Original Article

Serum lipid profile among pediatric folk with idiopathic nephrotic syndrome: An Observational Study

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Abstract

Introduction: The most familiar kidney disease in children is nephrotic syndrome (NS), associated with dyslipidemia and causes various cardiovascular complications. Persistent hyperlipidemia can further raise difficulties of NS and relapse cases. Earlier diagnosis and appropriate intervention increase the possibility of saving other vital organs. ***Methods:*** An observational study was conducted with 85 children aged 2-15 years with a history of NS. The study group was divided into first NS and second-episode relapse cases. They were further sub-grouped into Frequent Relapse NS (FRNS) and Infrequent Relapse NS (IFRNS). Fasting lipid profiles were performed among active sufferers with a follow-up after 4 weeks. ***Results:*** The male-to-female ratio was 1.93:1. In the first episode of NS, all lipid parameters were high in the acute phase and returned to normal during remission. In relapse cases, lipid parameters were significantly higher even in remission. Serum triglyceride and very low-density lipoprotein were significantly more elevated in the FRNS group than in the IFRNS. Low-density lipoprotein was increased considerably in FRNS. Mean high-density lipoprotein was also significantly lower in the FRNS group than in the IFRNS. ***Conclusion:*** Persistent hyperlipidemia is most typical among FRNS. Hyperlipidemia management is urgent to prevent among pediatric NS.

Keywords: Hyperlipidemia, Frequent Relapse Nephrotic Syndrome, Infrequent Relapse Nephrotic Syndrome, Dyslipidemia

Introduction

NS in children and adults is the most prevalent kidney disease, showing edema, hypoalbuminemia, and massive proteinuria [1]. Clinical findings of NS consist of a triad of hypoalbuminemia (<2.5gm/dl), edema, and hyperlipidemia (cholesterol>200mg/dl) [2].

The incidence of Idiopathic NS is 1.15-16.9 per 100000 children, varying by ethnicity and region [3]. It is mainly a pediatric disease that is fifteen times more frequent in children than adults [4]. In Asian children, the prevalence of idiopathic NS is six times more than in European children [5]. The frequency of this disease is higher in males than in females, with a ratio of 2:1,

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and mainly appears in the age range of 2- 6 years.

NS can be idiopathic or originate due to diverse secondary causes or genetic causes involving genes like nephrotic syndrome by gene 1 (NPHS1) and nephrotic syndrome by gene 2 (NPHS2) [6]. The pathogenesis of Idiopathic NS is yet unknown. Still, evidence indicates that the immune system (T cell & B cell) plays a crucial pathogenic role in non-genetic Idiopathic NS [7]. In primary or Idiopathic Nephrotic syndrome, the specific cause remains unidentified. However, the involvement of proteins such as phospholipase A2 receptor, thrombospondin type-1 domain containing 7A, apolipoprotein 1, and soluble urokinase-type plasminogen activator receptor has been recently identified [8]. Causes of Idiopathic NS include minimal change disease (85%), mesangial proliferation [5%], and focal segmental glomerulosclerosis (10%). Idiopathic NS may be steroid-sensitive or steroid-resistant. FRNS, IFRNS, and steroid-dependent NS (SDNS) are the division of steroid-sensitive NS (SSNS) based on the response of steroids. About eighty to ninety percent of children who are steroid sensitive with nephrotic syndrome, and the cause is idiopathic, while the rest, 10-20%, are steroid-resistant [8].

Hyperlipidemia is a common complication of NS. Increased hepatic lipogenesis, the falling of oncotic pressure secondary to hypoalbuminemia giving rise to non-specific reactions, can probably be the reason for hyperlipidemia in patients with NS [9] (Figure 1). Dysregulated lipid metabolism leading to dyslipidemia is also seen in NS. These abnormalities include increased plasma cholesterol levels, triglycerides, and apolipoprotein B containing lipoproteins very low-density lipoprotein (VLDL) and Intermediate-density lipoprotein (IDL); decreased lipoprotein lipase activity in the endothelium, muscle, and adipose tissues; decreased hepatic lipase activity; and increased levels of enzyme preprotein convertase subtilisin kexin type 9 (PCSK9) [10].

