotein (HDL), and for better expression of the relationship between TGs and HDL-C, the log transformation molar ratio of TG/HDL-C is adopted, referred to as AIP [9].

Assessing endothelial dysfunction using biomarkers may aid in early identification of premature onset atherosclerosis and subclinical cardiovascular morbidity. CIMT is a non invasive measurement used to evaluate structural changes in arterial segments, serving as a surrogate marker for early stages of subclinical atherosclerosis [10]. hs-CRP has long been studied as an inflammatory biomarker with high sensitivity in several cardiovascular diseases [11]. It is a known marker of vascular endothelial damage, with its concentration rapidly increasing during inflammation and tissue damage. The determination of serum hs-CRP level is currently recommended by the American Heart Association (AHA) for all patients at risk of cardiovascular diseases. However, there are limited studies in the literature on the assessment of hs-CRP levels in children with NS [12].

Therefore, the aim of the present study was to assess indices of early vascular involvement in children with INS, aiming for early identification and prevention of cardiovascular complications.

MATERIALS AND METHODS

The present study was a case-control study conducted in the Department of Paediatrics, Pt. BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India, from August 2020 to October 2022, for a period of two years and two months. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) with approval number: BREC/Th/20/Ped005 before the commencement of the study. Informed written consent was obtained from the parents or Legally Acceptable Representatives (LAR) of all the enrolled children.

Inclusion criteria:

Cases: Children aged 1-14 years with NS who were being diagnosed as Frequent Relapsing NS or Steroid Resistant NS.

Relapse is defined as follows [13]:

1. Frequent Relapsing Nephrotic Syndrome (FRNS): Two or more relapses in the first six months, or four or more relapses in any 12-month period after the initial response to corticosteroids (standard case).
2. Steroid Resistant Nephrotic Syndrome (SRNS): Inability to induce remission within 4 weeks of daily steroid therapy (standard case).

Controls: Age and gender-matched children with no history of NS or use of steroids.

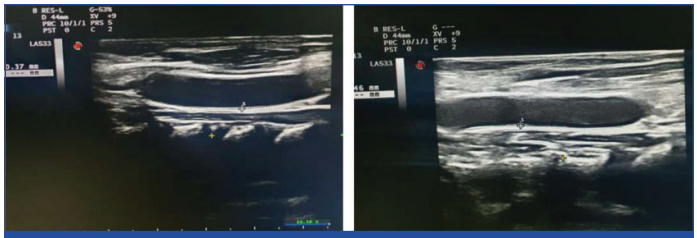
Exclusion criteria: Children less than one year old, children with less than one year since the first episode of the disease, children with pre-existing chronic renal disease and previous use of steroids were excluded from the study.

Sample size: The study enrolled 50 cases (Group I) and 50 controls (Group II) (age and gender-matched children with no history of NS or use of steroids). In Group I, 36 participants (72.0%) were males, and 14 participants (28.0%) were females. In Group II, 37 participants (74.0%) were males, and 13 participants (26.0%) were females.

Procedure

After taking a thorough history, each participant underwent a detailed clinical examination. Body Mass Index (BMI) was calculated after a thorough physical examination, and the study population was classified as follows: underweight (BMI <18.5 kg/m^2), normal range (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), and obese (BMI ≥30 kg/m^2) [14]. Blood Pressure (BP) of all the cases and controls was noted, and accordingly, the study population was divided into the following categories: Normotensive (BP ≤120/80 mmHg), Prehypertensive (BP 120/80 to ≤129/80 mmHg), Stage-1 hypertension (BP 130-139/80-89 mmHg), and Stage-2 hypertension (BP≥140/90 mmHg) [15]. Blood samples were collected to evaluate the lipid profile, including TGs, cholesterol, LDL, and HDL, as well as hs-CRP. A 24-hour urine sample was taken to determine 24-hour protein excretion. Depending on the child's age and the required blood volume, samples were collected from the heel, finger, or arm. The blood samples were processed within one hour of collection. After clotting, serum was separated by centrifugation at 2000 rpm for 10 minutes. The separated serum was stored at -70°C for future analysis.

