

Comparison of Lipid Profile in Different Types of Steroid Sensitive Idiopathic Relapsing Nephrotic Syndrome in Children during Active Disease and Remission

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Abstract

Introduction: Nephrotic syndrome is a disease of relapse and remission. Relapse rate is more than 80%. Hyperlipidemia and hypoalbuminemia are important characteristic of nephrotic syndrome. Hyperlipidemia persist even after remission of disease in frequent relapse nephrotic syndrome possibly due to frequent attack of disease and frequent use of steroid. Hyperlipidemia causes premature atherosclerosis, progressive renal injury leading to chronic renal failure, cardiac complications (myocardial infarction, hypertension), cerebrovascular disease and frequent relapse of nephrotic syndrome. **Objectives:** The aim of study was to see the lipid profile and comparison of lipid profile among different types of steroid sensitive idiopathic relapsing nephrotic syndrome during active disease and in remission. **Materials and Methods:** A cross sectional study included 120 (40 in each group) children aged 2-16 years with steroid sensitive idiopathic relapsing nephrotic syndrome patients who were admitted or attended in out patients department (OPD) in paediatric nephrology department Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, during December 2014 to December 2015. They were clinically examined and fasting lipid profile was done in each case during active disease and after one month of urinary remission. The study population were divided into three groups- Infrequent relapse nephrotic syndrome (IFRNS), frequent relapse nephrotic syndrome (FRNS) and steroid dependent nephrotic syndrome (SDNS) based on clinical response. **Results:** Total patients were 120 (40 in each group). The study showed a male predominance with a male to female ratio 2.24:1, male patients were 69%, female 31%. In all cases, there were increased mean total cholesterol, low density lipoprotein (LDL), triglyceride (TG) and high density lipoprotein (HDL) was normal during active disease, more raised in FRNS and SDNS. There was significant decrease in the mean level of total cholesterol, LDL and triglyceride during remission ($p < 0.001$). Cholesterol became normal but triglyceride and LDL remained elevated even after one month of urinary remission in FRNS and SDNS. **Conclusion:** Hyperlipidemia persist during remission of steroid sensitive relapsing nephrotic syndrome. Children with FRNS and SDNS should be addressed with lipid lowering medication, healthy foods and healthy life style. Multicenter prospective studies with larger sample are needed for validating the findings of the present study.

Keywords: Hyperlipidaemia, Serum albumin, Nephrotic syndrome.

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Introduction:

Nephrotic syndrome (NS) is a common renal disease in children. It is characterized by massive proteinuria (urinary total protein $>1\text{gm}/\text{m}^2/24$ hours), hypoalbuminemia (serum albumin $>250\text{mg}/\text{dl}$)¹. The incidence of idiopathic nephrotic syndrome (INS) varies with age, race and geography. The incidence in children in the USA and Europe is 2 to 2.7 per 100000 children below 18 years². The incidence of idiopathic nephrotic syndrome (INS) is six fold in Asians than in European children³. INS is less frequent in Africa⁴. In Indian subcontinent incidence is higher (90-100/million population). There is a male preponderance in children, with a male: female ratio of 2:1. Ninety percent childhood nephrotic syndrome are idiopathic, 85% of them are minimal change nephrotic syndrome (MCNS). Idiopathic nephrotic syndrome are two types such as steroid sensitive and steroid resistant. According to clinical response steroid sensitive nephrotic syndrome divided into infrequent relapse nephrotic syndrome (IFRNS), frequent relapse nephrotic syndrome (FRNS) and steroid dependent nephrotic syndrome (SDNS). Eighty to ninety percent of children with idiopathic nephrotic syndrome are steroid sensitive and rest 10-20% nephrotic syndrome are steroid resistant⁵. Ninety five percent of children with minimal change nephrotic syndrome (MCNS) are responsive to steroid therapy with complete clinical and biochemical remission and have excellent long term prognosis⁶. Idiopathic nephrotic syndrome is a disease of relapse and remission. Frequency of relapse is highly variable². Hyperlipidemia has long been

