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Risk factors associated with carotid intima-media thickness in pediatric nephrotic syndrome

Faktor risiko ketebalan tunika intima-media arteri karotis pada anak sindrom nefrotik

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Abstract

Nephrotic syndrome (NS) is the most frequently occurring kidney disease among children and increases the morbidity and mortality of cardiovascular disorders caused by hyperlipidemia, increased thrombogenesis, and endothelial dysfunction that occur in atherosclerosis. Carotid intima-media thickness (CIMT) is an accessible, noninvasive, and sensitive method for detecting subclinical atherosclerosis. This study aimed to determine the risk factors for CIMT in children with idiopathic nephrotic syndrome at RSUD dr. Zainoel Abidin Banda Aceh. This was an observational analytic study with a cross-sectional design, conducted from March 2024 until May 2024. This study included 35 patients with NS who were 2-18 years, receiving treatment for a minimum of 6 months, with a glomerular filtration rate exceeding 90 ml/minute/1,73 m^2, and no recent acute infections in the past 3 months. Bivariate analysis was performed using the Pearson correlation test, and independent T tests and multivariate analyses were performed using multiple linear regressions. We found a statistically significant correlation between CIMT and total cholesterol (p=0,004, r=0,471), steroid-resistant nephrotic syndrome (p=0,001) and systolic blood pressure (p=0,011, r=0,427) with a mean CIMT of 1,5 ± 0,4 mm. In conclusion, the total cholesterol level, steroid-resistant nephrotic syndrome, and systolic blood pressure are risk factors for CIMT in children with NS.

Keywords: Idiopathic nephrotic syndrome, carotid intima media thickness, risk factors, children

Abstrak

Sindrom nefrotik (SN) merupakan penyakit ginjal yang paling umum pada anak-anak yang dapat meningkatkan morbiditas dan mortalitas gangguan kardiovaskular disebabkan hiperlipidemia, peningkatan trombogenesis, dan disfungsi endotel yang menyebabkan aterosklerosis. Pengukuran ketebalan tunika intima-media (KTIM) arteri karotis, salah satu metode deteksi aterosklerosis subklinis yang mudah diakses, tidak invasif, dan sensitif. Penelitian ini bertujuan untuk mengetahui determinan faktor risiko ketebalan tunika intima media pada anak sindroma nefrotik idiopatik di RSUD dr. Zainoel Abidin Banda Aceh. Desain penelitian menggunakan studi analitik observasional dengan rancangan cross sectional sejak Maret 2024 sampai Mei 2024. Penelitian dilakukan pada 35 anak SN yang berusia 2-18 tahun, mendapatkan terapi lebih dari 6 bulan dengan laju filtrasi glomerulus (LFG) >90 ml/min/1,73m^2 dan tidak infeksi dalam 3 bulan terakhir. Data dianalisis secara bivariat dengan uji korelasi pearson dan uji T independent serta uji multivariat dengan uji regresi linier berganda. Penelitian ini menemukan KTIM berhubungan dengan kadar kolesterol total (p=0,004, r=0,471), sindroma nefrotik resisten steroid (SNRS) (p=0,001) dan tekanan darah sistolik (TDS) (p=0,011, r=0,427) dengan rata-rata KTIM arteri karotis 1,5 ± 0,4 mm. Kesimpulan, kolesterol total, SNRS dan TDS merupakan faktor risiko KTIM arteri karotis pada anak SNI.

Kata Kunci: Sindrom nefrotik idiopatik, ketebalan tunika intima media, faktor risiko, anak

Introduction

Nephrotic syndrome (NS) is the most prevalent kidney disorder in children, occurring 15 times more often than in adults, with symptoms such as massive proteinuria, hypoalbuminemia, dyslipidemia, and generalized edema (AbdelMassih et al., 2021; Qira & Kunci, 2018). Pediatric NS affects 16 of every 100.000 children, with a yearly occurrence rate of 2-7 cases per 100.000 children. In Indonesia, NS affects six in 100.000 children under the age of 14 years, with a ratio of two males to one female (Hilmanto et al., 2022).

Nephrotic syndrome (NS) is associated with high morbidity and mortality rates owing to cardiovascular disease (CVD). Patients with NS are more susceptible to cardiovascular diseases because of factors such as hyperlipidemia, increased thrombogenesis, and endothelial dysfunction. Additional risk factors include steroid toxicity (leading to obesity and impaired glucose metabolism), persistent massive proteinuria, hypoalbuminemia, oxidative stress, recurrent infections, thromboembolism, and the use of non-steroidal drugs, such as calcineurin inhibitors, which have hyperlipidemic, vasculotoxic, and nephrotoxic effects (AbdelMassih et al., 2021; Kamel et al., 2020). All of these risk factors can contribute to the development of atherosclerotic vascular lesions (Patnaik et al., 2018).

