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Original Article

Plasma lipids as risk factors in relapsing nephrotic syndrome

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Abstract

Background Nephrotic syndrome is primarily a pediatric disorder and is 15 times more common in children than in adults. Relapse rate after corticosteroid discontinuation is 39 – 59%. Hyperlipidemia is an important characteristic of nephrotic syndrome. The plasma concentrations of cholesterol, triglyceride, LDL, and VLDL are increased. Persistent hyperlipidemia after remission can be found in frequent relapse nephrotic syndrome.

Objective To determine plasma lipids as risk factor for relapsing nephrotic syndrome.

Methods Thirty children with nephrotic syndrome were included in this cohort study from March 2005 until June 2007 at Wahidin Sudirohusodo Hospital, Makassar. Thirty children without renal disease were enrolled as control. Blood specimens were collected to determine plasma lipids (cholesterol, triglyceride, LDL, and HDL) levels and LDL/HDL ratio. Plasma lipids were examined in the acute and remission phases. Follow up was carried out six months after remission to determine the occurrence of relapsing nephrotic syndrome.

Results Of 30 nephrotic syndrome patients, 12 had relapsed. There were highly significant differences in total cholesterol, HDL, LDL, triglyceride, and LDL/HDL ratio between acute nephrotic syndrome and nephrotic syndrome in remission. There were no significant differences in cholesterol, LDL, triglyceride, LDL/HDL ratio between nephrotic syndrome in remission and control. There was also no significant difference in the incidence in relapse between first attack and nephrotic syndrome with more than two attacks. Acute lipid fraction levels were not risk factors in relapsing mephrotic syndrome. Remission triglyceride level was a risk factor in relapsing nephrotic syndrome with the prevalence risk of 5.2 and CI 95% of 1.06 to 25.3.

Conclusion Persistent hypertriglyceride in remission phase is associated with an increased risk of relapse in children with nephrotic syndrome. **[Paediatr Indones. 2008;48:322-6]**.

Keywords: *nephrotic syndrome, hyperlipidemia, relapse, risk factors*

Nephrotic syndrome (NS) is the most common glomerular disorder in children. NS includes a large number of disorders, with common features of massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Proteinuria greater than 50 mg/kg body weight per day, and hyperlipidemia are important characteristics of NS. Hyperlipidemia is a constant appearance in minimal change nephrotic syndrome (MCNS) with 95% of children having serum cholesterol greater than 250 mg/dl.[1-2] Various lipid abnormalities have been described in MCNS during the active phase of the disease. These include increasing levels of serum cholesterol, triglyceride (TG), low density lipoprotein (LDL) and very low density lipoprotein (VLDL). High density lipoprotein (HDL) has been reported as low, normal, or elevated.[3-6]

Elevated plasma lipid levels are potential risk factors for atherosclerosis and progression of glomerular injury. Lipidemia may affect the kidneys directly or indirectly. Hyperlipidemia is also responsible for cardiovascular disease and progressive

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glomerular damage leading to renal failure. Persistent hyperlipidemia can lead to relapse of NS or treatment-resistant NS. Therefore, evaluation and treatment of lipid abnormalities are important aspects in the management of NS in children.[4]

Methods

This prospective cohort study was carried out from March 2005 until June 2007 at the Nephrology Division, Department of Child Health, Hasanuddin University, Wahidin Sudirohusodo Hospital. Sixty three children were enrolled comprising 33 children with NS and 30 children without renal disease or other diseases that may influence the plasma lipids control. These 30 children were suffered from tonsillopharyngitis (10 patients), acute diarrhea (2 patients), and dengue hemorrhagic fever (18 patients). Primary NS patients with first, second, or subsequent attacks were included in this study. Patients suffering from liver disease, hypothyroidism, severe malnutrition, pancreatitis, diabetes mellitus, NS with complications, and secondary NS were excluded from this study. Parental consent and Medical Ethics Committee approval were obtained.

NS was defined as a disease associated with edema, massive proteinuria, hypoalbuminemia, and hypercholesterolemia. Plasma lipids were determined in all patients during the acute phase using the enzymatic colorimetric test. Three ml of venous blood were taken during the acute phase using a sterile syringe then centrifuged at 3000 rpm for 10 minutes. The serum was divided into two labeled tubes (identity and date) and directly sent to the laboratory or stored in a refrigerator. The second sample of plasma lipids was collected during remission (maximum eight weeks after treatment).

Blood specimens from patients, with no renal or other diseases which may influence plasma lipids, were collected as control. After collecting blood specimens during the acute phase, patients were initially treated according to the International Study on Kidney Disease in Children (ISKDC) protocol. Patients who failed to achieve remission within eight weeks after treatment were diagnosed as having initial nonresponder NS and excluded from the study. During the remission phase, blood specimens for the determination of plasma lipids were collected. The patients were followed up six months after achievement of remission to determine whether they relapsed or were still in remission. Relapse was defined if there was massive proteinuria for three days continuously, whereas hyperlipidemia if the cholesterol level > 250 mg/dl, hypertriglyceridemia >200 mg/dl, high LDL >160 mg/dl, HDL >40 mg/dl and LDL/HDL ratio ≥ 3.

