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Research Paper

Lipid Profile of Children With Nephrotic Syndrome Admitted to a Tertiary Care Hospital

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ABSTRACT

Background and Aim: Hyperlipidemia is typically detected in active nephrotic syndrome (NS) and normalizes with the resolution of the proteinuria. This study assessed the lipid profile of children with NS during active disease and remission.

Methods: This prospective observational study was conducted at ICMH, Bangladesh, from July 2021 to June 2022. Sixty children with NS (1-18 years), including both first attack and relapse cases, were enrolled. A detailed history and thorough clinical examination were carried out. Serum fasting lipid profiles were measured during active disease and again 4 weeks after achieving remission. After collecting all the required data, analysis was conducted using SPSS software, version 24.0.

Results: The majority of children (70%) were relapse cases. The mean age of the study participants was 5.15±2.97 years, with a predominance of males (61.7%). Mean serum cholesterol, low-density lipoprotein (LDL), and triglycerides (TG) levels were elevated in all groups, while high-density lipoprotein (HDL) levels were normal in all groups during active disease. During remission, serum cholesterol, TG, and LDL levels were significantly reduced in both first attack and relapse cases. LDL levels returned to normal in all groups, but total cholesterol (TC) and TG remained high in the frequently relapsing NS (FRNS) and steroid-dependent NS (SDNS) groups. Serum albumin levels were low in all groups, with significantly lower levels observed in the FRNS group.

Conclusion: During active disease, serum cholesterol, TG, and LDL levels were elevated in both first attack and relapse cases. Serum TC and TG remained persistently high in FRNS and SDNS.

Keywords: Nephrotic syndrome (NS), Hyperlipidemia, Lipid profile

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Introduction

Nephrotic syndrome (NS) is the most common kidney disease in children characterized by heavy proteinuria (>1gm/m^2/day or >40mg/m^2/hr), hypoalbuminemia (serum albumin <3 mg/dl), and generalized edema. Its incidence ranges from 1.15 to 16.9 per 100,000 children [1].

Idiopathic NS includes multiple histologic types, with minimal change disease (MCD) being the most common, accounting for 85% of total cases of NS. Other types include focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis [2].

In NS, there are various immune and non-immune insults to the podocyte that lead to foot process effacement, a decrease in the number of functional podocytes, and altered slit diaphragm integrity, which causes increased protein leakage through the glomerular capillary wall into the urinary space [3].

Idiopathic NS is classified into steroid-sensitive (SSNS) or steroid-resistant (SRNS) types, with the former further subdivided into infrequent relapsing (IFRNS), frequently relapsing (FRNS), and SDNS [2].

Hyperlipidemia in patients with NS probably results from increased lipoprotein production, secondary to hypoalbuminemia, along with reduced lipid breakdown due to decreased lipoprotein lipase activity [4]. In NS, elevated levels of triglycerides (TG), Apo B, Apo C, and Apo E, along with decreased levels of Apo A-I and Apo A-II, can be characteristic features of hyperlipoproteinemia. Compromised function of lipolytic enzymes, owing to renal excretion of HDL and other liporegulatory factors, results in reduced cholesterol and lower-density lipoprotein clearance [5].

The level of hyperlipidemia tends to correlate with the severity of hypoalbuminemia [6]. Recent studies have shown that NS may have prolonged periods of hyperlipidemia even after clinical remission. Persistent hyperlipidemia and severity of lipid changes correlate well with the duration of the disease and the frequency of relapses. Hyperlipidemia occurs while the patient has active NS, followed by normalization with correction of proteinuria; however, this abnormality may persist in cases of FRNS [7]. Hyperlipidemia persists during remission in both FRNS and SDNS groups [8]. Serum cholesterol levels serve as a predictor of relapse in childhood idiopathic NS [9]. Children with persistent hypertriglyceridemia during remission had a 5.4 times higher risk of relapse [10]. Elevated lipid levels, particularly serum cholesterol during the remission phase, are associated with subsequent relapse in idiopathic nephrotic syndrome. Conversely, low levels of cholesterol may serve as a protective factor against relapse [11].

