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Original Article

High Sensitivity C-Reactive Protein (Hscrp) Level And Its Association with Hyperlipidemia in Children with Nephrotic Syndrome

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ABSTRACT

Background: *Hyperlipidemia is one of the important characteristics of nephrotic syndrome (NS) and it is responsible for atherosclerotic changes which can be due to vascular endothelial dysfunction that reflect the inflammatory response to tissue damage. Hyperlipidemia in childhood can induces atheroma formation among susceptible individual.* ***Methods and materials:*** *This cross-sectional analytical study was conducted in the Department of Pediatric Nephrology, National Institute of Kidney Diseases & Urology, Sher-E-Bangla Nagar, Dhaka and Department of Biochemistry, Dhaka Shishu Hospital, Dhaka, from December 2019 to June 2021. Data were collected by using a structured questionnaire. Collected data were analyzed by the SPSS 24.* ***Results:*** *Average age of all study children was 6.44±3.29 years (range: 2 - 12 years) with male predominance in both group A and group B (63.33 and 60%, respectively). Minimal change disease (MCD) was found in majority cases of group A (91.67%).*

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Nephrotic children had significantly higher mean of total cholesterol, triglyceride, LDL, VLDL, and HDL compared to healthy children. The mean±SD (median) of serum hsCRP were higher in nephrotic children than healthy children [2.13±1.70, (1.50) vs 0.86±0.55, (0.60) mg/L, P < 0.001]. Pearson correlation analysis showed that serum hsCRP had significant moderate positive correlation with total cholesterol and LDL, weak positive correlation with triglyceride and VLDL among nephrotic children (p value <0.05). ***Conclusion:*** *Serum hsCRP was found to be higher in NS children and positively correlated with hyperlipidemia. However, further studies are needed to validate these findings.*

Keywords: *hsCRP, Nephrotic Syndrome, Hyperlipidemia*

INTRODUCTION

Nephrotic syndrome (NS) is the most common childhood kidney disease, characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia [1]. The incidence of idiopathic nephrotic syndrome (INS) is estimated to be 1.15 to 16.9 per 100,000 children, with variations observed across different ethnicities and regions [2]. Notably, South Asian children have the highest incidence [3]. The disease presents various complications, including infections, thromboembolism, cardiovascular diseases, hypovolemic crisis, anemia, and acute renal failure [4]. Thromboembolism is a significant early complication of nephrotic syndrome, affecting approximately 3% of children [5]. The risk of thromboembolism is particularly elevated among children with membranous nephropathy and membranoproliferative glomerulonephritis [6]. Notably, the occurrence of deep vein thrombosis (DVT) among nephrotic children is associated with triglyceride levels greater than 300 mg/dL [7]. Dyslipidemia, a common and often under-treated complication of nephrotic syndrome, can persist even during remission, with nearly half of the nephrotic syndrome patients experiencing sustained hyperlipidemia [8]. The severity and persistence of lipid changes in NS are associated with the disease's duration and frequency of relapses. The underlying pathology of nephrotic hyperlipidemia is complex and multifactorial. Increased cholesterol synthesis in response to hypoalbuminemia is observed in the liver, leading to increased albumin synthesis [9]. Additionally, the loss of urinary proteins, lipoproteins, or other lipo-regulatory substances stimulates hepatic lipid synthesis [10]. Dyslipidemia in childhood can lead to atheroma formation, especially among susceptible individuals, and is a significant risk factor for atherosclerosis and cardiovascular diseases. Atherosclerosis, in turn, can promote the development of cardiovascular diseases and is accompanied by hyper-reactive platelets, increasing the risk of thrombosis. Oxidized low-density lipoprotein (ox-LDL) is considered a crucial atherogenic factor, causing damage to endothelial and smooth muscle cells [11]. Active INS is associated with impaired vascular endothelial function, contributing to atherosclerosis and platelet aggregation [12]. In addition to hyperlipidemia, other risk factors for atherosclerosis-induced vascular damage in NS patients include endothelial dysfunction, hypertension, elevated oxidant stress, insulin resistance, and immunosuppressive therapy. Inflammatory markers are commonly used to assess the progression of the atherosclerotic process. High-sensitivity C-reactive protein (hs-CRP) is a well-