recognized as a frequent metabolic abnormality in patients with nephrotic syndrome, having first been documented in 1917. Hyperlipidemia is an important characteristic of idiopathic nephrotic syndrome in children. Hyperlipidemia occurs as a result of increase hepatic synthesis of lipoprotein due to hypoalbuminemia and decreased catabolism of individual lipid fraction due to loss of lipoprotein lipase and lipoprotein lipase receptor and due to drugs used (steroid, cyclosporine, tacrolimus) in the treatment of nephrotic syndrome. Hyperlipidemia is usually observed during the active phase of the disease and disappear with resolution of proteinuria³. The plasma concentrations of total cholesterol (CH), triglyceride (TG), low density lipoprotein (LDL), very low density lipoprotein (VLDL), apolipoprotein-b and lipoprotein(a) are increased during active phase of the disease. High density lipoprotein (HDL) has been reported as low⁸, normal or elevated¹⁰ during active disease. Persistent hyperlipidemia after remission can be found in frequent relapse nephrotic syndrome and steroid resistant nephrotic syndrome¹¹. Elevated plasma lipids are potential risk factors for premature atherosclerosis and progression of glomerular injury⁶. Hyperlipidemia is also responsible for cardiovascular disease and progressive glomerular damage leading to renal failure¹². The persistence and severity of lipid changes in serum correlates well with the duration and frequency of the relapses, even during the remission which leads to increased risk of atherosclerosis in later life and the development of progressive renal injury¹³. Hence close monitoring of lipid levels during remission of nephrotic syndrome is necessary to select high risk patients. The intensity of hyperlipidemia is usually related to the severity of proteinuria and hypoalbuminemia¹⁴. Hyperlipidemia may be possible to control by using lipid lowering drugs¹⁵. Lipoproteins play an important role in the transport of plasma lipids, their increase or alteration in various fractions may be responsible for hypercholesterolemia in nephrotic syndrome. In addition to these quantitative changes, the lipoprotein composition is markedly changed, with a higher ratio of cholesterol to triglycerides in the (apo-B containing) lipoproteins and an increase in the proportion of cholesterol, cholesterol ester, and phospholipids compared with proteins.

Materials and Methods:

This is a Prospective observational study conducted in the Department of Paediatric Nephrology, BSMMU, Dhaka from December 2014 to December 2015. One hundred twenty (120) children with steroid sensitive nephrotic syndrome of both sexes between age group of 2-18 years (both admitted and attended in the OPD) were included. During study period whose parents agreed to participate (by written informed consent) and who met the inclusion criteria were enrolled. For incidence of disease 80% with 95% confidence interval & precision of 10%, we needed a sample size of 345 children. Due to financial constrain and short duration of study period 120 patients were taken in this study. Children aged 2-18 years of both sexes having nephrotic syndrome of 1st episode and relapse- Infrequent relapse nephrotic syndrome (IFRNS) and frequent relapse nephrotic syndrome (FRNS). Steroid dependent nephrotic syndrome (SDNS), Children with Congenital NS (onset of nephrotic syndrome < 3 months of age), Children with steroid resistant nephrotic syndrome, Children already on lipid

lowering drugs, Patients who do not follow the dietary advice, Secondary nephrotic syndrome like SLE, HSP etc and those parents/patients who refused to participate were excluded from the study.

The following variable was noted in the study group as a. Demographic variable: i) Age and ii) gender Both male and female patients. b. Biochemical variables: i) Serum Total Cholesterol (CH) ii) Serum Triglyceride (TG) iii) Serum Low Density Lipoprotein (LDL) iv) Serum High Density Lipoprotein (HDL) v) Serum Albumin vi) Serum creatinine vii) 24 hours Urinary Total protein (UTP) and clinical type of nephrotic syndrome. Clinical history was noted including age of onset of 1st attack of nephrotic syndrome, duration of disease, number and type of relapse. On follow up (after one month of remission) complete blood count, urine for routine and microscopic examination, serum albumin, spot urinary protein creatinine ratio, serum fasting lipid profile, were evaluated during remission of disease. After taking informed written consent, 6 ml of venous blood collected from each patient, the sample divided into two- sample of 3 ml each. One sample for determining biochemical parameter & other sample used to determine serum lipid profile. The patients were followed up after one month of remission. Proper dietary history, physical examination and fasting lipid profile was done in all group (IFRNS; FRNS and SDNS). After collection, all the data were checked and edited. Then data were entered into computer with the help of software SPSS for windows programmed version 16. After frequency run, data were cleaned and frequencies were checked. An analysis plan was developed keeping in view with the objectives of the study. Chi-square, paired t-test and ANOVA test was done whenever required. Proportion was expressed as percentage and between groups comparison of fasting lipid profile was done expressed with p value. p value < 0.05 was statistically significant. Prior to commencement of this the research, protocol was approved by the Institutional review board (IRB). Study procedure was elaborated to guardian in easily understandable local language and written consent from guardians of patient were obtained.