In this disease, abnormalities of lipid metabolism may result in crucial systemic complications. Blood vessels become sclerosed, cardiac diseases occur, skeletal muscles and adipose tissue weaken, with renal vessels are also affected. Late renal complication includes chronic kidney disease (CKD). These children are prone to thromboembolic and cardiovascular problems [12]. Therefore, early evaluation and treatment of lipid abnormalities are important aspects of managing NS in children. This study aimed to assess the lipid profile of active NS as well as during remission among Bangladeshi children.

Methods

This prospective observational study was conducted at the Department of Paediatrics, Institute of Child and Mother Health (ICMH), Dhaka, Bangladesh, from July 2021 to June 2022. All children aged 1-18 years with NS who were admitted to the inpatient department during the one-year study period were enrolled. Children under 1 year and over 18 years of age, those with NS secondary to systemic disease, SRNS, those with a family history of hypercholesterolemia, a history of liver disease, a history of CKD, and those who refused to participate in the study were excluded.

The sample size was calculated using the Equations 1 and 2:

1. $n=z^2pq/d^2$

(n=the desired sample size, p=the frequency of hyperlipidemia among children in remission for idiopathic NS, which was 19%=0.19) [9].

2. $q=(1-p)$

z=5% level of significance or 95% confidence level, d=degree of accuracy or acceptable error, set at 10% (0.1). Therefore, a total of 60 children were included in this study.

A thorough history and clinical examination were conducted and recorded on a data collection sheet. Biochemical and other necessary investigations were performed to fulfill the inclusion criteria (serum albumin, serum creatinine, spot urine protein creatinine ratio, 24-hour urinary total protein). Baseline data for patients, including age, gender, age of first attack, and the number of attacks within the one-year study period, were recorded.

The following investigations were conducted to exclude NS due to other diseases, including secondary causes: ASO titre, serum C3, HBsAg, anti-HCV, and anti-ds DNA. Children with secondary causes of NS were excluded from the study.

An ethical clearance certificate was obtained from the institutional review board (IRB) of ICMH. Informed written consent was obtained from each legal guardian participating in the study.

Children with NS were divided based on the number of attacks and relapses. Group 1 comprised those with initial episodes, while Group 2 comprised relapse cases, which were further subdivided into IFRNS, FRNS, and SDNS.

After diagnosis, 5 ml of fasting venous blood (10-12 hours fasting) was drawn aseptically from the antecubital vein using a disposable syringe. Serum cholesterol levels were measured by the enzymatic calorimetric method. Serum TG levels were estimated using the GPO-PAP method. Serum LDL levels were estimated using the Friedewald formula/equation, and serum HDL and albumin levels were measured by the endpoint photometry method. All values were measured with the SELECTRA PRO M automated machine.

All children were treated with prednisolone according to the standard protocol: 60 mg/m²/day for 6 weeks, followed by 40 mg/m²/day every other day for another 6 weeks in the case of the initial attack. For IFRNS cases, 60 mg/m² daily was administered until urinary remission for 3 consecutive days, followed by 40 mg/m² on alternate days for 4 weeks, and then gradual tapering over 4-6 weeks. FRNS and SDNS were treated with oral prednisolone along with second-line drugs (levamisole, cyclophosphamide, and MMF). Cyclophosphamide was given for 3 months, while MMF or levamisole was administered for up to 2 years to maintain remission for a longer duration. Patients who failed to respond within 6 weeks of prednisolone therapy were excluded from the study.

The time required for the normalization of lipid profile during remission of NS is unspecified. Most researchers have followed up on the lipid profile after 4 weeks of urinary remission. Therefore, in our study, serum fasting lipid profiles were measured again after 4 weeks of achieving urinary remission and were compared with their previous values during the active phase.

