Original Article

Carotid Intima-Media Thickness Assessment in Children with Nephrotic Syndrome

Nasrin Esfandiar[1], Masoumeh Mohkam[۲], Reza Dalirani[3], Seyed Mohammad Taghi Hosseini Tabatabaei[3], Mitra Khalili[4], Mahmoud Hajipour[5], Maedeh Yavari[6*], Reyhaneh Jamily[4], Samaneh Ahmadi[7]

[1]Department of Pediatric Nephrology, School of Medicine, Pediatric Nephrology Research Center, Shahid Labbafinezhad Hospital,
[2]Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Pediatric Nephrology Research Center, Research institute for children's Health. Shahid Beheshti University of Medical Sciences, Tehran.Iran.
[3]Department of Pediatric Nephrology, School of Medicine, Pediatric Nephrology Research Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Radiology, School of Medicine, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences Tehran, Iran
[5]Pediatric Gastroenterology, Hepatology and Nutrition Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6]Resident of Pediatrics, School of Medicine, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences Tehran, Iran
[7]Skull Base Research Center, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Received: 04 October, 2023; Accepted: 25 December, 2023

Doi: 10.22037/nbm.v12i2.43422

Abstract

Background: Carotid intima medial thickness (CIMT) is a reliable marker for assessing large and medium blood vessel atherosclerosis. This study aimed to investigate the carotid intima-media thickness in children with nephrotic syndrome admitted to Mofid Hospital during 2019-2021.

Materials and Methods: This case-control study was conducted in Mofid Hospital for two years (2019-2021). The samples were selected in the case group from hospitalized children with nephrotic syndrome and the control group from hospitalized children without nephrotic syndrome.

Results: The mean thickness of the right and left carotid intima-media thickness in the case group was 0.07 ± 0.43 and 0.43 ± 0.07 millimeters, respectively, and these two values were lower and equal to 0.42 ± 0.05 millimeters in the control group, respectively (P-value= 0.02, P-value = 0.016). There was a negative and significant relationship between the level of phosphate and CIMT on the left side, and with an increase of one unit in phosphate, the value of left CIMT decreased by 0.277 times. Also, there was a negative and significant relationship between right CIMT and the level of albumin at discharge time, so with an increase of one unit in albumin, the value of right CIMT decreased by 0.256 times.

Conclusion: It is concluded that nephrotic syndrome causes an increase in CIMT and vascular damage in children. The increase of blood albumin and phosphate was associated with the decreased CIMT.

Keywords: Nephrotic syndrome, Children, Carotid intima-media thickness

***Corresponding Author:** Maedeh Yavari, Department of Pediatrics, School of Medicine, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences Tehran, Iran. Tel: (+98) 918 8564362. Email: maedehyavari@yahoo.com

Please cite this article as: Esfandiar N, Mohkam M, Dalirani R, Hosseini Tabatabaei SMT, Khalili M, Hajipour M, et al. Carotid Intima-Media Thickness Assessment in Children with Nephrotic Syndrome. Novel Biomed. 2024;12(2):49-54.

Introduction

Nephrotic syndrome is a glomerular disease characterized by severe proteinuria, hypo-albuminemia, hypercholesterolemia, and edema[1]. The global incidence of Nephrotic syndrome is 16 children per 100,000 people, and developing countries show a higher incidence rate[1-3]. Nephrotic syndrome is more common in boys than girls (6:1), and the mean age of the presence of this disease is four years[4]. Complications of nephrotic syndrome are infections, thromboembolism, cardiovascular diseases, hypovolemia, and anemia[5]. Arterial and venous thrombosis are common in patients with nephrotic syndrome[6].

Children with nephrotic syndrome are at increased cardiovascular risk. Atherosclerosis is one of the main mechanisms involved in macrovascular diseases in patients with nephrotic syndrome, which occurs due to increased arterial wall thickness, atheroma plaque formation, and vascular calcification[7]. Today, new tools are used to check vascular function. One of these tools is carotid intima-media thickness (CIMT) measurement, a non-invasive method performed by ultrasonography[8]. It is known that an increase in CIMT indicates the development of atherosclerosis of coronary arteries[9]. Epidemiological studies defined CIMT as an indicator for cardiovascular events risk assessment[10]. Various studies have shown that the increase in the thickness of the intima-media of the carotid artery in adults can be a reliable predictor for cardiovascular events[11]. Increased CIMT in children is associated with other cardiovascular risk factors such as familial hypercholesterolemia, growth hormone deficiency, diabetes, and other arteriopathy diseases such as William's syndrome and Kawasaki disease[12]. There are few studies about assessing CIMT children with nephrotic syndrome, so in this study we aimed to investigate the thickness of the intima-media of the carotid artery in children with nephrotic syndrome.