The cause of nephrotic hyperlipidemia and dyslipidemia is multi-factorial, and its mechanism is very complex. The abnormalities of serum lipids and lipoproteins in NS are primarily due to their impaired clearance and, to a lesser content, their altered biosynthesis [11]. NS results in increased expression of the critical enzymes involved in fatty acid biosynthesis and downregulation of genes encoding proteins involved in fatty acid catabolism in the liver [12]. New research has found two major
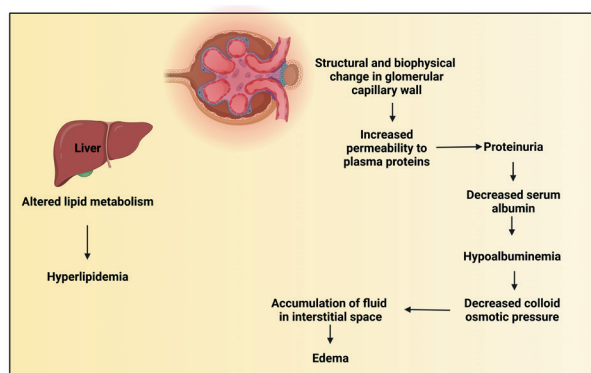
Figure 1: Pathophysiology of nephrotic syndrome. This figure has been drawn utilizing the premium version of BioRender with the License number (JC25IWMQT6). **Image Credit**: Susmita Sinha.

post-translational regulators of Low-density lipoprotein (LDL) Receptors that play a critical role in LDL metabolism are PCSK9 [8] and the inducible degrader of the LDL receptor (IDOL). Upregulation of these two leads to impaired clearance and a rise in LDL levels. Altered lipid metabolism leading to dyslipidemia is often an under-recognized but common complication of relapsing NS. So, lipid profile assessment is crucial in children suffering from NS. Persistent hyperlipidemia can lead to a relapse of NS [13].

Patients showing remarkable variance in high-density lipoprotein (HDL), cholesterol, LDL, triglyceride, and LDL/HDL ratio between their acute and remission phases of NS suffer from relapse of NS, which is about 40% of the patient, according to one earlier research report [13]. Hyperlipidaemia has been associated with an increased risk of accelerated cardiovascular and progressive kidney disease. High serum lipid levels may damage the kidney directly or indirectly. Dyslipidaemia is a significant risk factor for atherothrombotic diseases in children suffering from NS. Dyslipidaemia during NS is also clearly associated with an increased risk of nephrotoxicity, which can manifest as progressive kidney disease [14]. The current study aims to see the difference in lipid parameters in the acute phase of the illness and during remission.

Materials and Methods

This observational study was carried out over 12 months, from June 2021 to May 2022, in the Department of Paediatrics, Rajendra Institute of Medical Sciences (RIMS). Inclusion criteria in this study include 85 children, incorporating both sexes

and ages ranging from 2-15 years, presenting with minimal characteristics like decreased urine output and generalized edema starting from facial puffiness and urine protein 3+ or more (Figure 2). Children with features of secondary nephrotic syndrome, steroid-resistant nephrotic syndrome, and chronic kidney disease and those who were not willing to participate were excluded from the study. Patients previously diagnosed with NS at our hospital, with relapse, were also included. The Institutional Ethics Committee approved this study, Rajendra Institute Medical Sciences, with Reference No.: IEC- 177, Dated March 20, 2021. Detailed information was given regarding the disease's nature, course, and prognosis. Written informed consent was taken from the parents before the sample collection. One principal investigator carried out the study groups' detailed history in the current investigation. Another Investigator was blinded about the study, which carried out clinical parameters of all the study groups. So, to avoid double-blind, the data gathering cannot be biased.

Diseases that are associated with massive proteinuria (urinary total protein >1 gm/m^2/24 hr), generalized edema, hypoalbuminemia (Albumin<2.5gm/dl), and hyperlipidemia (Cholesterol>200mg/dl) can be defined as NS [15]. Remission of NS was defined as children with urine protein: creatinine ratio <0.2 or <+1 protein on urine dipstick testing for three consecutive days.

Once the patient was admitted, a detailed history and clinical examination were done. Two (2) ml of blood was collected in a red vacutainer fasting at the time of presentation and after 4 weeks of follow-up. All patients were advised not to take fatty meals 1 day before sample collection. The blood sample was analyzed on the same day in the RIMS biochemistry department using the ABBOTT ARCHITECT Chemistry Analyser. The lipid profile was measured:- cholesterol by the CHOD-POD method, triglyceride using the GPO-PAP method, HDL by enzyme colorimetric method, and LDL & VLDL were calculated using the Fredrickson-Freidwald formula. Lipid profile was observed at the time of admission in the hospital and again after 4 weeks in follow-up. Patients were treated per protocol after blood sample collection during the acute phase.

