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Original Article

Correlation between lipid profile and C-reactive protein in children with nephrotic syndrome

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Abstract

Background Nephrotic syndrome (NS) causes dyslipidemia in children, which can be long term or intermittent. Dyslipidemia has long been established as a risk factor for atherosclerosis. An early sign of atherosclerosis is elevated high sensitivity C-reactive protien (hsCRP). Atherosclerosis early in life, especially in childhood, warrants an assessment for NS. Study on a correlation between lipid profile and hsCRP, as a marker of atherosclerosis, in pediatric NS patients has been limited.

Objective To assess for a correlation between lipid profile and hsCRP in childhood nephrotic syndrome.

Methods This cross-sectional study was undertaken on 29 children with NS in Dr. Kariadi Hospital. Serum hsCRP, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were examined in the active phase. Spearman's test was used to analyze a possible correlation between total cholesterol, LDL, HDL and hsCRP levels.

Results Mean levels of total cholesterol (454 mg/dL) and LDL (288 mg/dL) in this study were high, while the HDL level (55 mg/dL) was normal, according to *US Department of Health and Human Services* classifications. The median hsCRP level was 0.33 mg/L and 9 (31%) subjects had high hsCRP levels of more than 1 mg/L. There was a positive correlation between LDL level and hsCRP ($r=0.423$; $P<0.05$).

Conclusions There is a weak positive correlation between LDL and hsCRP levels in children with NS. **[Paediatr Indones. 2015;55:1-6.]**

Keywords: *nephrotic syndrome, dyslipidemia, total cholesterol, hsCRP, LDL, HDL*

Nephrotic syndrome is the most common kidney disease in children, consisting of massive proteinuria, severe hypoalbuminemia, edema, and leads to dyslipidemia.[1,2] In the US, the annual incidence of NS was reported 2-4 new cases/100,000 children. This incidence may higher in Asian and African children. In Indonesia, there are 6-10 new cases/100,000 children annually.[1] The NS incidence in the Pediatrics Department of Dr Kariadi Hospital according to medical records was 102 out of 184 cases of children with renal disease from 2002 to 2006.[3]

Nephrotic syndrome causes dyslipidemia in childhood. Children with NS have abnormal lipid metabolism, characterized by increased synthesis and decreased lipid degradation activity. Increased cholesterol synthesis follows increased albumin synthesis in the liver, in reponse to hypoalbuminemia. The relative contributions of each factor on increased serum lipids remains unclear, due to the multifactorial and complex nature of the problem.[4] Lipid profiles in children with NS are characterized by increased total cholesterol, triglycerides, and LDL levels, as well as

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normal or decreased HDL level.[5] Most NS patients experience relapse and repeated remission. Children with frequent relapse and steroid- resistant NS may have persistent hypercholesterolemia which occurs during both relapse or remission. This condition is a risk factor for atherosclerosis.[6] Dyslipidemia may persist during the remission phase, with increased plasma cholesterol (46%), triglycerides (42%), LDL (29%), and very low-density lipoprotein (VLDL) (40%) in NS patients.[7] Almost 50% of NS patients in the remission phase have dyslipidemia, so regular monitoring of lipid profiles is recommended, especially in frequently relapsing patients.[8]

Dyslipidemia is a risk factor for atherosclerosis, hence, children with NS have a higher risk for vascular disease due to atherosclerosis.[2,9,10] Cholesterol totals > 200 mg/dL may increase the risk for atherosclerosis.[6] Acute myocardial infarction was reported in a 7-year-old child, known to be a frequently relapsing NS patient, and suspected to be due to dyslipidemia.[11] Cardiovascular disease that occurs in NS patients is probably due to dyslipidemia, with the duration of dyslipidemia as the most influential factor.[4] Cardiovascular disease occurs 5–6 times more in NS patients compared to non-NS patients.[4] Another study with smaller sample size reported that the risk increased 85 times, with cardiovascular disease occurring in 53% of NS patients.[12] Dyslipidemia may increase the progression of atherosclerosis and platelet aggregation.[10] Atherosclerosis in NS may be due to endothelial dysfunction of blood vessels.[13] From a pathological point of view, atherosclerosis reflects the inflammatory response to tissue damage, so inflammation markers are often used as parameters to assess the incidence of the atherosclerosis-creating process while it is in progress. One potential inflammation marker is high sensitivity CRP.[14,15] C-reactive protein examination is sensitive and can detect very low hsCRP levels, known as high-sensitivity C-reactive protein.[14] Many studies mention hsCRP as a predictor of risk for cardiovascular disease, because it could also be used to detect the incidence of thromboembolism caused by atherosclerosis.[14-16] Atherosclerotic lesions are asymmetric focal thickenings of the innermost layer of the artery. They consist of cells, connective-tissue elements, lipids, and debris. Arterial infarction occurs when the atheromatous process prevents blood flow through the coronary artery. The infiltration and retention of LDL in the arterial intima initiate an inflammatory response in the artery wall.[17]