established inflammation marker produced in the liver. Monitoring Hs-CRP levels can help identify the presence of subclinical inflammation and indicate cardiovascular risk. Notably, Hs-CRP levels below 1 mg/L indicate low risk, 1-3 mg/L indicate average risk, and 3-10 mg/L indicate high cardiovascular risk [13]. The measurement of Hs-CRP has been recommended by the American Heart Association (AHA) and the European Society of Arterial Hypertension as an indicator of vascular damage [14]. In light of these considerations, our study aims to assess serum Hs-CRP levels in children with nephrotic syndrome and investigate its association with lipid profiles. The measurement of Hs-CRP in these children may serve as a valuable screening tool to identify individuals at risk of developing atherosclerosis and associated cardiovascular consequences. Early detection and implementation of preventive measures can be crucial in mitigating the long-term cardiovascular risks in these patients. However, the study aimed to investigate the association between high-sensitivity C-reactive protein (Hs-CRP) levels and lipid profiles in pediatric nephrotic syndrome

METHODS & MATERIALS

This cross-sectional study was conducted at the Department of Paediatric Nephrology, National Institute of Kidney Diseases & Urology, Sher-E-Bangla Nagar, Dhaka, and the Department of Biochemistry and Molecular Biology, Dhaka Shishu Hospital, Dhaka, between December 2019 and June 2021. The study population included 60 children with nephrotic syndrome (Group A) and 60 age-matched healthy children (Group B) as controls. The purposive sampling method was used in this study. After obtaining informed written consent and ethical clearance, detailed history, clinical examination, and relevant investigations were performed on the participants. Blood samples were collected from fasting subjects, and serum was separated for subsequent estimation of high-sensitivity C-reactive protein (hs-CRP) and lipid levels. Hs-CRP was measured by immunofluorescence assay, while serum total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured by enzymatic methods. Statistical analysis was conducted using SPSS 24, with a significance set at a p-value of <0.05. The study ensured ethical considerations, confidentiality, and the participant's right to withdraw from the study. The manuscript presents the association between Hs-CRP and lipid profile in children with nephrotic syndrome compared to healthy controls, providing valuable insights into the vascular inflammation in this patient group.

Inclusion criteria:

- Group A: Children with nephrotic syndrome aged between 2-12 years, having no sign of acute infection, no hypertension and hyperglycemia.
- Group B: age matched healthy children not having signs of acute infection, no hypertension and hyperglycemia.

Exclusion criteria: -

- Children with aged <2years and >12 years (atypical presentation of NS)
- Nephrotic syndrome due to secondary causes.

RESULTS

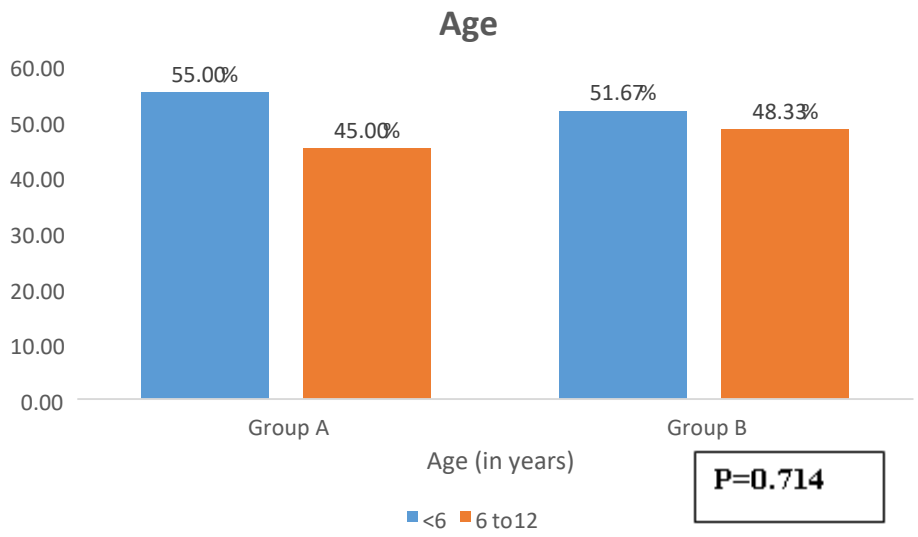

Figure 1: Distribution of study children according to Age (n=120).

The mean age of all study children was 6.44±3.29 years (range: 2-12 years). The highest percentage of patients from both group-A and group B were aged less than 6 years (55% and 51.67% respectively). However, there were no significant differences between the two groups of children regarding both mean age and age group distribution (p value >0.05).