Parameters studied: The CIMT was measured by a blindfolded experienced radiologist. Ultrasound measurements were obtained using a single Esaote ultrasound machine equipped with a broad-band linear probe operating at a frequency of 3 MHz to 13 MHz. The same machine was used for all patients to ensure accuracy. CIMT measurements were taken on both carotid arteries, and the mean of the left and right common carotid arteries was used in the study. [Table/Fig-1,2] shows an ultrasound image illustrating CIMT measurement.



[Table/Fig-1-2]: Ultrasound images showing measurement of CIMT.

The AIP was calculated using the following equation: AIP=log$_{10}$(TG/HDL-C) [9]. TG, HDL, and cholesterol levels were measured using a coupled enzymatic reaction system with a calorimetric assay. AIP was calculated as the log-transformed molar ratio of TG/HDL-C.

hs-CRP levels were determined using the Calbiotech CRP ELISA kit, which employs a solid-phase direct sandwich method. The normal value ranges for these parameters can be found in [Table/Fig-3] [9,16,17].

AIP [9]	Low cardiovascular risk=-0.3-0.1
	Medium cardiovascular risk=0.1-0.24
	High cardiovascular risk=>0.24
CIMT (mm; mean±SD) [16]	Male=0.43±0.06
	Female=0.42±0.05
hs-CRP (mg/L) [17]	Low cardiovascular risk=<1
	Average cardiovascular risk=1-3
	High cardiovascular risk=3-10

[Table/Fig-3]: Range of normal values of different parameters [9,16,17].

STATISTICAL ANALYSIS

Descriptive statistics were performed on all the data, and the results were reported in terms of the mean and Standard Deviation (SD). Appropriate statistical tests of comparison were applied. The Kolmogorov-Smirnov test was used to check the normality of the data. Categorical variables were analysed using the Chi-square test and Fisher's exact test, where applicable. Continuous variables were analysed using the t-test if the variables were normally distributed; otherwise, the Mann-Whitney U test was applied. Statistical significance was considered at p<0.05. The data were analysed using the trial version 22.0 of SPSS and Microsoft Excel.

RESULTS

The following results were obtained from the present study. The comparison of the demographic, anthropometric, and biochemical profiles among the two groups is shown in [Table/Fig-4].

Variables	Group I	Group II	p-value
Mean age (years) M±SD	6.13±2.95	6.16±2.93	0.963
Gender n (%)			
Male	36 (72)	37 (74)	0.822$
Female	14 (28)	13 (26)	
Mean BMI (kg/m^2)	16.47±2.83	16.76±3.16	0.922
Blood Pressure (BP)	Normotensive-40%	Normotensive-94%	<0.001$
	Prehypertensive-16%	Prehypertensive-6%	
	Hypertensive-44%	Hypertensive-0	
Mean serum cholesterol (mg/dL)	380.94±98.26	92.98±14.61	<0.001
Mean serum TGs (mg/dL)	322.90±114.54	60.24±22.41	<0.001
Mean LDL (mg/dL)	258.24±77.07	59.9±5.95	<0.001
Mean HDL (mg/dL)	47.92±10.35	55.68±8.08	<0.001

[Table/Fig-4]: Comparison of demographic, anthropometric and biochemical profile in two groups.
Statistical test used Chi-square test ($) and t-test

The various vascular indices used in the present study were CIMT (in mm), AIP (calculated as $\log_{10}$ TG/HDL), and hs-CRP (mg/L). The association between the vascular indices in the two groups is shown in [Table/Fig-5].

Vascular indices	Group I	Group II	p-value
CIMT (mm) (Mean±SD)	0.67±1.39	0.31±0.04	<0.001
Distribution of CIMT			
0.20-0.35	16	36	<0.001
0.36-0.50	29	14	
>0.50	5	0	
AIP {$\log_{10}$ (TG/HDL)}] (Mean±SD)	0.80±0.19	0.02±0.16	<0.001
Distribution of AIP			
-0.3-0.1	0	43	<0.001
0.1-0.24	1	5	
>0.24	49	2	
hs-CRP (mg/L) (Mean±SD)	4.64±5.87	0.85±0.10	<0.001
Distribution of hs-CRP			
<1	15	48	<0.001
1-3	8	2	
>3	27	0	

[Table/Fig-5]: Association of vascular indices in two groups.
Statistical test used t-test, Chi-square test and Fisher-exact test

The association of characteristics of NS children with CIMT is shown in [Table/Fig-6].