Few studies have reported on lipid profiles and hsCRP in pediatric NS. The aim of this study was to assess for a correlation between lipid profile (total cholesterol, LDL, and HDL) and hsCRP levels in children with NS.

Methods

This cross-sectional study was conducted in the Nephrology Division, Pediatrics Department, Diponegoro University Faculty of Medicine/Dr.Kariadi Hospital from January to September 2013. Subjects were NS outpatients and inpatients of the Nephrology Division, who fulfilled the inclusion criteria. Subjects were recruited by consecutive sampling. Inclusion criteria were children with NS aged 2 to 14 years at the time of onset, who were not obese and had no hypertension. Exclusion criteria were diabetes mellitus, acute inflammation and decreased renal function. Lipid profiles consisted of total cholesterol, LDL and HDL examined by a colorometric enzymatic method with a spectrophotometer. Plasma hsCRP was measured by hsCRP test with an enzyme-linked immunosorbent autoanalyzer device. Spearman's correlation test was used for statistical analysis. This study was approved by the Ethics Committee of the Medical Faculty of Diponegoro University/Dr. Kariadi Hospital. Subjects' parents provided informed consent.

Results

During the study period, 29 children visited our institution with NS attacks. Twenty-nine of them were included, consisting of 21 males and 8 females. The characteristics of subjects are shown in **Table 1.**

Patients with all types of NS had higher than normal levels of mean total cholesterol and LDL, but normal levels of mean HDL (**Table 2**). Nine subjects (31%) had hsCRP level > 1 mg/L, seven of whom were male.

Correlation analysis between lipid profiles and hsCRP was performed with Spearman's test, revealing a significant correlation between LDL and hsCRP

Table 1. Demographic characteristics of subjects

Characteristics	(n=29)
NS type, n (%)	
Initial attack	1 (3.4)
Infrequent relapser	15 (51.7)
Frequent relapser	10 (34.6)
Steroid-resistant	3 (10.3)
Mean age (SD), months	75 (40)
Mean BMI (SD)	16 (1.6)
Mean albumin (SD), g/dL	1.8 (0.7)
Mean leukocytes (SD), $10^3/mm^3$	10.1 (3.0)
Mean ureum (SD), mg/dL	24 (7)
Mean creatinine (SD), mg/dL	0.5 (0.1)
Mean blood glucose level (SD), mg/dL	107 (16)
Mean total cholesterol (SD), mg/dL	454 (96)
Mean HDL (SD), mg/dL	55 (26)
Mean LDL (SD), mg/dL	288 (91)
Median hsCRP (range), mg/dL	0.33 (0.02-5.97)

NS: nephrotic syndrome, BMI: body mass index, HDL: high-density lipoprotein, LDL: low-density lipoprotein, hsCRP: high sensitivity C-reactive protein

Table 2. Lipid profiles and hsCRP levels in subjects according to NS type

Variables	Initial attack (n=1)	Infrequent relapse (n=15)	Frequent relapse (n=10)	Steroid-resistant (n=3)
Mean total cholesterol (SD), mg/dL	477	463 (91)	455 (87)	398 (178)
Mean HDL (SD), mg/dL	73	45 (16)	61.6 (34)	75 (26)
Mean LDL (SD), mg/dL	174	308 (79)	307.7 (86)	155.7 (28)
Median hsCRP (range), mg/L	2.03	0.11 (0.04-5.97)	0.42 (0.18-3.63)	0.07 (0.02-0.09)