As per Kidney Disease Improving Global Outcomes (KDIGO) protocol [16], in terms of the first episode, divided doses of prednisolone- 60mg/m2/day were given daily for 6 weeks, and 40mg/m2/day was given

for another 6 weeks at every alternate day. Regarding relapse, divided doses of prednisolone 60mg/m2/day were given until the patient entered the remission phase. After that, 40mg/m2/day was given for the next 4 weeks on every alternate day. A child who has attained remission previously and has massive proteinuria for three successive days can be defined as a case of replase. All data were entered using Microsoft Excel and analyzed using the IBM SPSS Statistics version 20 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). The parametric data were presented as Mean±Standard Deviation. The student's (paired) t-test and Levene's test were used to compare the mean difference between the two groups. All statistical analysis was carried out with a 5% significance level, and $p<0.05$ was considered significant.
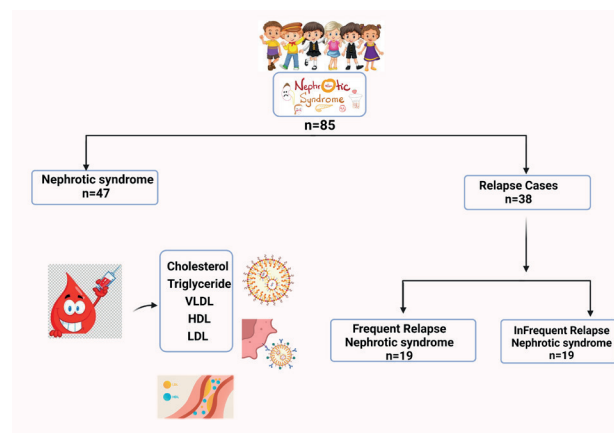
Figure 2: A Flow Chart Illustrating the Study Group. This figure has been drawn utilizing the premium version of BioRender with the License number (HI25DU13KK). **Image Credit**: Shreya Gajjar.

Statistical Methods

A multivariate regression model was employed to examine the mean differences in lipids between the first and second relapse episodes within the acute and remission phases. As lipids were assessed at two-time points during the acute phase and after remission, an autocorrelation was observed between the responses of each patient. To address this autocorrelation and investigate the effects of the relapse episode compared to the first episode on serum lipids over time, a generalized estimating equation (GEE) model was utilized, considering an exchangeable correlation matrix. To minimize confounding effects, the model was adjusted for age, sex, and time (two follow-ups). Observations were lower in the subgroup analysis of the

IFRNS and FRNS groups within the remission group.

Consequently, repeated measures ANOVA was employed to assess the longitudinal changes in lipids in these groups, adjusting for age and sex in the model. The statistical analysis was conducted using STATA-15, and the graph was generated using GraphPad Prism 8.3.2. A significance level of $p<0.05$ was considered statistically significant.

Table 1: Mean difference of serum lipid in first and relapse episode cases at the acute and remission phases.

	Acute phase (n=85)		Remission phase (n=85)	
	The first episode (n=47)	Relapse (n=38)	The first episode (n=47)	Relapse (n=38)
Cholesterol,	295.4±53.0	414.3±99.6	149.8±18.0	318.1±81.6
TG	341.9±96.2	342.0±164.8	98.4±27.8	264.9±131.3
VLDL	68.4±19.2	68.4±33.0	19.7±5.52	53.0±26.2
LDL	178.5±57.5	206.6±71.5	74.8±21.7	122.7±56.1
HDL	48.5±9.50	40.8±11.1	55.4±10.4	47.4±11.3