The association of the distribution of hs-CRP in NS children (Cases=Group I) with serum cholesterol is shown in [Table/Fig-7].

Characteristics		CIMT mean±SD	p-value
Age (years)	2.0 to 4.0	0.32±0.07	0.451 (Insignificant)
	4.1 to 10.0	0.62±1.34	
	≥10.1	0.39±0.08	
Blood Pressure (BP) (mmHg)	Normotensive	0.38±0.07	0.005 (Significant)
	Prehypertensive	2.09±3.28	
	Hypertensive	0.40±0.07	
BMI (kg/m^2)	<18.5	0.63±1.39	0.921 (Insignificant)
	18.5-24.9	0.79±1.48	
	25-29.9	0.35±0.00	
	>30	0.00±0.00	
Serum cholesterol (mg/dL)	≥400	0.41±0.07	0.242 (Insignificant)
	200-400	0.89±1.88	
	<200	1.0±0.00	
Serum TG (mg/dL)	>300	0.39±0.06	0.528 (Insignificant)
	100-300	1.02±2.07	
	<100	0.42±0.00	
Serum LDL (mg/dL)	≥400	0.00±0.00	0.843 (Insignificant)
	200-400	0.73±1.53	
	<200	0.40±0.08	
Serum HDL (mg/dL)	30-45	0.39±0.06	0.435 (Insignificant)
	45-60	1.07±2.17	
	>60	0.43±0.10	

[Table/Fig-6]: Association of characteristics of Nephrotic Syndrome (NS) children with CIMT.
Statistical test used t-test

hs-CRP (mg/L)	Serum cholesterol (mg/dL)			p-value
	Mean±SD	Median	Range	
<1	270.47±28.77	278.00	222-322	<0.001
1-3	332.50±22.67	321.00	303-368	
>3	456.67±62.41	465.00	290-544	

[Table/Fig-7]: Association of distribution of hs-CRP in Nephrotic Syndrome (NS) children (Cases=Group I) with serum cholesterol.
Statistical test used t-test

DISCUSSION

The current understanding of the pathogenesis of INS remains unknown, and it is thought to be the result of a primary immune disturbance [18]. In the present study, the mean age±SD in Group I was 6.13±2.95 years, and in Group II it was 6.16±2.93 years, respectively. This mean was lower compared to other studies conducted by Wasilewska A et al., where the mean age in Group I and Group II was 9.35±3.04 years and 6.55±2.74 years, respectively [12]. The gender distribution was similar to a study done by Wasilewska A et al., where males dominated the female population [12]. The mean weight, height, and BMI were comparable in both groups, which was in concordance with the study conducted by Patel S et al., where the mean BMI was 14.9±1.2 kg/m^2 in cases and 16±2.9 in controls [19].

Hypertension was more prevalent among nephrotics compared to the control group. It was mostly attributed to sodium retention, which likely plays a role in the development of hypertension in NS. Hypercholesterolemia was observed among nephrotics when compared with the control group. This finding was in accordance with the work of author Krishnaswany D et al., who conducted similar research on nephrotics [20]. Vaziri ND attributed this hypercholesterolemia to a defective regulatory response of 3-hydroxy-3-methylglutararyl-coenzyme A (HMG-COA) reductase and hepatic cholesterol 7α-hydroxylase in nephrotics [21]. These enzymes are rate-limiting enzymes in cholesterol biosynthesis and catabolism to bile acids in humans.

There was also an increased level of TGs in nephrotics compared to the control group, which was in agreement with the studies conducted by Joven J et al., [22]. This hypertriglyceridaemia observed in nephrotics is attributed to the downregulation of lipoprotein lipase found in nephrotics' skeletal muscle, myocardium, and adipose tissue, which are the principal sites of fatty acid consumption and storage [21].