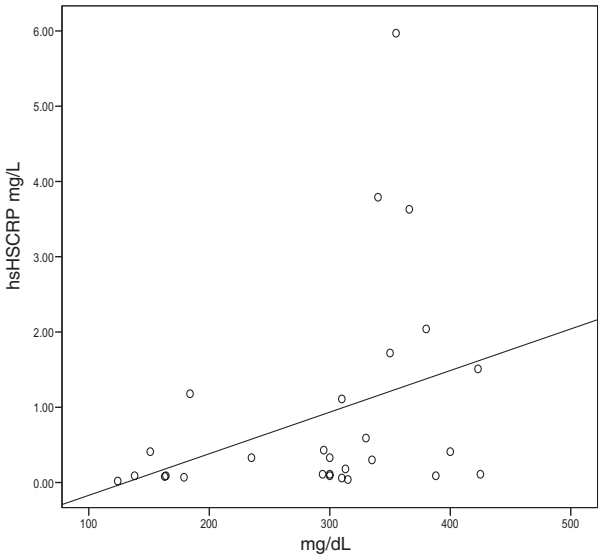

Figure 1. Distribution of LDL and hsCRP levels

(P<0.05) that was weakly positive. (r=0.423). However, no correlation was found between total cholesterol level or HDL and hsCRP. The distribution of LDL and hsCRP levels is shown in **Figure 1.**

Discussion

Abnormal lipid metabolism is common in patients with NS.[6,8,18,19] Many studies have suggested hypercholesterolemia to be a major risk factor in the pathogenesis of atherosclerosis.[4] We found that the mean level of total cholesterol was 454 mg/dL and mean LDL was 288 mg/dL, both twofold higher than normal levels, according to the *US Department of Health and Human Services* criteria. A previous study found that increased cholesterol levels are

approximately twofold higher than the upper limit of normal as established by an expert.[20] Another study found that subjects with NS had total cholesterol level > 200 mg/dL.[9]

The mean HDL level was normal in our subjects. HDL level is usually normal in NS patients, but can be increased or decreased.[5,18] Patients with steroid-resistant NS have better lipid profiles than any other group. Our three subjects in this group had cyclophosphamide therapy at least twice, as such, although they had proteinuria, their body responses to lipid metabolism differ from that of other NS patients. Similar results were found in other studies where mean total cholesterol levels in steroid-resistant NS were lower than in the relapse group.[21]

The normal hsCRP level in healthy children in Semarang was defined as 0.22 mg/L.[22] The clinical importance of hsCRP is as a marker of atherosclerosis. In adult populations, hsCRP levels < 1.0 mg/L indicate a low risk for the disease, 1.0–2.9 mg/L indicate moderate risk, and > 3.0 mg/L indicate high risk.[15,21] Thirty-one percent of subjects in our study showed levels of hsCRP > 1 mg/L, three of whom (10%) were included in the high risk category.

We found no correlation between total cholesterol and hsCRP levels. In contrast, a Polish study reported a correlation between total cholesterol and hsCRP levels in the NS relapse group ($r=0.486$; $P<0.05$).[21] Mean age of subjects from the two studies were similar, 74.5 months in our subjects and 81.2 months in theirs. The difference may be due to differences in characteristics of the subjects studied. The previous study obtained correlation between total cholesterol and hsCRP levels in their NS relapse group experienced relapse a minimum of 4 times, whereas we combined all three groups together in assessing the correlation between total cholesterol and hsCRP levels, due to the limited numbers of children with NS who suffered attacks during study period. Another difference was that in the previous study, children with hsCRP level > 10 mg/L were not excluded. High sensitivity CRP is an acute-phase protein induced by cytokines, therefore, levels in the blood increase as long as there is an inflammatory response to infection, the presence of tissue damage, or inflammatory disease. High sensitivity CRP level >10 mg/L is considered to be due to non-vascular inflammation conditions such as infections, certain diseases, and acute arthritis.[15,16,23] Therefore, in our study, children with hsCRP levels > 10 mg/L were excluded to focus on subjets with potential vascular inflammation.