The measurement of carotid intima-media thickness (CIMT) is one of the most accessible, noninvasive, and sensitive methods for detecting subclinical atherosclerosis. An increase in CIMT is correlated with a higher risk of developing coronary artery diseases. Atherosclerosis begins in childhood and leads to increased CIMT in children with hypertension, obesity, and chronic kidney disease. Thickening of blood vessels signifies alterations in the arteries, marked by modifications in the carotid intima (Paripović et al., 2020; Qu & Qu, 2015).

Charfeddine et al. (2021) documented a similar case in a 15-year-old boy diagnosed with SRNS at the age of 7 years. Mehta et al. (2019) found that the CIMT of NS patients ranged from 0,32 mm-0,45 mm (±0,09) compared to a control group range of 0,29 mm-0,33 mm (±0,06) stratified by age, while Kamel et al. (2022) obtained the mean CIMT of NS patients to be 0,47 mm (±0,04) compared to the control group's 0,39 mm (±0,03). Owing to the limited number of studies assessing CIMT in children with NS, we divided the participants into two categories: steroid-sensitive nephrotic syndrome (SSNS) and steroid-resistant nephrotic syndrome (SRNS). This study aimed to examine risk factors associated with CIMT in children with NS.

Methods

This was an observational analytical study using a cross-sectional approach. The sample consisted of patients with idiopathic nephrotic syndrome patients in the pediatric outpatient department from March 2024 to May 2024, at RSUD dr. Zainoel Abidin Banda Aceh. The sample size was calculated using a consecutive sampling method based on a correlation coefficient formula.

$$n = \left(\frac{Za+Z\beta}{0{,}5\ln[(1+r)/(1-r)}\right)^2 + 3$$

$$n = \left(\frac{1{,}96+0{,}842}{0{,}5\ln(1+0{,}5)/(1-0{,}5)}\right)^2 + 3 = 29{,}02 \sim$$

(increased to 30 respondents, then adjusted for a dropout rate of 10%, resulting in a total of 33 respondents)

Information:

N : Large sample
Zα : Alpha standard derivative (1,96)
Zβ : Beta standard derivative (0,842)
r : estimated correlation coefficient (0,5)
ln : natural logarithm

The inclusion criteria were ages 2-18 years, therapy for at least 6 months, glomerular filtration rate of > 90 ml/minute/1,73 m^2, and absence of acute infection in the preceding month. The exclusion criteria were a history of familial hypercholesterolemia, essential hypertension, diabetes mellitus, obesity, prematurity, low birth weight, or edema at the time of examination.

Primary data were collected through interviews with parents of children with NS, based on specific inclusion and exclusion criteria. They were asked to characterize their samples in terms of age and sex. Medical history including duration of disease, type of NS, previous illnesses, and medication use were recorded. Nephrotic syndrome is defined according to The Kidney Disease Improving Global Outcomes (KDIGO) and is characterized

by swelling, significant proteinuria on dipstick (3+), and low levels of serum albumin (≤ 25 g/L). Remission was defined as having less than 1+ protein on a urine dipstick for three days in a row. Based on how the body responds to steroid medication, nephrotic syndrome can be categorized as either steroid-sensitive or steroid-resistant. Remission was attained in steroid-sensitive nephrotic syndrome following 4 weeks of steroid treatment. Patients who experienced two relapses in a row while on or within 14 days of stopping corticosteroid treatment were classified as steroid dependent. Steroid-resistant nephrotic syndrome is defined as the inability to achieve remission after eight weeks of corticosteroid treatment (Paripović et al., 2020).

Patients' weight, height, nutritional status (mild malnutrition, normal weight, overweight, or obesity), and blood pressure were measured. The body mass index (BMI) was calculated. Blood pressure was measured using a digital or aneuroid sphygmomanometer unit placed on the right upper arm. Two parameters were recorded: systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension was defined as an average SBP and/or DBP greater than the 95th percentile based on sex, age, and height measured three or more times. (Khoury & Urbina, 2018).

Biochemical parameters were assessed using blood samples collected after a 12-hour fast. Lipid profiles (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglyceride [TG] levels) were measured using automated clinical chemistry equipment and an enzymatic colorimetric method. Albumin levels were determined by the bromocresol green method.