Results

Among the 60 study subjects with NS, 18(30%) presented during their first attack, while the remaining 42(70%) presented during relapse. Among the latter group of 42 children, 14(23.3%) had IFRNS, 20(33.3%) had FRNS, and 8(13.3%) were steroid-dependent (Figure 1). Most participants (39, 65%) were under 5 years old, followed by the 5-10 years group (15, 25%) (Table 1). There were 37(61.7%) boys and 23(31.3%) girls, resulting in a male-to-female ratio of 1.6:1. Boys were predominant in all subgroups of NS in this study (Figure 2).

Table 1. Age group of the children with NS (n=60)

Age Group (y)	No. (%)/Mean±SD					P
	1st Attack (n=18)	IFRNS (n=14)	FRNS (n=20)	SDNS (n=8)	Total (n=60)	
1-5	15(83.3)	9(64.3)	11(55.0)	4(50.0)	39(65.0)	
5-10	2(11.1)	4(28.6)	6(30.0)	3(37.5)	15(25.0)	
>10	1(5.6)	1(7.1)	3(15.0)	1(12.5)	6(10.0)	0.063
Total	18(100.0)	14(100.0)	20(100.0)	8(100.0)	60(100.0)	
	3.73±2.44	5.01±2.53	6.15±3.33	6.06±2.96	5.15±2.97	

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Table 2. Groupwise lipid profile in active NS (n=60)

Lipid Profile	Mean±SD			
	1st Attack (n=18)	IFRNS (n=14)	FRNS (n=20)	Steroid-dependent (n=8)
TC (mg/dl)	384.6±98.4 (190-557)	399.1±94.1 (191-520)	564.5±109.1 (375-791)	470.3±116.4 (332-600)
HDL (mg/dl)	39.6±13.1 (10-59)	46.0±20.7 (10-90)	34.6±11.7 (21-54)	42.0±4.0 (35-47)
LDL (mg/dl)	168.8±41.4 (60-250)	174.3±55.6 (60-289)	273.5±158.6 (160-662)	200.4±46.3 (160-274)
TG (mg/dl)	275.5±134.2 (115-628)	323.6±132.1 (130-556)	425.9±179.9 (230-1138)	353.5±188.5 (187-628)

Groups	P of Post Hoc Test			
	TC (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	TG (mg/dl)
1st attack vs IFRNS	1.000	1.000	1.000	1.000
1st attack vs FRNS	<0.001*	1.000	0.018*	0.029*
1st attack vs SDNS	0.340	1.000	1.000	1.000
IFRNS vs FRNS	<0.001*	0.146	0.061	0.410
IFRNS vs steroid-dependent	0.760	1.000	1.000	1.000
FRNS vs steroid-dependent	0.203	1.000	0.547	1.000

FRNS: Frequently relapsing NS; IFRNS: Infrequent relapsing NS.

P: ANOVA among groups and the Bonferroni post hoc test between groups, *P<0.05.

Indicated accordingly Lipid profiles estimated the levels of total cholesterol (TC), low-density lipoprotein (LDL), TG, and high-density lipoprotein (HDL) in each attack and were compared accordingly. In active disease, TC levels were significantly higher in FRNS than in the first attack and IFRNS, respectively. LDL and TG levels were significantly higher in FRNS than in the first attack. During active disease, HDL levels showed no significant fluctuations (Table 2). In the remission stage of disease, TC and TG levels were significantly higher in FRNS than in the first attack and IFRNS. HDL as well as LDL showed no significant fluctuations (Table 3). The changes in lipid profiles during both the active stage and remission were further analyzed, revealing statistically significant elevations of TC, LDL, and TG in the active stage compared to remission. HDL was significantly higher in the remission stage only in FRNS (Table 4).

Lipid profiles were correlated with serum albumin levels accordingly and were depicted in the scatter plot. TC, LDL, and TG levels were negatively correlated with higher serum albumin levels, while HDL levels showed a positive correlation with higher serum albumin levels (Figures 3, 4, 5 and 6).

Discussion

NS is a common pediatric kidney disease characterized by a course of relapse and remission. Hyperlipidemia is a hallmark of NS. The mechanism of cholesterol distribution between plasma lipoproteins and the increased liver synthesis of lipoprotein lipids is not well understood. Various degrees of lipid profile alterations have been reported in the active stage of NS [13].