Methods

This research received the ethics code from the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1400.025). This case-control study aimed to determine the carotid intima-media thickness in children with nephrotic syndrome. This study was conducted in Mofid Hospital on children hospitalized with nephrotic syndrome as a case group and children hospitalized for other reasons (without nephrotic syndrome) as a control group for two years (2019-2021). The inclusion criteria had nephrotic syndrome, having at least two years and passing at least one year since the onset of the disease, having normal serum compositions in the last three months, having GFR more than 90 ml/minute/1.73 m2, and not having any acute infection in the last three months. The exclusion criteria did not have consent to participate in the study: diabetes involvement, excessive weight, familial hypercholesterolemia, congenital heart disease, and cardiac rheumatism. The data were obtained by reading the medical records of the patients, detailed clinical examinations, laboratory and biochemical tests, and carotid ultrasounds. In the clinical examinations, children's height and weight, arterial blood pressure, and presence of edema were measured. A children's heart examination was done to determine the absence of congenital problems and rheumatic heart disease. All patients with nephrotic syndrome underwent echocardiography during hospitalization by an expert cardiologist. We used the documents in the file for this case.

A previous similar study (Hooman et al.) (13) was used to determine the sample size, measured as 210 children. Laboratory tests included the levels of vitamin D, calcium, potassium, C3, blood urea, creatinine, and albumin. Urine tests were also assessed. Complete lipid profile was measured for all children, including total cholesterol, HDL, LDL, VLDL, and triglycerides.

The present study considered a GFR of more than 90 ml/minute/1.73 m2 normal. CIMT was determined for all samples using a carotid ultrasound. CIMT was measured based on the Manheims Consensus (2012)[13] guidelines and by an experienced radiologist who was unaware of the condition of the children (blinded). Ultrasound measurements were performed with an ultrasound device with a high linear frequency converter (7.5 MHz). The position of the

patient to determine the thickness of CIMT was the supine position for ten minutes, and during the sonography, the patient's head was tilted to the opposite side. Finally, the thickness of the carotid artery was measured on both sides.

Mean, standard deviation, frequency, and percentage were used to describe the data. Chi-square and Fisher tests were used to check the statistical difference in the distribution of qualitative variables. Independent t-tests and ANOVA were also used for quantitative variables. Pearson's correlation coefficient was calculated to calculate the correlation between the CIMT index and other variables. All analyses were performed using SPSS 26 software. A P-value less than 0.05 was considered statistically significant.

Results

A total of 210 patients were included in the study and divided into two groups: 60 patients as case group and 150 patients as control group. The mean age in the case group was 7.65±3.28 years, and in the control group was 8.32±3 years (P=0.157, based on T-test). In the case group, 31 patients were male (51.7%) and 29 were female (48.3%). These amounts in the control group were 75 (50%) for both genders (P=0.827, based on chi-square). The mean weight in the case and control groups were 29.9±13.31 and 32.25±9.5 kilograms, respectively (P=0.152, based on T-test). The mean height in the case and control groups were 121.55 ± 19.04 and 122.91±12.81 centimeters, respectively (P =0.55, based on T-test).

Table 1: Assessment of correlation between the demographic and anthropometric data with CIMT.

Group	Variable	Analysis	Right CIMT	Left CIMT
Case	Age	1	-0.14	-0.19
		2	0.27	0.14
	Weight	1	-0.05	-0.17
		2	0.70	0.17
	Height	1	-0.07	-0.17
		2	0.56	0.18
Control	Age	1	-0.009	-0.01
		2	0.91	0.85
	Weight	1	-0.06	-0.05
		2	0.46	0.49
	Height	1	-0.06	-0.05
		2	0.45	0.52

Table 2: Determining the correlation between factors related to nephrotic syndrome and carotid intima media thickness.