Notes: Data was presented as mean±SD. The multivariate regression model was used to estimate the p-value, and the model was adjusted by age and sex. Notes: Milligrams per deciliter (mg/dL), Millimoles per liter (mmol/L).
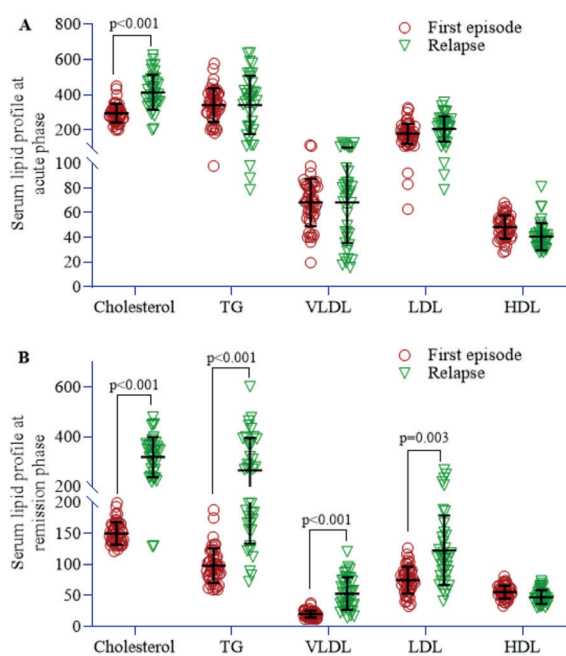
Figure 3: Mean difference of serum lipid in first and relapse episode cases at the acute and remission phases. The multivariate regression model was used to estimate the p-value, and the regression model was adjusted by age and sex.

Table 1 presents the mean difference in serum lipid levels between cases experiencing the first episode and relapse during the acute and remission phases. In the acute phase, there were 85 participants, with 47 experiencing the first episode and 38 relapses. Comparing the lipid levels, participants with relapse had significantly ($p<0.001$) higher mean cholesterol (414.3±99.6) levels compared to those with the first episode (295.4±53.0). However, in the remission phase, both groups showed a significant decrease in cholesterol and LDL levels, with the first episode group having a mean cholesterol of 149.8±18.0 and LDL of 74.8±21.7. In contrast, the relapse group had a mean cholesterol of 318.1±81.6 and LDL of 122.7±56.1. Triglyceride (TG) levels remained similar between the two groups throughout both phases, but in the remission phase, a significantly higher TG was noted in the relapse episode ($p<0.001$). During the acute phase, participants with a relapse had lower mean HDL levels (40.8±11.1) than those with the first episode (48.5±9.50). Still, both groups showed a significant increase in HDL levels during the remission phase, with the first episode group having a mean HDL of 55.4±10.4 and the relapse group having a mean HDL of 47.4±11.3 (Table 1 and Figure 3).

Analysis by GEE method exhibited an overall significant increase in cholesterol (β=140.7; 95% CI=109.6, 171.8, $p<0.001$, in TG (β=67.8; 95%=21.4, 114.1, p=0.004), in VLDL (β=13.5; 95% CI=4.26, 22.8, p=0.004) and LDL (β=27.5; 95% CI=4.95, 50.0, p=0.017), from acute and remission phases (Table 2).

Table 2: Longitudinal changes in serum lipids in the relapse episode compared to the first.

Relapse episode	β Coff (95% CI)	p-value
Cholesterol	140.7(109.6, 171.8)	<0.001
TG	67.8(21.4, 114.1)	0.004
VLDL	13.5(4.26, 22.8)	0.004
LDL	27.5(4.95, 50.0)	0.017
HDL	-3.79(-8.41, 0.84)	0.108

Notes: Milligrams per deciliter (mg/dL), Millimoles per liter (mmol/L).

The generalized estimating equation (GEE) model was performed, considering an exchangeable correlation matrix to estimate the p-value. To minimize the confounding effects, the model was adjusted by age, sex, and time (2 follow-ups).

During the acute phases, the serum LDL levels were notably elevated in the FRNS group compared to the IFRNS group (p<0.001), and this difference continued to be significant during the remission phase (p<0.001) (Figure 4). In the remission phase, the FRNS group exhibited higher levels of TG (p=0.033) and VLDL (p=0.033) compared to the IFRNS group among the subgroup of participants experiencing a relapse.
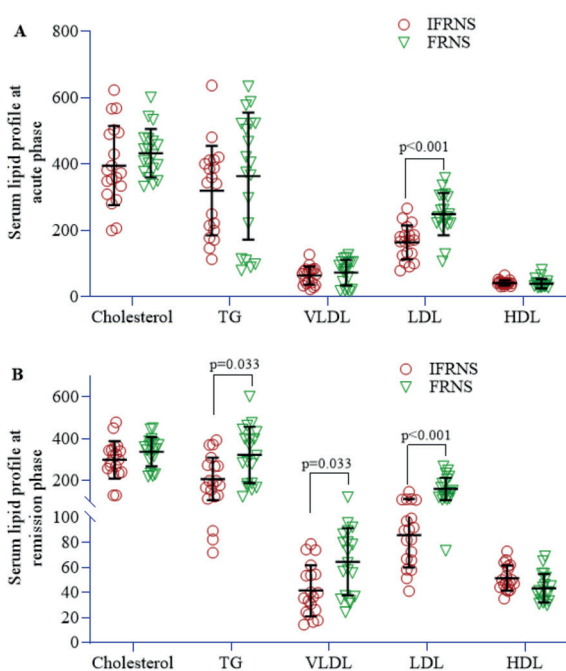
Figure 4: Mean difference of serum lipid in sub-group of relapse episode of IFRNS and FRNS group. The multivariate regression model was used to estimate the p-value, and the regression model was adjusted by age and sex.