Table 3. Groupwise lipid profile in NS remission (n=60)

Lipid Profile	Mean±SD			
	First Attack (n=18)	IFRNS (n=14)	FRNS (n=20)	Steroid-dependent (n=8)
TC (mg/dl)	195.2±52.0 (115-290)	183.4±51.8 (115-318)	312.5±142.9 (127-600)	249.5±59.1 (140-318)
HDL (mg/dl)	42.7±13.9 (29-84)	43.5±13.9 (29-83)	47.6±23.1 (28-134)	42.9±9.7 (30-60)
LDL (mg/dl)	116.2±29.6 (56-180)	118.6±23.4 (81-160)	136.4±41.0 (56-185)	132.9±29.9 (80-160)
TG (mg/dl)	153.2±56.8 (73-296)	157.0±62.5 (67-290)	227.7±86.5 (132-421)	174.0±59.6 (100-300)

Groups	P of Bonferroni Post Hoc Test			
	TC (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	TG (mg/dl)
First attack vs IFRNS	1.000	1.000	1.000	1.000
First attack vs FRNS	0.002*	1.000	0.381	0.011*
First attack vs Steroid-dependent	1.000	1.000	1.000	1.000
IFRNS vs FRNS	0.001*	1.000	0.756	0.031*
IFRNS vs Steroid-dependent	0.707	1.000	1.000	1.000
FRNS vs Steroid-dependent	0.686	1.000	1.000	0.428

FRNS: Frequently relapsing NS; IFRNS: Infrequent relapsing NS.

P=ANOVA among groups and the Bonferroni post hoc test between groups.

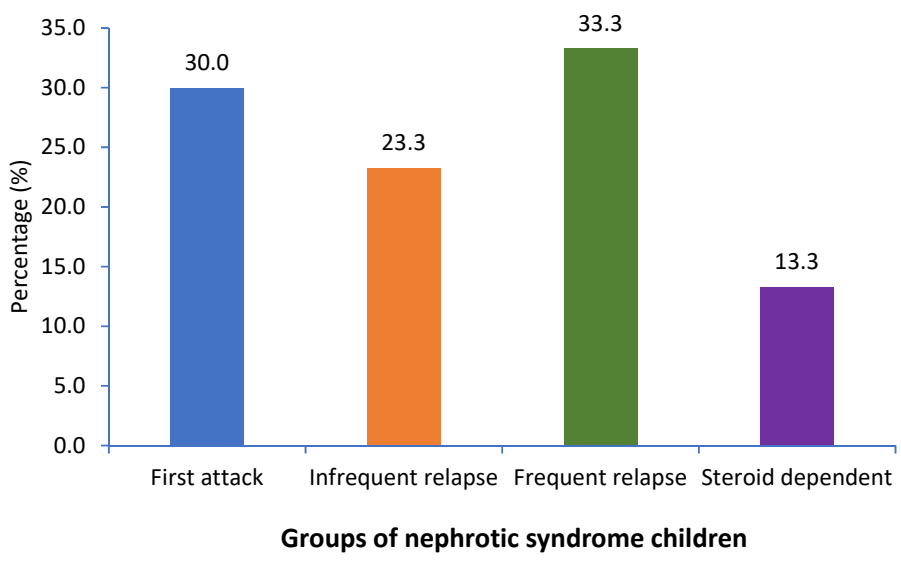

Figure 1. Different groups of children with NS

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Table 4. Groupwise comparison of lipid profiles in active NS and remission (n=60)