Results:

A total of 120 children with nephrotic syndrome of both male and female included in this study. Maximum patients were in age groups 5 – 10 years in all three groups. In the present study, most of the patients were of 5-10 year (53.2%) age group followed by 2-5 years age group (30.8%) and more than 10 years age group 25%. Among 120 patients male were 83 (69.2%) and female were 37 (30.8%). Male female ratio was 2.24 : 1. Male were predominant than female in each groups. Male female ratios were 2.07:1, 1.85:1 and 3.0:1 in IFRNS, FRNS and SDNS groups respectively.

Table I: Comparison of lipid profile (Mean values) among different groups of study subjects during active disease (n=40 in each group).

Parameters	Mean ± SD	p value
Cholesterol (mg/dl)		
IFRNS (a) (n=40)	388.9 ± 88.1	
FRNS (b) (n=40)	481.1 ± 108.7	
SDNS (c) (n=40)	441.2 ± 86.2	
Statistical analysis		
a vs b vs c		<0.001***

Parameters	Mean ± SD	p value
a vs b		<0.001***
a vs c		0.046 *
b vs c		0.169 ^{ns}
Triglyceride (mg/dl)		
IFRNS (a) (n=40)	272.0 ± 67.0	
FRNS (b) (n=40)	372.5 ± 147.5	
SDNS (c) (n=40)	331.4 ± 83.2	
Statistical analysis		
a vs b vs c		<0.001***
a vs b		<0.001***
a vs c		.039*
b vs c		.248 ^{ns}
LDL (mg/dl)		
IFRNS (a) (n=40)	282.9 ± 88.7	
FRNS (b) (n=40)	353.3 ± 100.5	
SDNS (c) (n=40)	335.4 ± 87.5	
Statistical analysis		
a vs b vs c		0.003**
a vs b		0.003**
a vs c		0.038*
b vs c		1.000 ^{ns}
HDL (mg/dl)		
IFRNS (a) (n=40)	52.6 ± 17.0	
FRNS (b) (n=40)	54.6 ± 17.9	
SDNS (c) (n=40)	56.8 ± 12.8	
Statistical analysis		
a vs b vs c		.505 ^{ns}
a vs b		1.000 ^{ns}
a vs c		0.730 ^{ns}
b vs c		1.000 ^{ns}

ANOVA test was done to measure the level of significance among groups and Bonferroni test between groups.

Table I showing comparison of lipid profiles among groups and between groups during active disease. There were significant differences among groups and between IFRNS & FRNS and IFRNS & SDNS in total cholesterol during active disease but no significant difference between FRNS & SDNS. There were significant differences among groups and between IFRNS & FRNS and IFRNS & SDNS in triglyceride during active disease but no significant difference between FRNS & SDNS. There were significant differences among groups, between IFRNS & FRNS and IFRNS & SDNS in LDL during active disease but no significant difference between FRNS & SDNS. There were no significant differences among groups and between groups in HDL during active disease.

Table II: Comparison of lipid profile (Mean values) among study groups during remission (n=40 in each group).