CIMT was measured by a single operator, who was a pediatric cardiologist, following the guidelines set out in the Mannheim Consensus 2011. A single Hitachi Aloka ultrasound machine with a linear high-frequency transducer was used to obtain the ultrasound measurements of the carotid artery. The patients were seated 10 min before the measurement. A linear array transducer was used to longitudinally scan the distal carotid artery in Mode B. Carotid IMT was assessed 1 cm from the bifurcation. The average of three measurements taken on each side was used for the additional analysis.

Statistical analyses were performed using the SPSS version 23 software. Pearson's correlation was used to examine the association between two numerical variables (age, disease duration, systolic blood pressure, diastolic blood pressure, total cholesterol, TG, LDL, HDL, and albumin) and CIMT. An independent t-test was used to analyze categorical variables (type of NS, proteinuria, and cyclosporine use) and numerical variables (CIMT). Previously, the data were subjected to a normality test using the Kolmogorov–Smirnov test, which revealed that the distribution of data was normal. Multiple linear regression analysis was conducted to explore the connections between more than two variables with p-values lower than 0,05 in the initial bivariate analysis, with p-values lower than 0,05. Risk factors for CIMT were determined.

This study was approved by the Health Research Ethics Committee of dr. Zainoel Abidin Regional Public Hospital, Banda Aceh (Number Reference. 012/ETIK-RSUDZA/2024). Parental consent was obtained before patients participated in the study.

Result and Discussion

This study included 35 patients with idiopathic nephrotic disease, who met the inclusion and exclusion criteria. Baseline characteristics were comparable between the groups (Table 1). Most of the subjects in this study were 6–10 years old, with an average age of 10,2 years. This finding is in accordance with a previous study Kamel et al. (2022), which reported that among 40 subjects diagnosed with NS, 17 (42,5%) were aged 6–10 years, 14 (35%) were aged >10 years, and 9 (22,5%) were aged ≤ 5 years, with an average age of 8,5 years. Most subjects were male, accounting for 65,7% of the cases. This result is consistent with the research of Ephraim et al., (2017), who found that among 172 patients with NS, 65,1% were male and 34,9% were female. There is no theoretical explanation regarding sex characteristics; however, it is associated with thymus gland abnormalities, which are more common in boys.

Among the subjects, 11 (31,4%) were steroid-responsive, and 24 (68,6%) were steroid-resistant. Regarding immunosuppressive treatment, only seven subjects (20%) used cyclosporine, while the majority (28 subjects, 80%) did not. According to a previous study Paripović et al. (2020), 10 subjects (25%) used cyclosporine, whereas 20 subjects (50%) did not in a study of Caucasian children with NS (p=0,303).

Table 1. Basic characteristics of research subjects (n= 35)

Basic Characteristics	Mean ± SD /Frequency n (%)
Age	
2-5 years	4 (11,4)
6-10 years	18 (51,4)
10-18 years	13 (37,2)
Gender	
Male	23 (65,7)
Female	12 (34,3)
Nutritional status	
Mild malnutrition	1 (2,8%)
Normal	31 (88,6)
Overweight	3 (8,6)
Duration of disease (year)	2,86 ± 2,56
Body mass index (kg/m^2)	16,32 ± 2,63
Type of NS	
SSNS	11 (31,4)
SRNS	24 (68,6)
Systolic hypertension	
Yes	6 (17,1)
No	29 (82,9)
Dyastolic hypertention	
Yes	4 (11,4)
No	31 (88,6)
Systolic blood pressure (mmHg)	105,89 ± 10,52
Dyastolic blood pressure (mmHg)	70,97 ± 10,95
Use of cyclosporin	
Yes	7 (20)
No	28 (80)
Proteinuria	
Negative	24 (68,6)
Positive	11 (31,4)
Total cholesterol (mg/dl)	230,06 ± 78,1
Triglyceride (mg/dl)	120,31 ± 51,99
LDL (mg/dl)	146,54 ± 71,85
HDL (mg/dl)	51,86 ± 20,04
Albumin (g/dl)	4,2 ± 0,94
CIMT (mm)	1,5 ± 0,4

Table 2. Bivariate analyzed by Pearson's correlation between CIMT and NS

Characteristics	Mean ± SB	r	p-value
Age (year)	10,2 ± 3,86	0,174	0,316
BMI (kg/m^2)	16,32 ± 2,63	0,153	0,381
Duration of disease (year)	2,86 ± 2,56	0,19	0,275
Systolic blood pressure (mmHg)	105,89 ± 10,52	0,427	0,011
Dyastolic blood pressure (mmHg)	70,97 ± 10,95	0,186	0,284
Total cholesterol (mg/dl)	230,06 ± 78,1	0,471	0,004
Trigliserida (mg/dl)	120,31 ± 51,99	-0,099	0,571
LDL (mg/dl)	146,54 ± 71,85	-0,077	0,660
HDL (mg/dl)	51,86 ± 20,04	0,134	0,444
Albumin (g/dl)	4,2 ± 0,94	0,249	0,149