Lipid Profile		Mean±SD		P
		During Active Disease	During Remission	
TC (mg/dl)	1st attack	384.6±98.4	195.2±52.0	<0.001*
	IRNS	399.1±94.1	183.4±51.8	<0.001*
	FRNS	564.5±109.1	312.5±142.9	<0.001*
	Steroid-dependent	470.3±116.4	249.5±59.1	<0.001*
HDL (mg/dl)	1st attack	39.6±13.1	42.7±13.9	0.440
	IRNS	46.0±20.7	43.5±13.9	0.663
	FRNS	34.6±11.7	47.6±23.1	0.01*
	Steroid-dependent	42.0±4.0	42.9±9.7	0.838
LDL (mg/dl)	1st attack	168.8±41.4	116.2±29.6	0.004*
	IRNS	174.3±55.6	118.6±23.4	0.01*
	FRNS	273.5±158.6	136.4±41.0	<0.001*
	Steroid-dependent	200.4±46.3	132.9±29.9	0.023*
TG (mg/dl)	1st attack	275.5±134.2	153.2±56.8	<0.001*
	IRNS	323.6±132.1	157.0±62.5	0.002*
	FRNS	425.9±179.9	227.7±86.5	<0.001*
	Steroid-dependent	353.5±188.5	174.0±59.6	0.027*

FRNS: Frequently relapsing NS; IFRNS: Infrequent relapsing NS.

P=Paired t-test; *Significant.

