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

SM Shamsul Hoque¹, Md. Ashraful Islam², Taslima Akter³, Ranjit Ranjan Roy⁴, Md Habibur Rahman⁵

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 outpatient 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 a 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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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 increased 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 proteinuria. The plasma concentrations of total cholesterol (CH), triglyceride (TG), low density lipoprotein (LDL), very low density lipoprotein (VLDL), apolipoprotein-b and apolipoprotein(a) are increased during active phase of the disease. High density lipoprotein (HDL) has been reported as low, normal or elevated during active disease. Persistent hyperlipidemia after remission can be found in frequent relapse nephrotic syndrome and steroid resistant nephrotic syndrome. Elevated plasma lipids are potential risk factors for premature atherosclerosis and progression of glomerular injury. Hyperlipidemia is also responsible for cardiovascular disease and progressive glomerular damage leading to renal failure. 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 injury. 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 hypoalbuminemia. Hyperlipidemia may be possible to control by using lipid lowering drugs.

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 nephritic syndrome (IFRNS) and frequent relapse nephritic syndrome (FRNS). Steroid dependent nephritic 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 varibles: 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) & 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 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).*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFRNS (a) (n=40)</td>
<td>389.9 ± 88.1</td>
<td></td>
</tr>
<tr>
<td>FRNS (b) (n=40)</td>
<td>481.1±108.7</td>
<td></td>
</tr>
<tr>
<td>SDNS (c) (n=40)</td>
<td>441.2±86.2</td>
<td></td>
</tr>
<tr>
<td>Statistical analysis</td>
<td></td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>

* Statistically significant
The objective of this study is to examine the determinants of Low Birth Weight (LBW) in children born at Khulna Medical College Hospital (KMCH) during the study period. Data was collected from Institutional Review Board (IRB) of KMCH. Mothers who delivered at KMCH during the study period were included in the study. The majority of mothers (58.3%) had anemia in the case group. Nineteen (39.6%) mothers reported a history of hypertension, more than 17 (35.4%) in the control group. Preterm delivery was significantly associated with LBW. It was 3-5 times more likely to develop LBW in preterm delivery. And it is similar to other studies. Anemia, hypertension, and urinary tract infection were identified as major risk factors for LBW. Table II shows the distribution of study patients according to factors (n=96).

Table II: Distribution of study patients according to factors (n=96).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Case: 39.6% Control: 22.4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Case: 35.4% Control: 22.4%</td>
</tr>
<tr>
<td>Urinary Infection</td>
<td>Case: 35.4% Control: 22.4%</td>
</tr>
</tbody>
</table>

Acknowledgement:
Authors are very grateful to Prof. Choudhury Habibur at home.

References:
4. Hoque, et al. Comparison of lipid profile (Mean values) among study groups during remission (n=40 in each group).

**Comparison of Lipid Profile in Different Types of Steroid Sensitive Idiopathic Relapsing Nephrotic Syndrome in Children**

- **Cholesterol (mg/dl):**
  - FRNS (a) (n=40) 194.0 ± 44.0
  - FRNS (b) (n=40) 236.8 ± 48.4
  - SDNS (c) (n=40) 230.0 ± 55.7
- **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

**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).**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>During active disease (Mean ± SD)</th>
<th>During remission of disease (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFRNS (a) (n=40)</td>
<td>388.9 ± 88.1</td>
<td>194.0 ± 44.0</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>FRNS (b) (n=40)</td>
<td>481.1 ± 108.7</td>
<td>236.8 ± 48.4</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>SDNS (c) (n=40)</td>
<td>441.2 ± 86.2</td>
<td>230.0 ± 55.7</td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>

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 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 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.

Conclusion:
In conclusion parity, anemia, hypertension, urinary tract infection were related factor wanted pregnancy was 41(85.4%) in case group and 22(45.8%) in control group. More than 17(35.4%) in control group. Nineteen (39.6%) mothers reported a history of hypertension, more than 17 (35.4%) in the control group. Preterm delivery was significantly associated with LBW. And it is similar to other studies. Anemia, hypertension, and urinary tract infection were identified as major risk factors for LBW.
Determinants of Low Birth Weight (LBW)

The objective of this study is to identify the risk factors for LBW. Before starting this study, ethical clearance was taken from the relevant authorities. P value < 0.05 is considered to be statistically significant. The chi-square test and student 't' test were performed for risk factors. The summarized data was presented in the table and chart. The chi-square test and student 't' test were performed for risk factors. The summarized data was presented in the table and chart.

Inclusion criteria

It was a Case control study conducted in Department of Pediatrics, Khulna Medical College Hospital, from December 2015 to November 2016.

Risk factors

Risk factors were the reasons for this phenomenon leading to LBW. The study was carried out with an aim to identify the determinants of LBW. The study was carried out with an aim to identify the determinants of LBW.

Comparison of Lipid Profile in Different Types of Steroid Sensitive Idiopathic Relapsing Nephrotic Syndrome in Children

Table I showing comparison of lipid profiles among groups and Bonferroni test between groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>During active disease (Mean ± SD)</th>
<th>During remission of disease (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IFRNS (n=40)</td>
<td>272.0 ± 67.0</td>
<td>126.9 ± 40.8</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>• FRNS (n=40)</td>
<td>372.5 ± 147.5</td>
<td>194.2 ± 62.5</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>• SDNS (n=40)</td>
<td>331.4 ± 83.2</td>
<td>182.2 ± 56.3</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IFRNS (n=40)</td>
<td>282.9 ± 88.7</td>
<td>115.8 ± 38.8</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>• FRNS (n=40)</td>
<td>353.3 ± 100.5</td>
<td>152.3 ± 43.9</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>• SDNS (n=40)</td>
<td>335.4 ± 87.5</td>
<td>141.2 ± 46.7</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IFRNS (n=40)</td>
<td>52.6 ± 17.0</td>
<td>52.9 ± 18.3</td>
<td>0.923 ns</td>
</tr>
<tr>
<td>• FRNS (n=40)</td>
<td>54.6 ± 17.9</td>
<td>48.9 ± 11.7</td>
<td>0.008**</td>
</tr>
<tr>
<td>• SDNS (n=40)</td>
<td>56.8 ± 12.8</td>
<td>50.3 ± 14.4</td>
<td>0.007**</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Albumin (gm/L)</th>
<th>During active disease</th>
<th>During remission of disease</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFRNS</td>
<td>16.8 ± 8.8</td>
<td>33.8 ± 5.2</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>FRNS</td>
<td>15.1 ± 5.5</td>
<td>30.7 ± 4.1</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>SDNS</td>
<td>14.5 ± 4.1</td>
<td>34.0 ± 3.8</td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>

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 2:1 which was similar to present study. Balgopal et al and shah et al 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. Arie et al 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 al 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 al 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 al also observed significantly persistent high level of TG in relapsing nephrotic syndrome even during remission. Adu E M 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 al studied 22 cases of nephrotic syndrome and observed LDL level was elevated in 100% cases during active disease and remission. Chowdhury et al 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 al found that HDL was low in nephrotic syndrome and Appel et al and Joven et al observed normal level of HDL during active disease and remission of disease. Hyperalbuminemia 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 al 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 al. found inverse correlation between serum cholesterol and albumin. Hypoalbuminemia causes hyperlipidemia. Mallik et al. 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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