Table 3. Bivariate analyzed by independent T test between CIMT and NS

Characteristic	p-value
Type of NS	
SSNS	
SRNS	0,001
Proteinuria	
Negative	
Positive	0,131
Use of cyclosporin	
Yes	
No	0,701

From the bivariate analysis, Tables 2 and 3 show the relationships between CIMT and systolic blood pressure (p=0,011, r=0,427), total cholesterol (p=0,004, r=0,471), and steroid-resistant nephrotic syndrome (p=0,001). No associations were found between CIMT and age (r=0,174, p=0,316), BMI (r=0,153, p=0,381), disease duration (r=0,19, p=0,275), or diastolic blood pressure (r=0,186, p=0,284). No associations were observed between carotid intima-media thickness (CIMT) and LDL (r=0,066, p>0,05), HDL (r=0,134, p>0,05), or triglyceride levels (r=0,099, p>0,05) in the comparison with serum lipid levels.

In this study, the average duration of illness was 2,86 years, and there was a weak correlation with CIMT. The finding aligns with research byKari et al., (2017), which reported a mean duration of 3,4 years in 8 SRNS subjects. In contrast, Kamel et al., (2022) reported a relationship between the duration of illness and carotid artery CIMT thickening in the NS group (p=0,05 and r=0,31). The NS duration was an

independent predictor of CIMT. An increase in tunica intima thickness occurs in patients with a disease duration of more than two years(Ahmed et al., 2021). In this study, the mean duration of illness was not more than two years, which may explain the lack of association between the duration of illness and CIMT.

Proteinuria was observed in 11 patients (31,4%) patients. Although the relationship between proteinuria and the development of atherosclerosis remains unclear, Jiang et al., (2021) proteinuria is an indirect risk factor for carotid atherosclerosis (OR=1,191, p=0,033). Children with nephrotic syndrome are at risk of macro- and micronutrient deficiencies, growth disorders, decreased muscle mass, and cognitive impairment. Nutritional disorders may result from diseases, poor dietary intake, or steroid therapy (Au et al., 2018). Based on nutritional status, most subjects (88,6%) were normal, with an average body mass index (BMI) of 16,32 kg/m^2. There was no relationship between BMI and CIMT, consistent with the results of a study of Mehta et al. (2019) 66 NS patients, where 60 people (90,9%) obtained good nutrition (p>0,05, r=0,173). In contrast, Kamel et al., (2022) a significant relationship was found between BMI and CIMT (p=0,01) between patients in the NS and control groups. However, no correlation was found between the three groups of patients: steroid-sensitive nephrotic syndrome (SSNS), steroid-dependent nephrotic syndrome (SDNS), and SRNS (p=0,4). In this study, only a few patients had nutritional disorders, which was the reason for this finding.

The mean albumin level in this study was 4,2 g/dl, and no significant relationship was found between the albumin level and CIMT. This finding is in accordance with a previous study Praisey et al. (2024) that reported that serum albumin levels did not correlate significantly with CIMT in 25 patients with NS. Hypoalbuminemia is associated with reduced breakdown of lipoproteins in children with NS, leading to dyslipidemia and potentially causing endothelial cell edema, which is a risk factor for increased CIMT (Au et al., 2018).

In this study, no relationship was observed between lipid levels (TG, LDL, and HDL) and CIMT in NS patients. Abnormal lipid levels in NS include elevated total cholesterol, TG, LDL cholesterol, and various lipoproteins (such as VLDL, IDL, and lipoprotein), while HDL levels remain normal. In contrast, the HDL-to-total cholesterol ratio was decreased. The main reason for these lipid abnormalities is a disruption in the breakdown of lipoproteins and cholesterol, and increased lipoprotein biosynthesis in the liver (Baek, 2022). Sodal (2018) reported a decrease in total cholesterol, triglyceride, and LDL lipid levels, with normal HDL levels obtained after one month of treatment. The lack of a significant relationship between TG, LDL, and HDL levels and CIMT in this study may be due to the normal albumin levels and the fact that most subjects were in remission, leading to no disturbances in lipid levels.