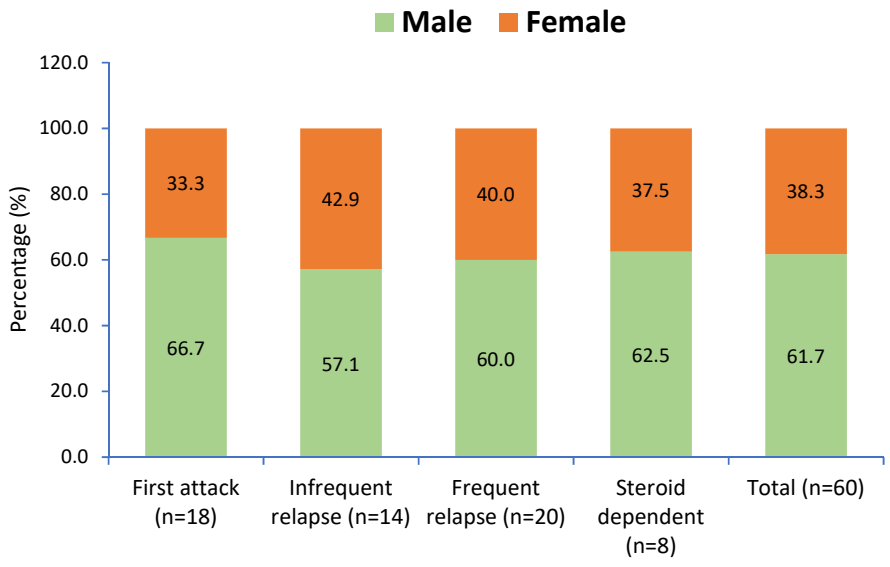

Figure 2. Gender distribution in NS subgroups

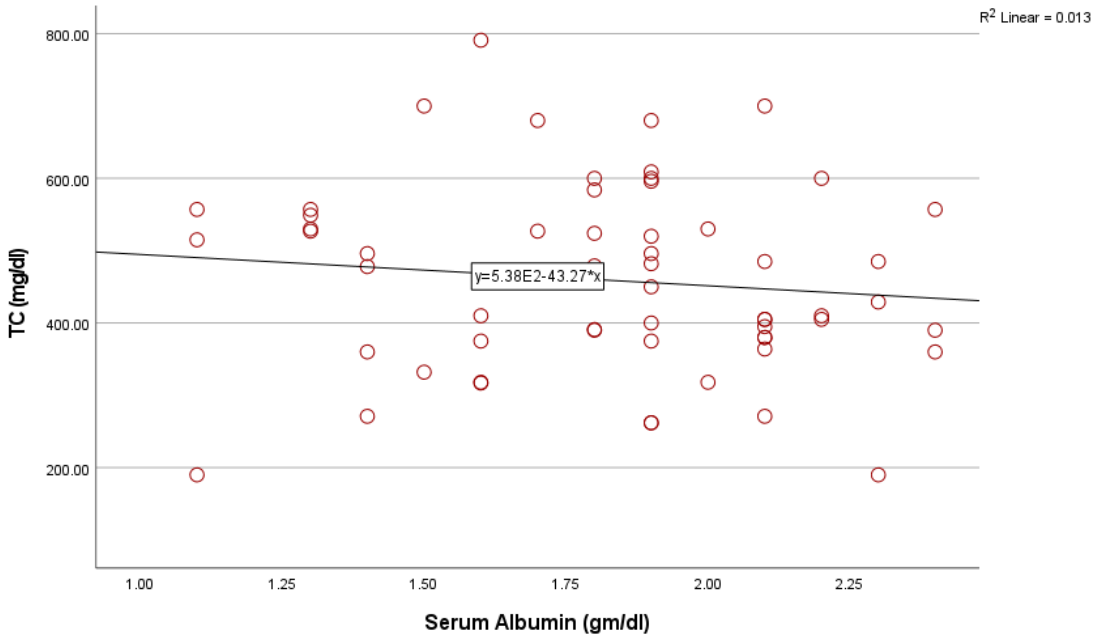

Figure 3. Correlation between TC levels and serum albumin levels

The current study observed a predominance of the 1-5 years of age group, with a male-to-female ratio of 1.6:1. In the study by Upadhyay et al. they found that the majority of subjects were male and between 1-5 years of age [14]. Bangalia et al. also showed that the majority of children were between 1-5 years, with males being predominant [15]. The study conducted by Kabir et al. also found male predominance, with the majority of them aged between 2-6 years [10].

The present study showed that TC levels were increased during active disease and were statistically significant among the four study groups of NS. There were also significant differences in TC between the first attack and FRNS, as well as between IFRNS and the FRNS