Factors	Results	Right CIMT	Left CIMT
Family history	Positive	0.46±0.07	0.43±0.05
	Negative	0.43±0.07	0.43±0.07
	P-value	0.414	0.988
Gross hematuria	Positive	0.43±0.07	0.44±0.07
	Negative	0.43±0.08	0.43±0.07
	P-value	0.921	0.597
Hypertension	Positive	0.42±0.03	0.45±0.05
	Negative	0.43±0.08	0.43±0.07
	P-value	0.763	0.428
Type of nephrotic syndrome	Neonatal	0.48±0.03	0.43±0.05
	Pediatric	0.43±0.08	0.43±0.07
	P-value	0.209	0.924
Treatment	Positive	0.44±0.04	0.45±0.07
	Negative	0.43±0.08	0.43±0.07
	P-value	0.624	0.42
Biopsy	Positive	0.45±0.04	0.43±0.04
	Negative	0.43±0.08	0.43±0.08
	P-value	0.425	0.835
Response to treatment	SSNS	0.42±0.09	0.42±0.08
	SRNS	0.44±0.04	0.46±0.07
	SDNS	0.42±0.04	0.44±0.06
	FRNS	0.46±0.08	0.43±0.06
	P-value*	0.633	0.54

P-value based on T-test, **P-value based on ANOVA

The mean thickness of the right and left carotid intima-media in the case group was 0.43 ±0.07 cm. These two values were less in the control group and were 0.42±0.05 cm for both sides. There were significant differences between the two groups regarding the mean CIMT (P=0.02 for the Right carotid, P=0.016 for the left carotid).

Table 3 determined the relationship between laboratory findings and carotid intima-media thickness. There was a statistically significant relationship between Left CIMT and the amount of phosphate. With an increase of one unit in phosphate, the value of Left CIMT decreases by 0.277 times (or vice versa). The relationship between the two variables is negative

(P=0.032).

Table 3: Determining the relationship between laboratory findings and carotid intima media thickness.

Parameters	Analysis	Right CIMT	Left CIMT
Vitamin D	1	-0.23	-0.03
	2	0.07	0.80
Calcium	1	0.08	0.02
	2	0.54	0.84
Phosphate	1	-0.02	**-0.27***
	2	0.84	**0.03**
Alkaline phosphatase	1	-0.00	-0.13
	2	0.96	0.30
Triglycerides	1	-0.15	0.05
	2	0.25	0.69
Cholesterol	1	0.03	0.08
	2	0.81	0.53
Albumin	1	0.06	0.14
	2	0.60	0.20
Albumin at discharge	1	**-0.25***	-0.19
	2	**0.04**	0.14
Creatinine	1	-0.08	-0.13
	2	0.50	0.30
Creatinine at discharge	1	-0.10	-0.07
	2	0.42	0.55

There was a statistically significant relationship between Right CIMT and the value of albumin level at the discharge time. With an increase of one unit in albumin level at the discharge time, the value of Right CIMT decreases by 0.256 times (or vice versa). The relationship between the two variables was negative (P=0.049).

The relationship between the CIMT and disease duration was assessed. There was no association between right and left CIMT with disease duration (right CIMT [Pearson Correlation: 0.008, P=0.950] and left CIMT [Pearson Correlation: -0.096, P=0.466]). Assessment of the relationship between the right and left CIMT and the number of disease relapses showed that there was no relationship in this respect (right CIMT [Pearson Correlation: 0.107, P-value: 0.417] and left CIMT [Pearson Correlation: 0.025, P=0.848]).

Discussion

The mean age, gender, and height were the same between the two groups. The mean right and CIMT in the case and control groups differed significantly. There was no relationship between CIMT and age, height, weight, family history, underlying disease history, time of illness, number of relapses, and treatment. It was seen that the laboratory findings of children with nephrotic syndrome and CIMT are in correlation. There were negative and significant relationships between the level of phosphate with left CIMT and the level of albumin at the discharge time with Right CIMT. There is limited data about the assessment of CIMT in children with nephrotic syndrome. The current study was conducted to assess this parameter in these patients, and it was one of the advantages of the current study. The other advantage of the current study is greater sample size than some other studies conducted until now[14,15].

Endothelial dysfunction is an early reversible step in the pathogenesis of atherosclerosis and can predict cardiovascular diseases. CIMT is an indirect indicator of atherosclerosis and target organ damage in adults. Its utility in children is still under evaluation, but an increasing number of studies on children with risk factors for vascular injury are needed[16].

Youssef et al. investigated the relationship between cardiovascular risk factors and CIMT and brachial artery flow-mediated dilation in patients with idiopathic nephrotic syndrome. They found that serum cholesterol, LDL, and triglyceride levels in the case group were significantly higher than the control group. HDL level and albumin level were significantly lower in the case group. CIMT of the common carotid artery in the case group was significantly higher than the control group. Finally, a significant increase in weight and body mass index was observed in the patient with relapse compared to the patient without relapse[15]. The current study observed that CIMT in children with nephrotic syndrome was significantly higher than in children without nephrotic syndrome, which means that these two studies are similar. In the current study, it was seen that phosphate and albumin were factors that were related to CIMT, but there was no correlation between lipid profile and CIMT, which was a difference between these two studies. One of the other differences between

Yusuf et al.'s study and the current study was the lack of correlation between anthropometric data and CIMT in our study. This difference can be caused by the difference in the sample size of the two studies because, in our study, 210 people were examined in two groups, but in the study of Yousef et al., 61 people were evaluated.

