

Relation between plasma lipids and relapse of idiopathic nephrotic syndrome in children

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Abstract

Background: Nephrotic syndrome (NS) is one of the most common renal diseases in children. It is a chronic childhood disorder with a course of relapse and remission. Hyperlipidemia is a constant feature (95% cases) of minimal change nephrotic syndrome (MCNS) having serum cholesterol >250 mg/dl. Both increased synthesis and decreased clearance of lipoproteins may contribute to the hyperlipoproteinemia which frequently complicates the NS. Persistent hyperlipidemia can lead to relapse of NS which is a potential risk factor for progression of glomerular injury. Persistent hyperlipidemia and frequent relapse of NS are further responsible for cardiovascular disease and progressive glomerular damage leading to renal failure. This study was done to determine relationship between plasma lipids and relapse of idiopathic NS in children.

Methods: This prospective study was carried out from July 2015 to June 2017 at the Department of Paediatrics in Sylhet MAG Osmani Medical College Hospital. Patients with the diagnosis of NS fulfilling the inclusion criteria were included in this study purposively. A total of 50 children were included into this study. The primary end point was to determine plasma lipids level in children having idiopathic NS at acute phase, in remission and at 6 months after completion of treatment. The secondary end point was to evaluate the relationship between persistent hyperlipidemia in remission phase and relapse of NS.

Results: Among 50 children with clinical diagnosis of NS, 35 were first episode and 15 were in relapse cases. Among the first episode NS cases serum lipids level were decreased significantly during remission but HDL was increased, whereas in relapse cases even during remission serum lipids level were significantly higher. After six months of follow up, out of 50 patients 28 patients had persistent remission and 22 patients had relapsed. The relationship between plasma lipids 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 5.4 and 95% CI [1.06, 25.4].

Conclusion: Persistent hypertriglyceridemia and hypercholesterolemia in remission phase is a risk factor for relapse of idiopathic NS in children.

Key words: Idiopathic nephrotic syndrome, plasma lipids, persistent remission, relapse.

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Introduction

Nephrotic syndrome (NS) is one of the most common renal diseases in children. It is a chronic childhood disorder with a course of relapse and remission. NS is the clinical manifestation of glomerular disease associated with massive (nephrotic range) proteinuria, hypoalbuminemia (≤ 2.5 g/dl), generalized edema, and hyperlipidemia (cholesterol >200 mg/dl). Nephrotic range proteinuria is defined as proteinuria ≥ 1 g/m²/24 hours or >40 mg/m²/hours.¹ Globally the incidence of NS is 1-3 per 100,000 children per year. NS may be primary or secondary to various systemic diseases and drugs. Most children with NS have a form of primary or idiopathic NS (90%), and rest of them has secondary NS. Idiopathic NS comprises minimal change NS (85%), focal segmental glomerulosclerosis, mesangio proliferative glomerulonephritis and membranous nephropathy.²

Hyperlipidemia is a constant feature (95% cases) of minimal change NS (MCNS) having serum cholesterol >250 mg/dl.³⁻⁴ Various degree of lipid profile 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.⁵⁻⁷ The main cause of hyperlipidemia in patients with NS is probably increased hepatic lipogenesis, a non-specific reaction to falling oncotic pressure secondary to hypoalbuminemia.⁸ Both increased synthesis and decreased clearance of lipoproteins may contribute to the hyperlipoproteinemia which frequently complicates NS with increased levels of total and LDL cholesterol as the most characteristic abnormality. The hyperlipoproteinemia may also be characterized by elevated levels of triglycerides, increased concentrations of Apo B, Apo C and Apo E and reduced levels of Apo A-I and Apo A-II. The increased lipoprotein synthesis occurs in partly undefined mechanisms related to proteinuria, hypoalbuminemia and possibly increased availability of mevalonate as a substrate for cholesterol synthesis. Urinary loss of HDL components and other liporegulatory factors may contribute to decreased activity of lipolytic enzymes and result in impaired clearance of cholesterol- and triglyceride-rich lipoproteins of lower densities and altered composition

of HDL. The variability in these two metabolic abnormalities may account for the corresponding variability in lipoprotein profiles of patients with NS.⁹ Lawang SA et al. showed that 40% patients had relapse of NS those had highly significant differences in total cholesterol, HDL, LDL, triglyceride and LDL/HDL ratio between acute phase of NS and NS in remission.^{10,11} 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 glomerular damage leading to renal failure. Persistent hyperlipidemia can lead to relapse of NS.⁶ Therefore the current study is designed to see the relationship of lipid abnormalities and relapse of NS in children.

Methods

This prospective observational study was carried out from July 2015 to June 2017 at the Department of Paediatrics in Sylhet MAG Osmani Medical College Hospital. Patients admitted into paediatric wards with diagnosis of NS fulfilling the inclusion criteria (Children aged 2-10 years with typical features of minimal change NS like scanty micturition, generalized oedema and bed side heat coagulation test of urine for albumin +++ or more) were included in this study. Children with prior history of diabetes mellitus, hypothyroidism, familial hypercholesterolemia, steroid resistance NS, persistent haematuria and hypo-complementemia were excluded from the study as they may have influence on plasma lipids level. Ethical clearance was sorted from the institute's ethical clearance committee. Written informed consent was taken from the parent/guardian prior to enrollment into the study. Data were collected by using pre-tested structured data collection sheet meeting the objectives of the study.