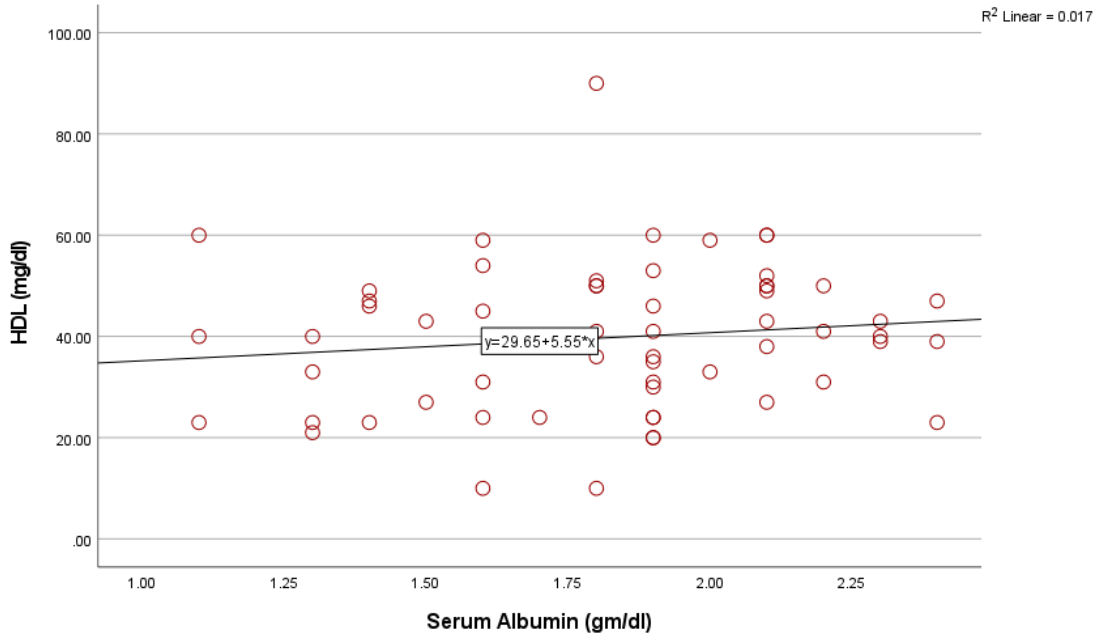

Figure 4. Correlation between HDL levels and serum albumin levels

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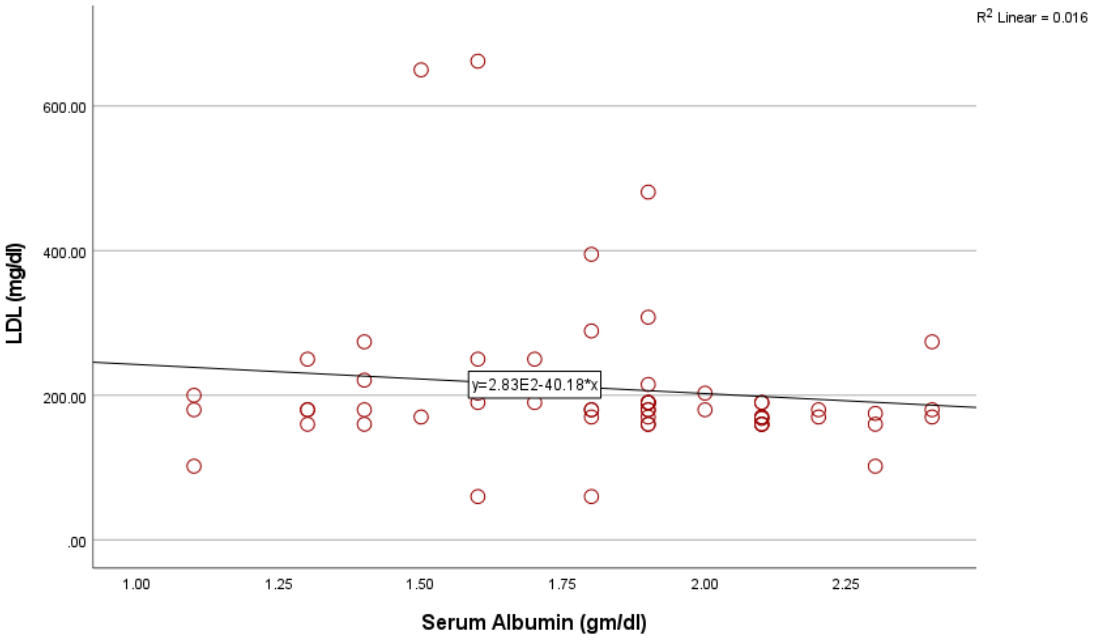

Figure 5. Correlation between LDL levels and serum albumin levels

group during active disease. A recent study conducted by Hoque et al. found that the mean serum cholesterol was elevated in all relapse groups during active disease, with significant differences observed between the IFRNS and FRNS groups, which was similar to the findings of the present study [8]. They also found a significant difference in TC between the IFRNS and SDNS groups; however, the present study showed no such significance. This discordance might be coincidental or due to the small sample size of this study.

The studies conducted by Bangalia et al. [15] and Kabir et al. found that the mean serum cholesterol levels were high in both the first attack and relapse cases during the acute phase, but it was significantly higher in relapse cases than in the first attack [10, 16]. We have observed