Parameters	Mean ± SD	p value
Cholesterol (mg/dl)		
IFRNS (a) (n=40)	194.0 ± 44.0	
FRNS (b) (n=40)	236.8 ± 48.4	
SDNS (c) (n=40)	230.0 ± 55.7	
Statistical analysis		
a vs b vs c		<0.001***
a vs b		0.001**

Parameters	Mean ± SD	p value
a vs c		0.005**
b vs c		1.000 ^{ns}
Triglyceride (mg/dl)		
IFRNS (a) (n=40)	126.9 ± 40.8	
FRNS (b) (n=40)	194.2 ± 62.5	
SDNS (c) (n=40)	188.2 ± 56.3	
Statistical analysis		
a vs b vs c		<0.001***
a vs b		<0.001***
a vs c		<0.001***
b vs c		1.000 ^{ns}
LDL (mg/dl)		
IFRNS (a) (n=40)	115.8 ± 38.8	
FRNS (b) (n=40)	153.2 ± 43.9	
SDNS (c) (n=40)	141.2 ± 46.7	
Statistical analysis		
a vs b vs c		0.001**
a vs b		0.001**
a vs c		0.030*
b vs c		0.657 ^{ns}
HDL (mg/dl)		
IFRNS (a) (n=40)	52.9 ± 18.3	
FRNS (b) (n=40)	48.9 ± 11.7	
SDNS (c) (n=40)	50.3 ± 14.4	
Statistical analysis		
a vs b vs c		0.476 ^{ns}
a vs b		0.690 ^{ns}
a vs c		1.000 ^{ns}
b vs c		1.000 ^{ns}

ANOVA test was done to measure the level of significance among groups and Bonferroni test between groups.

Table II showing comparison of lipid profiles among groups and between groups during remission of disease. There were significant differences among groups and between IFRNS & FRNS and IFRNS & SDNS in total cholesterol during remission of disease but no significant difference between FRNS & SDNS. There were significant differences among groups and between IFRNS & FRNS and IFRNS & SDNS in triglyceride during remission of disease but no significant difference between FRNS & SDNS. There were significant differences among groups, between IFRNS & FRNS and IFRNS & SDNS in LDL during remission of disease but no significant difference between FRNS & SDNS. There were no significant differences among groups and between groups in HDL during remission of disease.

Table III: Comparative analysis of serum Lipid profile (Mean values) during active disease and remission in each group of study subjects (n=40 in each group)

Parameters	During active disease (Mean ± SD)	During remission of disease (Mean ± SD)	p value
Cholesterol (mg/dl)			
• IFRNS (n=40)	388.9 ± 88.1	194.0 ± 44.0	<0.001***
• FRNS (n=40)	481.1 ± 108.7	236.8 ± 48.4	<0.001***
• SDNS (n=40)	441.2 ± 86.2	230.0 ± 55.7	<0.001***

Parameters	During active disease (Mean ± SD)	During remission of disease (Mean ± SD)	p value
Triglyceride (mg/dl)			
• IFRNS (n=40)	272.0 ± 67.0	126.9 ± 40.8	<0.001***
• FRNS (n=40)	372.5 ± 147.5	194.2 ± 62.5	<0.001***
• SDNS (n=40)	331.4 ± 83.2	188.2 ± 56.3	<0.001***
LDL (mg/dl)			
• IFRNS (n=40)	282.9 ± 88.7	115.8 ± 38.8	<0.001***
• FRNS (n=40)	353.3 ± 100.5	153.2 ± 43.9	<0.001***
• SDNS (n=40)	335.4 ± 87.5	141.2 ± 46.7	<0.001***
HDL (mg/dl)			
• IFRNS (n=40)	52.6 ± 17.0	52.9 ± 18.3	0.923 ^{ns}
• FRNS (n=40)	54.6 ± 17.9	48.9 ± 11.7	0.008**
• SDNS (n=40)	56.8 ± 12.8	50.3 ± 14.4	0.007**

Paired t test was done to measure the level of significance

Table III shows comparison of lipid profile between active disease and remission of disease in each group of study subjects. There were significant differences between active disease and remission of disease in total cholesterol in each group. There were significant differences between active disease and remission of disease in triglyceride in each group. There were significant differences between active disease and remission of disease in LDL in each group. There were significant differences between active disease and remission of disease in HDL in FRNS and SDNS groups.

Table IV: Comparison of mean serum albumin level in relapsing nephrotic syndrome during active disease and remission.

Albumin (gm/L)	During active disease	During remission of disease	p value
IFRNS	16.8 ± 8.8	33.8 ± 5.2	<0.001***
FRNS	15.1 ± 5.5	30.7 ± 4.1	<0.001***
SDNS	14.5 ± 4.1	34.0 ± 3.8	<0.001***

Paired t test was done to measure the level of significance

Table IV shows comparison of serum albumin between active disease and remission of disease. The difference between serum albumin level during active disease and in remission was highly significant ($P < 0.001$) in each group of relapsing nephrotic syndrome.