In Mehta et al.'s study, the mean age in the case and control groups was 6.71 ± 3.3 years and 7.89 ± 3.95 years, respectively. CIMT thickness was higher in nephrotic syndrome than in controls at all ages, but this difference was statistically significant only after four years. The correlation between CIMT and age, disease duration, and number of relapses was statistically significant but weakly positive. There was no association between CIMT and hypertension, body mass index, serum creatinine, and dyslipidemia. A negative but not statistically significant correlation was observed between CIMT, serum albumin, and serum cholesterol[17]. In the current study, it was seen that the mean age in the two groups was 7.65 ± 3.28 years and 8.32 ± 3 years, which was almost similar between the two studies. The current study had no relationship between CIMT and children's age, disease duration, number of relapses, high blood pressure, weight, height, serum creatinine, and dyslipidemia. CIMT was correlated with serum albumin at the discharge time.

In the study of Paripović et al., it was seen that the thickness of carotid intima-media was significantly higher in children with nephrotic syndrome compared to healthy children. Carotid intima-media thickness was associated with duration of nephrotic syndrome, body mass index, and systolic blood pressure[14]. In the current study, it was seen that there was no relationship between the thickness of the carotid intima-media and the duration of nephrotic syndrome, height, weight, and systolic blood pressure at night. In this issue, the two studies were completely different, but the thickness of carotid intima-media in children with nephrotic syndrome was significantly higher than in healthy children. It was similar in two studies. Among the differences between the two studies, we can mention the difference in the sample size. The sample size in the current study was much larger than the study by Paripović et al., which can be one of the influencing factors on the difference in the results of the two studies.

In Ahmed et al.'s study, it was mentioned that CIMT is greater in children with nephrotic syndrome and has a significant relationship with the duration of the disease. It was concluded that children with nephrotic syndrome are at increased risk of developing atherosclerosis[18]. In the current study, it was seen that CIMT is greater in children with nephrotic syndrome, but this parameter was not related to the duration of the disease, which is different between the two studies.

We found that the Left CIMT value was associated with phosphate level, and with an increase of one unit in phosphate, the value of Left CIMT decreased by 0.277 times. Also, there was a relationship between Right CIMT and albumin level at the discharge time, and with an increase of one unit in albumin level at the discharge time, the value of Right CIMT decreased by 0.256 times. Kuswardhani et al. found that CIMT had a negative correlation with albumin and phosphate levels in patients with hemodialysis[19]. Kuswardhani et al.'s findings were similar to those of the current study about the relationship of serum albumin and phosphate with CIMT. However, our study was conducted on children, and Kuswardhani et al.'s study was conducted on adults.

In Kamel et al.'s study, the mean CIMT was significantly higher in patients with nephrotic syndrome (0.477±0.04 cm) compared to the control group (0.39±0.03 cm). CIMT in patients receiving non-steroidal immunosuppressive therapy was significantly higher than those who received steroids alone. The CIMT was positively correlated with disease duration, body mass index, number of relapses, and diastolic blood pressure[20]. In our study, it was seen that the mean carotid intima-media thickness in the case group was 0.43 ± 0.07 cm, and in the control group, it was less and equal to 0.42 ± 0.05. There was a statistically significant difference between the two groups, although the numbers obtained in the two studies are different. This difference in the obtained numbers of CIMT can be due to the difference in genetics or the age of the children examined in the two studies, which needs to be investigated in future studies. Based on our findings, CIMT was not related to the duration of the disease, body mass index, number of relapses, diastolic blood pressure, and type of treatment, which is one of the differences between the two studies. This difference can

also be caused by the difference in the sample size of the two studies, which was larger in our study. That was one of the advantages of the current study.

It is suggested that timely treatment be done in children with nephrotic syndrome to prevent future cardiovascular events. Also, future studies should be conducted with a larger sample size and long-term examination of these patients.