NS was defined as a disease associated with massive proteinuria (urinary total protein ≥ 1 gm/m²/day), hypoalbuminemia (S. albumin <2.5 gm/dl), generalized edema, and hypercholesterolemia (S. cholesterol >250 mg/dl). After admission into paediatric wards, detailed history was taken and thorough clinical examination was done along with bed side heat coagulation test of urine for albumin. Blood was collected in fasting state in the early morning and sent the hospital laboratory. The samples were analyzed for serum total proteins, serum albumin, serum globulin,

blood urea, serum creatinine and lipid profile (total cholesterol, triglycerides, LDL, HDL). Lipid profile was measured at admission into the hospital, again in remission (when urinary protein trace or nil for consecutive three days in early morning sample) and at 6th months after completion of treatment. Plasma lipids were determined in all patients using the enzymatic colorimetric test. Three ml of venous blood were taken during the acute phase using a sterile syringe then directly sent to the laboratory or stored in a refrigerator after proper labeling. The second sample of plasma lipids was collected during remission (within 2 weeks maximum eight weeks) and third sample at 6th months after completion of treatment. After collecting blood specimens during the acute phase, patients were initially treated according to Kidney Disease Improving Global Outcome (KDIGO) protocol.² In case of first episode, prednisolone 60 mg/m²/day daily (maximum dose 80mg) was given in 3 divided doses for 6 weeks, followed by 40 mg/m²/day, every alternate day as a single morning dose for another 6 weeks. Patient who failed to achieve remission within eight weeks after treatment were diagnosed as steroid resistant NS and excluded from the study. In case of relapse, prednisolone 60 mg/m²/day (maximum dose 80 mg) was given in 3 divided into doses until child enters into remission,

followed by 40 mg/m²/day, every alternate day as a single morning dose for next 6 weeks.

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 consecutive days,² 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 was e³.¹ Data were analyzed both manually and by using the SPSS version 21.0 software. Comparison of plasma lipids levels during the acute phase and remission phase was analyzed by using student t-test. The significant relationship between plasma lipids and relapses were analyzed by using the X² test.

Results

A total of 50 children with clinical diagnosis of NS were included into this study. Among them 35 were first episode and 15 were in relapse. It was observed that more than half (54.2%) of the patients belonged to age 2-6 years in NS 1st attack group and 9 (64.6%) in NS relapse group. There was no significant difference (p>0.05) of mean age, mean weight and mean height among two groups during enrolment into the study. The male-female ratio was 2.4:1 in NS 1st attack group and 3:1 in relapse group. The difference was not statistically significant (p>0.05) (Table I).

Table I Baseline characteristics of the study population (N=50).

Variables	1 st attack (n=35)		Relapse (n=15)		p value
	n	%	n	%	
Age (year)					
2-6	19	54.2	9	64.6	
>6-10	16	45.8	6	35.4	
Mean±SD	5.4±2.6		5.3±0.45		0.669 ^a
Sex					
Male	25	70.8	11	75.0	0.646 ^b
Female	10	29.2	4	25.0	
		Mean±SD		Mean±SD	
Weight (kg)		17.65±5.68		16.7±5.44	0.405 ^a
Range (min, max)		8, 31		8.5, 30	
Height (cm)		102.6±17.5		100.2±15.0	0.472 ^a
Range (min, max)		72, 136		78, 126	

a- p value reached from student t-test, b- p value reached from x² test

In first episode of NS cases serum lipids decreased significantly during remission, but HDL was increased during remission and it was not statistically significant, whereas in relapse cases even during remission serum lipids were significantly higher but HDL increase was not statistically significant (Table II and III). 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 of follow up, out of 50 subjects, 28 subjects had persistent remission, 22 subjects had relapses, and all of them had infrequent relapse NS. There was no significant difference in the incidence of relapse between the first attack and second or subsequent attacks of NS ($p=0.14$). 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 IV).

Table II Comparison of plasma lipids level between acute phase and remission phase of nephrotic syndrome in first episode.

Plasma lipids	Acute phase (n=35)		Remission phase (n=35)		p-value*
	Mean±SD	Range (min, max)	Mean±SD	Range (min, max)	
Cholesterol (mg/dl)	375.30±122.60	230, 729	245.40±18.30	140, 330	0.04 ^a
Triglyceride (mg/dl)	268.50±92.10	131, 595	175.30±18.30	48, 433	0.04 ^a
LDL (mg/dl)	233.80±99.80	152, 430	159.20±15.40	79, 260	0.04 ^a
HDL (mg/dl)	50.50±20.20	12, 90	56.20±21.30	15, 95	0.34 ^b
LDL/HDL ratio	8.20±4.80	2, 30	2.6±1.23	0.9, 10	0.04 ^a

*p value reached from paired t-test, a- significant, b- not significant

Table III Comparison of plasma lipids level between acute phase and remission phase of nephrotic syndrome in relapse cases.