Discussion:

This study analyzed fasting lipid profile of 120 (40 in each group) children with steroid sensitive idiopathic relapsing nephrotic syndrome (NS) during active disease and after one month of urinary remission. The current study showed a male predominance with a male to female ratio 2.24:1. In this study, male patients were 69%, female 31%. Denison et al were also observed male predominance in their studies. Also found male and female ratio 2:1¹⁴ which was similar to present study. Balgopal et al¹⁵ and Shah et al¹⁷ found 2-6 years were common age for childhood nephrotic syndrome, 60.6% and 61.7%

respectively. Hyperlipidemia is an important feature of nephrotic syndrome. Present study showed, significantly raised level of total cholesterol during active disease in each study group. Among groups which was statistically significant ($p < 0.001$). During remission of nephrotic syndrome serum cholesterol became normal. Arije et al¹⁸ also observed raised level serum cholesterol during active disease. Present study showed there was normal serum cholesterol after one month of urinary remission. Banarejee et al¹⁹ found elevated level of cholesterol even after remission of disease. In the present study there was significantly raised level of serum triglyceride (TG) during active disease in each study group, among groups which was statistically significant ($p < 0.001$). Matsuda et al²⁰ observed that some patients were normo triglyceridemic but others show a moderate hypertriglyceridemic picture which although not uniformly expressed. Present study also showed serum triglyceride was persistently raised in the study subjects even after one month of urinary remission, more in FRNS and SDNS. Zilleurelo et al¹⁰ also observed significantly persistent high level of TG in relapsing nephrotic syndrome even during remission. Adu E M²¹ also found elevated triglyceride during active disease and remained raised after remission of disease ($P < 0.05$). Present study also showed low density lipoprotein (LDL) was significantly elevated during active disease among study groups and remained raised even after one month of urinary remission of disease. LDL level was more raised in FRNS and SDNS, which was statistically significant among study groups ($p < 0.003$). Metha et al²² studied 22 cases of nephrotic syndrome and observed LDL level was elevated in 100% cases during active disease and remission. Chowdhury et al²³ studied 25 cases of nephrotic syndrome reported that 96% cases had elevated level of cholesterol, 100% had raised LDL level. Present study showed mean serum high density lipoprotein (HDL) was within normal range during active disease and during remission in the study groups. All study subjects were on steroid therapy during remission. In this study, we can not evaluate hyperlipidemia whether due to disease or steroid. Alexander et al²⁴ found that HDL was low in nephrotic syndrome and Appel et al¹² and Joven et al.²⁵ observed normal level of HDL during active disease and remission of disease. Hypoalbuminemia is an important finding of idiopathic relapsing nephrotic syndrome in children due to loss of albumin in the urine. Albumin level decreases during active disease and increases during remission of disease. In the present study, there was an inverse correlation between albumin and cholesterol, triglyceride and low density lipoprotein. Present study showed, there was significant difference of serum albumin in each group of study subjects during active and remission ($p < 0.001$). Thomas et al²⁶ found no correlation between the development of hyperlipidemia and hypoalbuminemia and postulated that the severity of hyperlipidemia is related to the amount of nephrotic kidney tissue

present. Thomas et al²⁶ found inverse correlation between serum cholesterol and albumin. Hypoalbuminemia causes hyperlipidemia. Mallik et al.²⁷ observed a direct correlation between serum albumin and HDL. When albumin was low the HDL was also low.

Conclusion:

The present study concluded that hyperlipidemia were associated with childhood idiopathic nephrotic syndrome during active disease. Serum cholesterol, triglyceride and low density lipoprotein were elevated during active disease. Serum cholesterol became normal after one month of urinary remission but triglyceride and LDL level remained elevated even after one month of urinary remission. Serum cholesterol, triglyceride and low density lipoprotein were more elevated in FRNS and SDNS during active disease, probably due to frequent attack of disease and use of steroid. High density lipoprotein remained within normal range in both active disease and during remission.

Conflict of Interest: None.

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