Table 4. Multivariate analysis

Characteristic	Coefficients	t	p-value
SBP	0,001	2,069	0,047
Total cholesterol	0,000	2,889	0,007
Type of NS	0,026	2,380	0,024

* Type of NS: 1. SNSS, 2. SNRS

In addition, a multiple linear regression test was performed to identify risk factors for CIMT in children with nephrotic syndrome. The statistical test results presented in Table 4 show that total cholesterol, SRNS, and systolic blood pressure are risk factors for CIMT in children with nephrotic syndrome.

A significant positive relationship was observed between CIMT and both total cholesterol (t=2,889, p=0,007) and SRNS (t=2,380, p=0,024). Praisey et al., (2024) We Kniazewska et al., (2009) also found a statistically significant increase in total cholesterol (p<0,001) in patients with NS compared to the control group. Tunica intima thickening is a stereotypical response to vascular injury, often caused by hypercholesterolemia, which is a significant risk factor for atherosclerosis formation, even in the absence of other factors (Vijay et al., 2017). Hypercholesterolemia in NS results from hypoalbuminemia with increased albumin synthesis in the liver. This can result in alterations in the permeability of arterial endothelial cells, enabling lipids, particularly LDL particles, to migrate through arterial walls. This can increase the formation of various atherogenic biomolecules, causing vascular changes such as fatty streak formation, intimal thickening, fibroatheroma, and plaque formation (Al Qahtany et al., 2018; Astuti et al., 201).

Frequent relapse and SRNS can lead to hypercholesterolemia during relapse or remission.

During the remission phase, dyslipidaemia may develop in patients with NS, with increased levels of plasma cholesterol (46%), triglycerides (42%), LDL (29%), and VLDL (40%) (Primashanti Dewi, 2019). Patients with steroid-resistant NS have an increased likelihood of developing atherosclerosis owing to greater damage to endothelial dysfunction than those with infrequent relapses. Steroid-resistant nephrotic syndrome is also associated with higher levels of endothelial dysfunction markers such as thrombomodulin, plasminogen activator inhibitor-1, tissue plasminogen activator, and von Willebrand factor, all of which are associated with endothelial activation (Sharma et al., 2014).

This study also showed a significant relationship between SBP and CIMT in children with NS, with a mean of 105,89 mmHg (t=2,069, p=0,047). This finding is in accordance with that of Vijay et al. (2017), who identified SBP as a risk factor for CIMT in children with NS, with a mean SBP of 105 mm Hg (p=0,0117). Hypertension in NS patients is caused by the body holding sodium more than usual and is influenced by factors such as resistance to atrial natriuretic peptide (ANP) and an increase in epithelial sodium channels (Idris et al., 2020). In hypertension, small blood vessels experience vasoconstriction, whereas large vessels show changes such as thickening of the intima media and thinning of the vessel walls. In atherosclerosis, blockages occur in medium and large blood vessels, such as the carotid arteries. In small arteries, there are microvascular alterations that involve a decrease in the size of the inner opening and an increase in the ratio of the wall thickness to the inner opening size, resulting in elevated overall resistance in the periphery and blood pressure. In large arteries, stiffness of the arterial wall leads to a decreased ability to pump blood out of the left ventricle, resulting in increased SBP and pulse strength (Dąbrowska & Narkiewicz, 2023; Mills et al., 2016).

Cardiac output and proximal arterial capacity are factors that determine systolic blood pressure, whereas diastolic blood pressure (DBP) is influenced by volume and peripheral vascular resistance(Wang et al., 2024). Increased SBP can cause arterial pressure elevation, leading to arterial hypertrophy and hyperplasia compared with DBP, making SBP an independent predictor (Ferreira et al., 2016). Carotid changes precede left ventricular hypertrophy, making CIMT a convenient tool for the early detection of vascular changes before the development of conditions such as left ventricular hypertrophy (Ahmed et al., 2021).

The limitations of this study include its small sample size and cross-sectional design. It did not assess other risk factors such as inflammatory biomarkers, oxidative stress, cumulative doses of steroids, and immunosuppressants, nor did it assess carotid artery function such as elasticity, distensibility, and stiffness.

Conclusion

Increased CIMT in children with nephrotic syndrome is associated with elevated total cholesterol levels, SRNS, and SBP. Meanwhile, some factors such as age, BMI, disease duration, DBP, TG, LDL, HDL, albumin, proteinuria, and cyclosporine were not associated with CIMT. As increased CIMT is a substitute for atherosclerosis in children, evaluation of CIMT can be beneficial for the ongoing care of children with NS.

Therefore, this study recommends that future researchers use multicenter prospective cohort studies with larger sample sizes a better approach to identify risk factors for CIMT in patients with NS. In addition, regular measurement of blood pressure and evaluation of cholesterol levels are important to decrease the risk of cardiovascular problems.

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