Plasma lipids	Acute phase (n=15)		Remission phase (n=15)		p-value*
	Mean±SD	Range (min, max)	Mean±SD	Range (min, max)	
Cholesterol (mg/dl)	520.30±122.60	232, 829	445.40±18.30	146, 534	0.01 ^a
Triglyceride (mg/dl)	398.50±92.10	132, 695	265.30±18.30	48, 533	0.01 ^a
LDL (mg/dl)	433.80±99.80	152, 630	350.20±15.40	79, 460	0.01 ^a
HDL (mg/dl)	59.50±20.20	12, 90	55.20±21.30	15, 95	0.31 ^b
LDL/HDL ratio	9.20±4.80	2, 30	2.6±1.23	0.9, 10	0.01 ^a

*p value reached from student t-test, a- significant, b- not significant

Table IV Comparison of plasma lipids level between persistent remission and relapsing nephrotic syndrome after 6 months of remission (N=50)

Plasma lipids		Persistent remission (n=28)	Relapsing NS (n=22)	p-value*
		Mean±SD	Mean±SD	
Cholesterol (mg/dl)	Acute phase	445.40±168.30	575.40±158.30	0.42 ^a
	Remission phase	237±47.50	377.50±64.30	0.05 ^b
Triglyceride (mg/dl)	Acute phase	415.30±18.30	595.30±18.30	0.14 ^a
	Remission phase	172.70±88.30	295.30±28.30	0.05 ^b
LDL (mg/dl)	Acute phase	350.20±15.40	310.20±15.40	0.99 ^a
	Remission phase	150.20±41.40	180.20±45.40	0.10 ^a
HDL (mg/dl)	Acute phase	41.20±21.30	31.20±21.30	0.15 ^c
	Remission phase	64.22±21.10	61.20±20.20	0.85 ^c
LDL/HDL ratio	Acute phase	12.6±8.23	14.6±7.23	0.44 ^b
	Remission phase	2.6±8.23	3.6±7.23	0.14 ^b

*p value reached from student t-test, a-highly significant, b- significant, c-not significant

The relationship between plasma lipids 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 5.4 and 95% CI [1.06, 25.4]. This means that NS with persistent hyperlipidemia have 5.4 times more risk of relapse.

Discussion

Hyperlipidemia is a common feature of NS, the distribution of cholesterol among the plasma lipoproteins and the mechanism of the enhanced hepatic synthesis of lipoprotein lipids are not well understood. Thus, many hypercholesterolemic patients with unremitting NS may be at increased risk for atherosclerotic heart disease. A significant inverse correlation was found between the total plasma cholesterol concentration and both the plasma albumin concentration ($r = -0.528$) and the plasma oncotic pressure ($r = -0.674$), but not the plasma viscosity ($r = +0.319$). Enhanced hepatic synthesis of lipoprotein lipids may be stimulated by a decreased plasma albumin concentration or oncotic pressure.¹⁰ The sex ratio found in this study was 2.4-3:1 which was similar to previous studies. The mean age of the study population was 2-6 years which was also correspond to the previous study.¹¹

In the present study, there was significant rise in total cholesterol, triglycerides, LDL, LDL/HDL ratio, when compared with controls. These findings were similar with the work done by various authors.¹²⁻¹⁵ The mean serum cholesterol in relapse cases (mean = 520.30) was significantly higher than first episode NS cases (mean = 375.30). Arije et al also observed persistent rise in serum lipids in frequent relapse cases.¹⁶

In our study, the mean total cholesterol was 420.30 mg/dl and the highest value was 829 mg/dl. Dnyanesh et al in his study observed that the mean total cholesterol was 422.61 mg/dl and the highest value was 676 mg/dl.¹⁷ 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 loss of protein, hypoalbuminemia and reduced serum oncotic pressure leading to increased lipogenesis and decreased lipid catabolism.^{6, 18}

The present study shows that lipid profile in first episode of NS reaches normal value (245.40 mg/dl) during remission, whereas in relapse cases, there is persistent

elevation in the lipid profiles (445.40 mg/dl) even during the remission. Merouani et al. observed hyperlipidemia during the active phase of the disease and disappeared with resolution of the proteinuria and was persistently abnormal in frequently relapsing children.¹⁹ Mahmud S et al. observed that children with frequently relapsing NS have prolonged periods of hypercholesterolemia and concluded that serum cholesterol may be regarded as predictor of relapse in childhood idiopathic NS.²⁰

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 for 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.²¹

In this study, both persistent hypertriglyceridemia and hypercholesterolemia was identified as a risk factor in relapsing NS. Patients with persistent hyperlipidemia had a 5.4 times risk of relapse. Persistent hypertriglyceridemia and hypercholesterolemia could be a marker for relapsing NS. Persistent hyperlipidemia may cause premature atherosclerosis. Therefore, diet and antihyperlipidemic drugs could be considered in the management of the disease.

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. Using the same treatment protocol for all patients was the strength of this study. In conclusion, persistent hypertriglyceridemia and hypercholesterolemia in remission phase is a risk factor for relapsing NS.

Conflict of interest: Nothing to declare.

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