The HDL-C level of nephrotics was significantly decreased compared to the control group in this study. This finding was in accordance with the documented studies conducted by Adekoya AO et al., [23]. A plausible explanation for the low level of HDL-C in nephrotics observed in the present study is the urinary losses of Lecithin: Cholesterol Acyltransferase (LCAT), which leads to severe deficiency and limits the HDL-mediated uptake of surplus cholesterol from extrahepatic tissues [21]. These limitations greatly affect the homeostasis of HDL-C in nephrotics.

The present study also observed an increased level of LDL-C in nephrotics, which was in agreement with studies conducted by Krishnaswany D et al., and Joven J et al., [20,22]. The increased LDL can be explained by the severe reduction of hepatic LDL receptor protein abundance in nephrotics, despite normal LDL receptor mRNA abundance and gene translation rate. These findings point to inefficient translation and/or increased LDL receptor protein turnover as a cause of LDL receptor deficiency in NS [24].

Children with INS had a higher CIMT than the control group (p-value <0.001). This finding was consistent with the studies conducted by Chaubey DS et al., (p-value <0.0014) [25], Skrzypczyk P et al., (p-value=0.0002) [26], and Mehta A et al., (p-value <0.0001) [27]. However, the present study showed a statistically insignificant

association between the age of the children and CIMT (p>0.05). Nonetheless, the study conducted by Hooman N et al., [28] revealed a statistically significant but weak positive association between CIMT and age.

In the INS group, children with arterial hypertension had significantly higher CIMT than normotensive children, which was consistent with the studies conducted by Skrzypczyk P et al., and Hooman N et al., [26,28]. The present study did not find a association between CIMT and BMI, whereas Litwin M et al., reported a weak positive correlation between them [29]. Additionally, the study found no association between CIMT and LDL, HDL, and TG, except for a statistically insignificant negative association with cholesterol levels. Other researchers have also not shown any association between cIMT and dyslipidaemia [28,30].

The serum hsCRP level was significantly higher in NS children (mean 4.64±5.87 mg/L) compared to healthy controls (mean 0.85±0.10 mg/L). The majority of cases presented with hsCRP levels greater than 3 mg/L. A higher hs-CRP level in NS than controls was also reported in the studies conducted by Wasilewska A et al., and Shostak E et al., [12,31]. Furthermore, the study found a positive association between serum hs-CRP and cholesterol levels in cases.

To better express the relationship between TGs and HDL-C, the log-transformed molar ratio of TG/HDL-C was adopted, referred to as AIP (Atherogenic Index). In the present study, the AIP was observed to be elevated (mean=0.80±0.19) compared to the control subjects (mean 0.02±0.16). When comparing the AIP of the study population with the guidelines, it appeared that nephrotic syndrome patients had an unfavourable risk profile for cardiovascular disease. These findings were consistent with the findings of Adu EM [32]. The majority of NS children had an AIP greater than 0.24, which is considered a high cardiovascular risk factor according to the study conducted by Dobiasova M [9].

Based on the above study, it was found that early assessment of vascular involvement indices, such as CIMT, hs-CRP, and AIP, can aid in the early identification and prevention of cardiovascular complications in children with INS.

Limitation(s)

The study had a main limitation, which was a lack of long-term follow-up to observe changes in CIMT over time, especially during the remission phase. Additionally, the effects of steroids and immune suppressants on CIMT and hs-CRP were necessary to strengthen their role. Another issue was the small number of subjects in the study.

CONCLUSION(S)

As increased CIMT is a surrogate marker of atherosclerosis in children, assessing CIMT can benefit the long-term care of children with NS. There was a steep rise in serum hs-CRP and cholesterol, which showed a positive association with CIMT. In the later part of life, the inflammatory response plays a critical role, increasing the risk of atherosclerosis in children with NS. Identifying such children early may enable early intervention to slow down the atherosclerotic process and prevent or delay cardiovascular diseases. Therefore, of indices of vascular involvement such as CIMT, hs-CRP, and AIP in children with INS helps in the early identification and prevention of cardiovascular complications.