Conclusion

The CIMT is related to nephrotic syndrome in children, and children with nephrotic syndrome have higher CIMT than children who do not have nephrotic syndrome as a factor in checking the vascular condition. This finding shows the impact of nephrotic syndrome on systemic vascular diseases, which requires rapid and appropriate preventive and therapeutic interventions for children with nephrotic syndrome. In these children, higher levels of albumin at the discharge time and phosphate were associated with reduced CIMT.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

References

1. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. *The Lancet*. 2018;392(10141):61-74.

2. KNOWN IAW. Diagnosis and management of nephrotic syndrome. *Practitioner*. 2017;261(1801):11-15.

3. Greenbaum LA, Benndorf R, Smoyer WE. Childhood nephrotic syndrome—current and future therapies. *Nature reviews nephrology*. 2012;8(8):445-458.

4. Lennon R, Watson L, Webb NJ. Nephrotic syndrome in children. *Paediatrics and Child Health*. 2010;20(1):36-42.

5. Park SJ, Shin JI. Complications of nephrotic syndrome. *Korean journal of pediatrics*. 2011;54(8):322.

6. Sethna CB, Merchant K, Reyes A. Cardiovascular disease risk in children with kidney disease. Paper presented at: Seminars in Nephrology2018.

7. Hari P, Khandelwal P, Smoyer WE. Dyslipidemia and cardiovascular health in childhood nephrotic syndrome. *Pediatric Nephrology*. 2019:1-19.

8. Skrzypczyk P, Kuźma-Mroczkowska E, Kułagowska J, Brzewski M, Okarska-Napierała M, Pańczyk-Tomaszewska M. Carotid intima-media thickness in children with idiopathic nephrotic syndrome: a single center cross-sectional study. *Clinical Nephrology*. 2019;91(6):353.

9. Alegría-Torres GA, Aguilar-Kitsu MA, Estrada-Loza MdJ, Villasís-Keeverd MÁ. Cardiovascular risk factors in children with primary nephrotic syndrome. *Revista Médica del Instituto Mexicano del Seguro Social*. 2015;53(S3):284-293.

10. Mosepele M, Hemphill LC, Palai T, et al. Cardiovascular disease risk prediction by the American College of Cardiology (ACC)/American Heart Association (AHA) Atherosclerotic Cardiovascular Disease (ASCVD) risk score among HIV-infected patients in sub-Saharan Africa. *PLoS One*. 2017;12(2):e0172897.

11. Manabe S, Kataoka H, Mochizuki T, et al. Maximum Carotid Intima-Media Thickness in Association with Renal Outcomes. *Journal of Atherosclerosis and Thrombosis*. 2020:57752.

12. Noto N, Okada T, Yamasuge M, et al. Noninvasive assessment of the early progression of atherosclerosis in adolescents with Kawasaki disease and coronary artery lesions. *Pediatrics*. 2001;107(5):1095-1099.

13. Touboul P-J, Hennerici M, Meairs S, et al. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). *Cerebrovascular diseases*. 2012;34(4):290-296.

14. Paripović A, Stajić N, Putnik J, Gazikalović A, Bogdanović R, Vladislav V. Evaluation of carotid intima media thickness in children with idiopathic nephrotic syndrome. *Néphrologie & Thérapeutique*. 2020;16(7):420-423.

15. Youssef DM, Gomaa MA, El-Akhras A, et al. Brachial artery flow-mediated dilatation and carotid intima-media thickness in children with idiopathic nephrotic syndrome. *Iranian Journal of Kidney Diseases*. 2018;12(6):331.

16. Adhikari MC, Guin A, Chakraborty S, Sinhamahapatra P, Ghosh A. Subclinical atherosclerosis and endothelial dysfunction in patients with early rheumatoid arthritis as evidenced by measurement of carotid intima-media thickness and flow-mediated vasodilatation: an observational study. Paper presented at: Seminars in arthritis and rheumatism2012.

17. 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. *Sudanese Journal of Paediatrics*. 2019;19(2):110.

18. Ahmed HM, Ameen EE-D, Awad MS, Botrous OE. Assessment of carotid intima media thickness and left ventricular mass index in children with idiopathic nephrotic syndrome. *Vascular Health and Risk Management*. 2021:349-356.

19. Kuswardhani RT, Wiradharma KG, Kandarini Y, Widiana GR, Martadiani ED. Factors associated with carotid intima-media thickness in patients on maintenance hemodialysis. *International journal of general medicine*. 2018:1-6.

20. Kamel AS, AlGhawass MME, Sayed MA, Roby SA. Evaluation of carotid intima media thickness in children with idiopathic nephrotic syndrome. *Italian Journal of Pediatrics*. 2022;48(1):195.