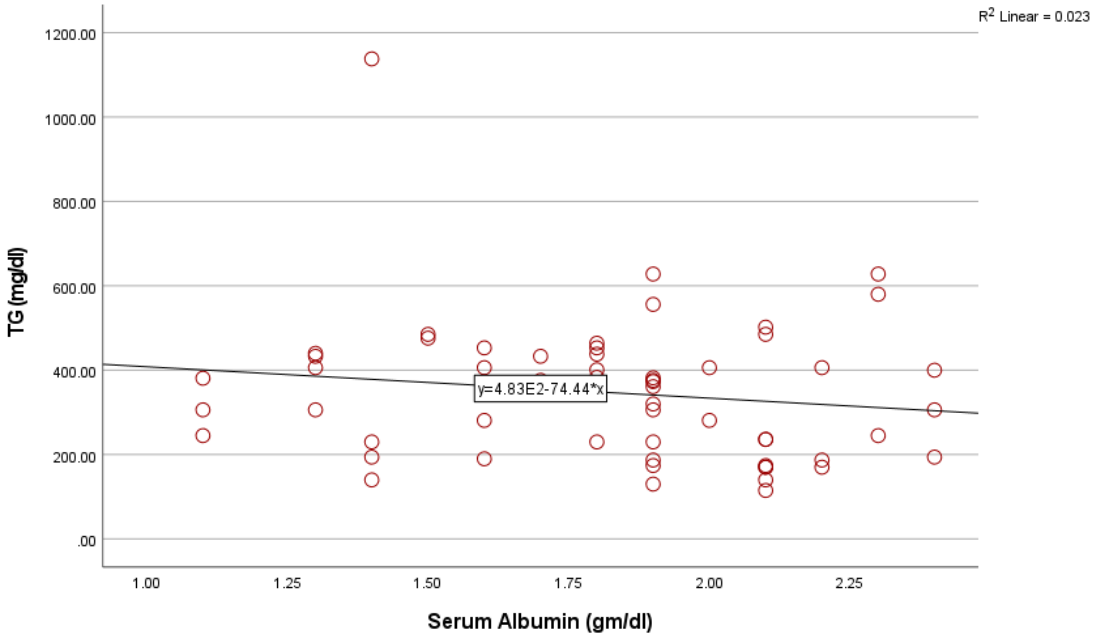

Figure 6. Correlation between TG levels and serum albumin levels

a significant elevation of LDL and TG levels in active NS, irrespective of the groups. Significant differences of LDL (P=0.018) and TG (P=0.029) levels were present between the first attack and FRNS during active disease.

Hoque et al. showed that LDL and TG levels were elevated in all three relapse groups during active disease, which had similarities to our study findings [8]. They found significant differences between IFRNS and FRNS, as well as between IFRNS and SDNS. However, the differences observed in our study were not statistically significant.

HDL levels were normal in each group during active NS, without any significant differences. Hoque et al. reported similar findings for HDL during active disease [8]. The current study showed that during remission, each study group had significantly reduced levels of TC, TG, and LDL compared to the active disease state. We found a significant increase in HDL levels during remission only in the FRNS group. Hoque et al. also found a significant reduction in TC, LDL, and TG levels between active disease and remission [8]. They also reported significant differences in HDL levels between the FRNS and SDNS groups, whereas our study showed a significant increase in HDL only in the FRNS group. Kabir et al. revealed results that are consistent with the above studies [10].

The current study demonstrated that TC levels approached the normal range following a month of remission in both the first attack (195.2±52.0 mg/dl) and IFRNS (183.4±51.8 mg/dl). However, it remained persistently elevated in the FRNS (312.5±142.9 mg/dl) and SDNS (249.5±59.1 mg/dl) groups. The FRNS group showed statistically significant differences in TC compared to the first attack and IFRNS groups during remission. The mean LDL levels became normal in all groups during remission. Serum TG levels remained persistently elevated following remission. Significant differences were observed between the first attack and FRNS and between IFRNS and FRNS after remission. Hoque et al. found increased TG and LDL levels even after a month of remission [8]. Our research findings are consistent with their findings, except concerning the LDL levels.

HDL levels were normal in remission in each study group, and no significant differences were found between any groups. Hoque et al. also showed that HDL levels were normal in remission , which is similar to our findings [8].

This study showed an inverse correlation between the serum TC, TG, and LDL levels and serum albumin levels . HDL was positively correlated with serum albumin levels, but this correlation was not statistically significant. Hoque et al. found that serum TC, TG, and LDL levels were inversely correlated with serum albumin levels, which is similar to our findings [8].

Conclusion

During the active stage of childhood NS, serum TC, LDL, and TG were elevated in both first attack and relapse cases. TC and TG levels remained persistently high in the FRNS and SDNS groups of children with NS, even after remission. LDL levels became normal during remission, and HDL levels remained normal throughout the disease.

Limitations

Conducted at a single center, the study included a relatively smaller sample size. The sample was not compared with healthy subjects either. Further multicenter studies with larger sample sizes and long-term follow-up are recommended to validate the findings of the present study.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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