The repeated measures ANOVA was used to analyze the subgroup differences between the IFRNS and FRNS groups. Cholesterol, TG, and VLDL declined throughout the acute and remission phases. However, only LDL exhibited a significant longitudinal decrease in the IFRNS group compared to the FRNS group (β=-78.9; 95% CI=-108.7, -49.1, p<0.001) (Table 3). Repeated measured analysis of covariance (ANOVA) was used to estimate the p-value, and the regression model was adjusted by age and sex.

**Table 3**: Longitudinal changes in serum lipids in the IFRNS group compared to the FRNS group.

IFRNS	β Coff(95% CI)	p-value
Cholesterol	-35.8(-97.2, 25.7)	0.245
TG	-68.8(-156.0, 18.3)	0.118
VLDL	-13.7(-31.2, 3.71)	0.119
LDL	-78.9(-108.7, -49.1)	<0.001
HDL	4.74(-2.73, 12.2)	0.206

Notes: Milligrams per deciliter (mg/dL), Millimoles per liter (mmol/L).

Discussion

The present study assessed the lipid profile and determined the lipid parameter pattern during presentation and remission. The current study showed a male predominance with a male-to-female ratio of 1.9:1. De La Torre *et al*., 2021 also observed male predominance in their research [17]. The rationale for our finding may be due to a more rapid disease progression in male children. It may also be due to a higher chance of deterioration in renal function and increased glomerular sclerosis in men compared to women due to some gender-related factors [18]. In this study, the mean age was 6.3 ± 2.8 years. The maximum number of patients was in the age group between 4-8 years. Carter *et al*., 2019 reported more patients between the 2-4 years of age group [19].

Our study showed that participants with relapse had significantly (p<0.001) higher mean cholesterol (414.3±99.6) levels compared to those with the first episode (295.4±53.0). However, both groups showed significantly decreased cholesterol levels in the remission phase. Simachew *et al*., 2022, [20] and Li *et al*., 2023 [21] also observed similar results. The present study showed normal serum cholesterol in remission in first-episode cases and persistently elevated cholesterol levels in relapse cases. Sreenivasa *et al*., 2016, [22] and Kabir *et al*., 2020 [23] observed the same. Vaziri *et al*., 2016 revealed elevated cholesterol levels even after the remission of the disease, which was contrary to our study [24]**.** Hilmanto *et al*., 2022 demonstrated that many children with MCNS during prolonged remission had elevated serum total cholesterol concentrations (Figure 5) [25]. This can be related to Increased liver synthesis of lipoproteins as the secondary event to hypoalbuminemia.
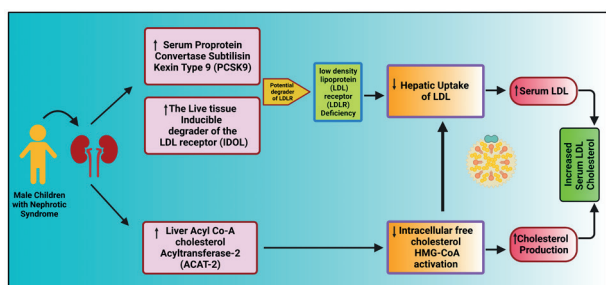
Figure 5: Chart diagram showing altered lipid metabolism results in elevated serum total cholesterol. This figure has been drawn utilizing the premium version of BioRender with the License number (ZQ25FDL88C). **Image Credit**: Susmita Sinha.