REFERENCES

[1] Eknoyan G, Lameire N. KDIGO clinical practice guideline on glomerular diseases. Public review draft. 2020. Pp. 74.

[2] Kliegman RM, Geme J. Nelson Textbook of Pediatrics, 2-volume set. 21st ed. Philadelphia, PA: Elsevier-Health Sciences Division; 2019.2522-28.

[3] Srivastav RN, Bagga A. Nephrotic Syndrome. In: Srivastav RN, Bagga A Paediatric Nephrology. 5th edition. New Delhi. 2011;159-200.

[4] Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International study of kidney disease in children. Kidney Int [Internet]. 1978;13(2):159-65.

[5] Churg J, Habib R, White RH. Pathology of the nephrotic syndrome in children: A report for the International study of kidney disease in children. Lancet [Internet]. 1970;760(1):1299-302.

[6] Lechner BL, Bockenhauer D, Iragorri S, Kennedy TL, Siegel NJ. The risk of cardiovascular disease in adults who have had childhood nephrotic syndrome. Pediatr Nephrol [Internet]. 2004;19(7):744-48.

[7] Zilleruelo G, Hsia SL, Freundlich M, Gorman HM, Strauss J. Persistence of serum lipid abnormalities in children with idiopathic nephrotic syndrome. J Pediatr [Internet]. 1984;104(1):61-64.

[8] Agrawal S, Zaritsky JJ, Fornoni A, Smoyer WE. Dyslipidaemia in nephrotic syndrome: Mechanisms and treatment. Nat Rev Nephrol [Internet]. 2018;14(1):57-70.

[9] Dobiasova M. Atherogenic impact of lecithin cholesterol acyltransferase and its relation to cholesterol esterification rate in HDL (FERHDL) and AIP [log (TG/HDL-C)] biomarkers: The butterfly effect? Physiol Res. 2017;66:193-207.

[10] Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: The ARIC [Atherosclerosis Risk in Communities] study. J Am Coll Cardiol. 2010;55(15):1600-67.

[11] Roberts WL, CDC, AHA. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: laboratory tests available to assess inflammation-performance and standardization: A background paper: Application to clinical and public health practice: Laboratory tests available to assess inflammation-performance and standardization: A background paper. Circulation [Internet]. 2004;110(25):e572-76.

[12] Wasilewska A, Zoch-Zwierz W, Tobolczyk J, Tenderenda E. High-sensitivity C-reactive protein (hs-CRP) level in children with nephrotic syndrome. Pediatr Nephrol [Internet]. 2007;22(3):403-08.

[13] Bagga A. Revised guidelines for management of steroid-sensitive nephrotic syndrome. Indian J Nephrol [Internet]. 2008;18(1):31-39.

[14] BMI calculation: https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis. Accessed on 2023.

[15] Hardy ST, Urbina EM. Blood pressure in childhood and adolescence. Am J Hypert. 2021;34(3): 242-49.

[16] Baroncini LA, Sylvestre Lde C, Pecoits Filho R. Assessment of intima-media thickness in healthy children aged 1 to 15 year. Arq Bras Cardiol. 2016;106(4):327-32.

[17] Sudjaroen Y. High sensitive C-Reactive Protein (hs-CRP) level and biochemical parameters for prehypertension and prediabetes diagnosis. Ann Trop Med Public Health. 2015;8(5):177-81.

[18] Schnaper HW. The immune system in minimal change nephrotic syndrome. Pediatr Nephrol [Internet]. 1989;3(1):101-10.

[19] Patel S, Kumar M, Kabi A, Sharma S, Sahoo SS, Kabi C. Role of serum high sensitivity C reactive protein in children with nephrotic syndrome. New Indian J Pediat. 2017;6:197-202.

[20] Krishnaswany D, Indumati V, Satihkumar D, Vijay V, Maharudra S, Amareshwara M, et al. Serum proteins, initial and follow-up lipid profile in children with nephrotic syndrome. IJABPT. 2011;2(3):59-63.