Data were analyzed using the SPSS version 13.0 software. Comparison of plasma lipids levels during the acute phase and remission phase was analyzed using the student t test. The significant relationship between plasma lipids and relapses were analyzed using X^2 test.

Results

During the period from March 2005 to June 2007, 33 patients with NS and 30 children with no renal disease as control were enrolled in the study. Three of the 33 patients with NS were excluded because they belonged to initial non-responder NS. The characteristics of the study subjects are depicted in **Table 1.**

No significant differences in sex, age, and nutritional status were found between NS and control. Comparison of plasma lipids levels between the acute phase and remission phase is shown in **Table 2**.

There were significant differences in plasma lipids levels between NS during the acute phase and remission. Comparison of plasma lipids between NS during remission and the control group is shown in **Table 3**.

Significant differences were noted in total cholesterol, low density lipoprotein (LDL), triglyceride level, and LDL/HDL ratio between NS in remission and control except for HDL.

Table 1. Subjects' characteristics

Characteristics	NS	Control
Age (year)		
• Mean	7.6	8.6
• SD	7.5	9.0
• Minimum	0.9	1.0
• Maximum	15.6	14.8
Gender		
• Boys	22	20
• Girls	8	10
Nutritional status		
• Well-nourished	16	16
• Under-nourished	14	14

Table 2. Plasma lipid level the acute phase and remission phase

Plasma lipids	Mean	SD	Min	Max	P
Cholesterol (mg/dl)					
Acute phase	488.0	489.5	232.0	829.0	< 0.01
Remission phase	244.5	234.5	147.0	397.0	
Trygliceride (mg/dl)					
Acute phase	496.7	448.0	132.0	1695.0	< 0.01
Remission phase	208.3	141.0	45.00	751.0	
HDL (mg/dl)					
Acute phase	38.1	31.00	11.0	89.0	<0.01
Remission phase	66.1	62.00	20.0	124.0	
LDL (mg/dl)					
Acute phase	361.5	363.0	150.0	663.0	< 0.01
Remission phase	158.5	147.0	87.0	69.0	
LDL/HDL ratio					
Acute phase	12.3	7.8	2.0	34.6	< 0.01
Remission phase	2.7	1.9	0.9	11.5	

Table 3. Plasma lipids in NS in remission and control group

Plasma lipids	NS remission phase	Control	P
	mean (SD)	mean (SD)	
Cholesterol (mg/dl)	244.5 (61.2)	133.0 (28.0)	<0.0001
Triglyceride (mg/dl)	208.3 (157.7)	120.0 (30.4)	0.04
HDL (mg/dl)	66.1 (22.5)	58.2 (20.3)	0.16
LDL (mg/dl)	158.5 (49.5)	80.1 (31.7)	<0.0001
LDL/HDL ratio	2.7 (1.9)	1.8 (1.2)	0.03

There were no significant differences in lipid fraction levels between the first attack and the second or subsequent attacks of NS during the acute phase. During remission, only HDL level was not significantly different between first attack and the second or subsequent attacks of NS.

After six months follow up, out of 30 subjects, 18 subjects had persistent remission, 12 subjects had relapses, and all of them had infrequent relapses NS. There was no significant difference in the incidence of relapse between the first attack and second or subsequent attacks of NS (P = 0.114)

There were no significant differences in plasma lipids levels during the acute phase between the two groups. During remission only cholesterol and triglyceride levels showed a significant difference between the two groups **(Table 4)**.

The relationship between lipid plasma level and the incidence of relapse showed that acute lipid fraction levels were not risk factor in relapsing NS. Only the triglyceride level during remission was a risk factor in relapsing NS (P < 0.035) with OR 5.2 and confidence interval 95% of 1.06 to 25.3. This means that NS with persistent hypertriglyceridemia, have 5.2 times risk of relapse.