Serum triglyceride (TG) levels remained similar between the two groups throughout both phases, but in the remission phase, a significantly higher TG was noted in the relapse episode (p<0.001). Ohta and Matsuda., 1981 observed that some patients were normo-triglyceridemic, but others showed a moderate hyper-triglyceridemic picture, although not uniformly expressed [26]. Serum triglyceride level was persistently raised in relapse cases, even during remission, similar to others [22, 25]. Adu, 2013 also found elevated triglyceride during active disease and remained raised after remission of disease (P<0.05) [27].

VLDL also remained elevated in the remission phase of relapse cases. Multiple studies observed similar results [9, 10, 28]. Low-density lipoprotein (LDL) levels, with the first episode group having a mean cholesterol of 149.8±18.0 and LDL of 74.8±21.7, while the relapse group had a mean cholesterol of 318.1±81.6 and LDL of 122.7±56.1. LDL was significantly elevated during active disease among the acute phase of the first episode and relapse cases. The same was observed by Gencer *et al*., 2020 [29], and LDL remained raised even after one month, similar to the results reported by others [22].

The current study showed the participants with a relapse had lower mean HDL levels (40.8±11.1) compared to those with the first episode (48.5±9.50) during the acute phase. Still, both groups showed a significant increase in HDL levels during the remission phase, with the first episode group having a mean HDL of 55.4±10.4 and the relapse group having a mean HDL of 47.4±11.3. Upadhyay *et al*., 2018 have a similar finding [30]. Mahmud *et al*., 2011 found HDL was increased in the remission phase of first-episode cases [28]. Alexander *et al*., 1974 found that HDL was low in NS [31], and Appel *et al*., 1985 [32],

and He *et al*., 2017 observed normal levels of HDL during active disease and remission of the disease [11].

Hypercholesterolemia was observed in both FRNS & IFRNS cases, but the difference between these groups was not statistically significant. Mahmud *et al*., 2011 observed that children with frequently relapsing NS have prolonged periods of hypercholesterolemia and concluded that serum cholesterol might be regarded as a predictor of relapse in childhood idiopathic NS [28]. Hoque *et al*., 2022 observed that cholesterol returned to normal in the remission phase of FRNS [33].

In this study, a high level of triglyceride and VLDL was found in both FRNS & IFRNS groups in acute and remission phases. Still, mean values are higher in the FRNS group than the other, and they differ in these two groups significantly (p<0.001) (Figure 6). Other earlier studies showed similar findings [33-35]. LDL was found to be high in the acute phase in both FRNS & IFRNS, but in the remission phase, it was found to be lower in IFRNS than FRNS, and it was statistically significant between these two groups (p<0.001). Similar findings were revealed by earlier research [33].

Figure 6: Chart comparing findings between FRNS and IFRNS groups. This figure has been drawn utilizing the premium version of BioRender with the License number (WK25IUNWG7). **Image Credit**: Susmita Sinha.

In this study, HDL was found within the standard limit but had a higher mean value in the IFRNS group than FRNS both in the acute and remission phases. It was statistically significant between the groups (p<0.025). Hoque *et al.,* 2022 found raised HDL levels in FRNS cases that were unlike our result [33]. Mahmud *et al*., 2011 concluded that increased serum cholesterol levels during the remission phase might be associated with subsequent relapse in NS, and total serum cholesterol may be regarded as a predictor of relapse in childhood Idiopathic NS [28]. Kabir *et al*., 2020 reported that only the triglyceride level during remission was a risk factor in relapsing NS [23].

Limitations of the study

The sample size is small. We planned another randomized control multi-center clinical trial with larger sample sizes over a longer duration to generalize study results for India.

Conclusion

It is concluded that high serum lipid levels were associated with childhood idiopathic NS during the acute phase of the illness. Triglyceride, serum cholesterol, LDL, and VLDL were found to be increasingly high in the active state of disease and returned to normal during remission in newly diagnosed NS. In both acute and remission phases, serum triglyceride, LDL, and VLDL were more elevated in FRNS than in IFRNS. So, children with frequently relapsing NS need to be followed up at regular intervals for the development of complications due to hyperlipidemia in the future. HDL stayed standard in both of its phases - acute and remission.

Conflict of Interest

The authors declare no conflicting interest.

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Data Availability

This is an original paper. All data are available for only research purposes from principal investigators.

Authors' Contribution

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the essay has been submitted; and agree to be accountable for all aspects of the work.

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