The subjects in this study had a mean blood glucose of 107 mg/dL. We assessed diabetes through medical history and high blood glucose. High blood glucose levels may have proinflammatory effects, hence affecting hsCRP levels. As much as 75 grams of oral glucose increases reactive oxygen species (ROS) levels in the circulation, also called hyperglycemia-induced oxidative stress.[24] Acute hyperglycemia in individuals with glucose intolerance and in normal individuals can improve the circulation of proinflammatory cytokines. Increased cytokines are more affected by hyperglycemia compared to continuous hyperglycemia.[25]

According to the Framingham risk score which has been used extensively in determining the risk of disease due to atherosclerosis, HDL is considered to be a protective factor against atherosclerosis. HDL particles are heterogeneous molecules that transport cholesterol from the arteries to the liver for excretion into the bile duct. In addition, HDL particles contain various levels of oxidants and antioxidants that also modulate systemic inflammation. Several antioxidant enzymes associated with HDL are lecithin cholesterol acyltransferase (LCAT), poraoxonase-1 (PON1), platelet-activating factor acetylhydrolase (PAF-AH), and glutathione peroxidase. These enzymes play a role in preventing the formation of oxidized LDL and prevent further activation of oxidized LDL in atherosclerotic lesion formation. Another function of HDL is to prevent endothelial dysfunction by decreasing the expression of adhesion molecules, increasing the production of nitric oxide (NO), lowering and preventing apoptosis of endothelial cells.[26, 27]

The HDL levels in this study were not found to correlate with hsCRP levels. In contrast to the above explanation, some studies have not always observed the function of HDL in preventing the formation of atherosclerosis. This difference may occur because, among other factors, the function of HDL is strongly influenced by the presence of proinflammatory conditions. Past study has shown that in the acute phase, in experimental rabbits, mice, and humans, HDL loses its ability to prevent the formation of oxidized LDL.[28] The ability of HDL to prevent the

formation of oxidized LDL not only depends on HDL levels, but also depends on its function.[27] Although we found no correlation between HDL and hsCRP levels, this may be due to our examination of only HDL level, not HDL particle function.

Furthermore, we found a weak but significant correlation between LDL and hsCRP levels ($r=0.423$; $P<0.05$). The negative influence of high LDL levels on atherosclerosis formation has been known for a long time. A study on a multi-ethnic population suggested that LDL is the predominant form of lipid determinant for atherosclerotic lesions.[29] Atherogenesis involves LDL uptake in the vascular wall, followed by the activation of inflammatory factors and growth of vascular smooth muscle cells. Proinflammatory mediators such as interleukins and cytokines stimulate cell growth and atherogenesis. Growth of vascular smooth muscle cells is affected by activators and inhibitors of cell growth. Both growth factors and oxidative stress mediated by superoxide dismutase (SOD) affect the the growth of these cells.[30] All forms of proinflammatory stimuli, including oxidized LDL, change the surface of the artery to become more permeable, due to expression of monocyte adhesion molecules and chemokine secretion. Monocytes can enter the endothelial layer and transform to macrophages. These macrophages change lipid deposits into foam cells, an early form of atherosclerotic lesions.[31] C-reactive protein involvement in the mechanisms of atherosclerosis is still much debated. High sensitivity CRP might increase the expression of adhesion molecules and chemokine secretion, facilitating LDL uptake by macrophages, enhancing the activity of monocytes, and inducing monocytes to produce tissue factors.[32, 33]

The use of corticosteroids may also affect lipid metabolism.[4] According to the NS consensus on children in Indonesia, the first line of treatment should be corticosteroids.[1] Hence, lipid levels are significantly affected by how often the child has a relapse, because corticosteroid use in subjects varies in the length and frequency of doses, depending on the type of NS being treated.[8] A limitation of our study was that we did not take into account the doses and intensity of steroid therapy given to our subjects.

In conclusion, there is a weak but significant positive correlation between LDL and hsCRP levels in children with NS. Further study should be done to find out the correlation between lipid profile and hsCRP levels in children with NS, taking into account other influential factors, such as the dose and intensity of steroid therapy provided.

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