Table 4. Plasma lipids between relapsing NS and persistent remission

Plasma lipids	After 6 months remission		P
	Persistent remission	Relapses	
	mean (SD)	mean (SD)	
Cholesterol (mg/dl)			
Acute phase	467.9 (164.2)	518.0 (159.5)	0.41
Remission phase	227.0 (54.7)	270.6 (63.4)	0.05
Triglyceride (mg/dl)			
Acute phase	419.3 (223.8)	612.8 (470.8)	0.14
Remission phase	162.7 (95.4)	276.7 (207.3)	0.05
HDL (mg/dl)			
Acute phase	42.4 (21.1)	31.5 (17.2)	0.15
Remission phase	66.7 (22.0)	65.0 (24.2)	0.84
LDL (mg/dl)			
Acute phase	361.7 (134.5)	361.2 (139.9)	0.99
Remission phase	146.5 (47.3)	176.5 (49.1)	0.10
LDL/HDL ratio			
Acute phase	11.5 (8.0)	13.6 (7.7)	0.47
Remission phase	2.3 (0.8)	3.3 (2.7)	0.13

Discussion

Hyperlipidemia is an important characteristic of NS. Elevation of plasma total cholesterol, VLDL, or more specifically LDL, are the major lipid abnormality in NS, although hypertriglyceridemia may develop as the disorder progresses.[3,4,7] The pathophysiology of nephrotic hyperlipidemia is complex and probably influenced by many factors. The prevailing view is that both hepatic syntheses of lipids and of apolipoproteins are increased and that the clearance of chylomicron and VLDL is reduced.[4,8] Hyperlipidemia is also a risk factor for cardiovascular diseases and progressive glomerular damage leading to renal failure. Transient hypercholesterolemia in patients with steroid-responsive NS can be severe (e.g. serum cholesterol levels 300-500 mg/dL or more) but usually resolves when the NS has been treated successfully. Persistent hypercholesterolemia and hypertriglyceridemia are common in patients who have treatment-resistant NS.[9, 10]

The sex ratio found in this study was similar to previous studies. There were highly significant differences in total cholesterol, HDL, LDL, triglyceride levels, and LDL/HDL ratio between NS during acute phase and remission. The total cholesterol, LDL, triglyceride levels, and LDL/HDL ratio were higher in the acute phase but the HDL level was lower. This may be ascribed to the urinary

protein loss, hypoalbuminemia and reduced serum oncotic pressure leading to increased lipogenesis and decreased lipid catabolism.[4,8] Significant differences were noted in total cholesterol, LDL, triglyceride levels and LDL/HDL ratio between NS during remission and control, but not HDL levels. Two factors may explain this phenomenon. After remission, NS needs more time to reduce the plasma lipids to a normal level or the initial conditions of the patients when first admitted. Plasma lipids in patients who have a long duration of illness before admission may need a longer time to return back to normal. A cross sectional study by Sekarwana[11] showed that the mean level of each lipid profile in children with frequent relapses NS, infrequent relapses NS, and control was significantly different ($P < 0.05$). The different result in this study may be caused by different methods, our study was conducted by cohort study concerning risk factor in relapses NS.

Cholesterol and TG levels during remission were significantly different between persistent remission and relapse after six months remission. There was no significant difference in the incidence of relapse between the first attack and subsequent attacks of NS. The results of this study was different from a previous study done by Zilleruelo *et al*[7] which showed that a significant number of children with MCNS during prolonged remission had elevated serum concentration of total cholesterol (46%), triglyceride (42%), LDL (29%), and VLDL (40%). Persistence and severity of lipid changes correlated well with the duration of illness and frequency of relapses.

Acute lipid fraction levels were not risk factors in relapsing NS. Although the cholesterol and TG levels during remission were significantly different between persistent remission and relapse after six months but after statistical analysis cholesterol remission was not a risk factor in relapsing NS. Only triglyceride level during remission was a risk factor in relapsing NS. Persistent hyperlipidemia indicates that there is a progressive metabolic disorder which is related to the frequency of relapses or long term effect of corticosteroid therapy.[11] The primary finding in chronic renal failure and dialysis is hypertriglyceridemia. A study conducted by Rose and Appel[7] showed that in patients with chronic renal disease and end-stage renal disease, there were hypertriglyceridemia, hypercholesterolemia, as well as increased of LDL cholesterol levels.

In this study only persistent hypertriglyceridemia was identified as a risk factor in relapsing NS. Patients with persistent hypertriglyceridemia had a 5.2 times risk of relapse. This persistent hypertriglyceridemia may be due to the fact that some patients had chronic NS and they probably had progressive renal injury as well. Persistent hypertriglyceridemia could be a marker for relapsing NS. This may be used to educate and motivate parents for routine control, even if their children are already in remission, to prevent progressive renal injury. Persistent hyperlipidemia may cause premature atherosclerosis. Therefore diet and antihyperlipidemic drugs could be considered in the management of the disease.

According to Sekarwana,[11] the lipid profile levels in relapses NS were high, total cholesterol and LDL levels in infrequent and frequent relapses NS were significantly different ($P < 0.05$). The total cholesterol and sVCAM-1 (marker of atherosclerosis) level were correlated significantly.

The limitation of this study was that the diet of the patients at home and other factors that could trigger the relapses were not controlled. This study was a cohort study, one of the best studies to determine the risk factors of a disease. Using the same treatment protocol for all patients was the strength of this study.

In conclusion, persistent hypertriglyceridemia in remission phase is a risk factor for relapsing NS.

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