[21] Vaziri ND. Molecular mechanisms of lipid disorders in nephrotic syndrome. Kidney Int [Internet]. 2003;63(5):1964-76.

[22] Joven J, Villabona C, Vilella E, Masana L, Albertí R, Vallés M. Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. N Engl J Med [Internet]. 1990;323(9):579-84.

[23] Adekoya AO, Desalu ABJ, Aderibigbe OO. Pattern of lipid profile in adult nephrotic syndrome patients in Nigeria. Int J Bio Med Res. 2011;2:954-60.

[24] Warwick GL, Packard CJ, Demant T, Beedford DC, Bunlton JM, Shepherd J. Metabolism of apolipoprotein B-containing lipoproteins in subjects with nephrotic range protienuria. Kidney Int. 1991;40(1):129-38.

[25] Chaubey S, Singh VK, Singh P, Mittal M, Singh AK, Kushwaha KP. A study on intima- media thickness of carotid artery in children with nephrotic syndrome: A cross sectional study. Pediatr Rev Int J Pediatr Res [Internet]. 2017;4(2):89-99.

[26] Skrzypczyk P, Mroczkowska K, Kulagowska E, Brzewski J, Okarska-Napierala M, Panczyk-Tomaszewska M. Carotid intima media thickness in children with idiopathic nephrotic syndrome: A single center cross-sectional study. Clin Nephrol. 2019;91(6):353-62.

[27] Mehta A, Mishra S, Ahmad K, Tiwari HC, Singh V, Singh A. Carotid intima media thickness in children with nephrotic syndrome: An observational case control study. Sudan J Paediatr [Internet]. 2019;19(2):110-16.

[28] Hooman N, Isa-Tafreshi R, Otukesh H, Mostafavi SH, Hallaji F. Carotid artery function in children with idiopathic nephrotic syndrome. Nefrologia [Internet]. 2013;33(5):650-56.

[29] Litwin M, Wühl E, Jourdan C, Niemirska A, Schenk JP, Jobs K, et al. Evolution of large-vessel arteriopathy in paediatric patients with chronic kidney disease. Nephrol Dial Transplant [Internet]. 2008;23(8):2552-57.

[30] Tamura H, Suzue T, Jitsunari F, Hirao T. Evaluation of carotid arterial Intima-Media Thickness (IMT) and its relation to clinical parameters in Japanese children. Acta Med Okayama [Internet]. 2011;65(1):21-25.

[31] Shostak E, Krause I, Dagan A, Ben-Dor A, Keidar M, Davidovits M. Is serum CRP level a reliable inflammatory marker in pediatric nephrotic syndrome? Pediatr Nephrol [Internet]. 2016;31(8):1287-93.

[32] Adu EM. Serum lipid profile abnormalities among patients with nephrotic syndrome. Int J Med Biomed Res [Internet]. 2013;2(1):13-17.

PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Paediatrics, PGIMS, Rohtak, Haryana, India.
2. Junior Resident, Department of Paediatrics, PGIMS, Rohtak, Haryana, India.
3. Professor, Department of Biochemistry, PGIMS, Rohtak, Haryana, India.
4. Senior Professor, Department of Radiodiagnosis, PGIMS, Rohtak, Haryana, India.
5. Professor, Department of Paediatrics, PGIMS, Rohtak, Haryana, India.
6. Junior Resident, Department of Paediatrics, PGIMS, Rohtak, Haryana, India.
7. Junior Resident, Department of Paediatrics, PGIMS, Rohtak, Haryana, India.
8. Junior Resident, Department of Paediatrics, PGIMS, Rohtak, Haryana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Mukesh Saini,
PGIMS Doctor Hostel, Rohtak-124001, Haryana, India.
E-mail: mukesh211saini@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 15, 2023
- Manual Googling: May 16, 2023
- iThenticate Software: Aug 12, 2023 (13%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 11, 2023**
Date of Peer Review: **Apr 22, 2023**
Date of Acceptance: **Aug 14, 2023**
Date of Publishing: **Oct 01, 2023**