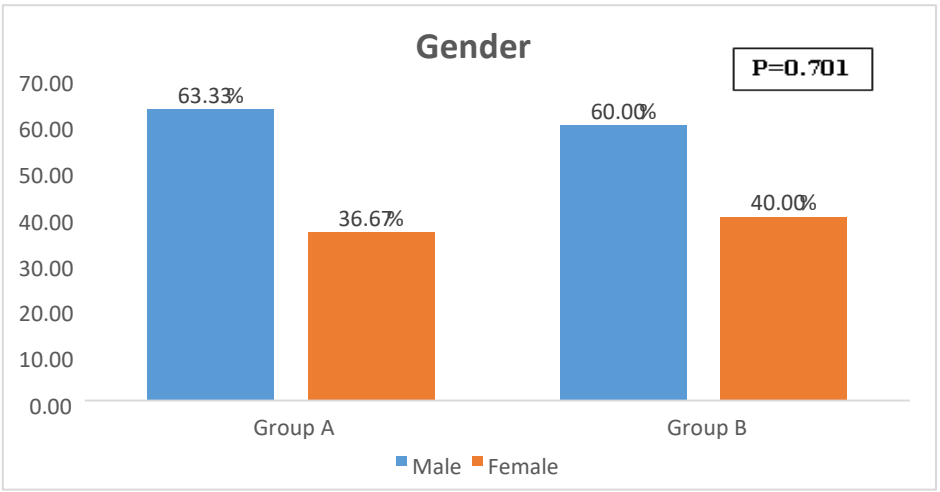

Figure 2: Gender distribution of study children (n=120).

Male was the predominant gender in both group A and group B (63.33 and 60%, respectively) without any significant difference between groups (p value =0.701).

Table I: Distribution of NS patients according to type & treatment of nephrotic syndrome (n=60).

Variable	Frequency	Percentage
Type of nephrotic syndrome (NS)		
Minimal change disease	55	91.67
Other than MCD (FSGS and	5	8.33
Number of episodes		
Initial episode	14	23.3
Infrequent relapse NS	24	40
Frequent relapse NS	10	16.7
Steroid dependent NS	9	15
Steroid resistant NS	3	5
Treatment history		
Corticosteroid alone	43	71.67
Corticosteroid plus other immunosuppressive (Mycophenolate	17	28.33

Table I shows that Minimal change disease (MCD) was found in 55 cases (91.67%); among the rest (8.33%) other than MCD patients 3 patients had focal segmental glomerulosclerosis (FSGS) and 2 patient membranoproliferative glomerulonephritis (MPGN). Initial episode of NS was found in 23.3% cases, while 40.0% cases had infrequent relapse NS and 16.7% had frequent relapse NS. Nine cases (15%) reported steroid dependent NS, while three (5%) had steroid resistant NS. Maximum NS children (71.67%) were being treated with corticosteroid only, while seventeen cases (28.33%) were treated with Corticosteroid plus other medications (Mycophenolate mofetil, Tacrolimus and Cyclosporin).

Table II: Comparison of lipid profile level between NS patients and healthy children (n=120).

Variables	Group B (n=60) Mean±SD	Group A (n=60) Mean±SD	p-value
Total cholesterol (mg/dL)	148.07±25.39	466.12±138.77	<0.001
Triglyceride (mg/dL)	114.30±50.73	340.65±175.83	<0.001
LDL (mg/dL)	77.00±20.12	336.27±136.84	<0.001

Table II shows that nephrotic children had a significantly higher mean of total cholesterol (466.12±138.77 vs 148.07±25.39 mg/dL), triglyceride (340.65±175.83 vs 114.30±50.73 mg/dL), LDL (336.27±136.84 vs 77.00±20.12 mg/dL), VLDL (67.85±35.03 vs 23.72±11.05 mg/dL), and HDL (57.89±34.65 vs 46.45±11.20 mg/dL) compared to healthy children as $p<0.05$.

Table III: Correlation between Hs-CRP and lipid profile among nephrotic children (n=60).

Parameters	R	p-value
Total cholesterol	0.47	<0.001
Triglyceride	0.315	0.014
LDL (mg/dL)	0.403	0.001
VLDL (mg/dL)	0.313	0.015
HDL (mg/dL)	0.083	0.531

Table III presents the correlation between high sensitivity C-reactive protein (hs-CRP) levels and lipid profile parameters in 60 nephrotic children. The table shows the correlation coefficient (R) and p-values for each parameter. The results reveal that Hs-CRP has a moderate positive correlation with total cholesterol (R=0.47, p<0.001), triglycerides (R=0.315, p=0.014), LDL (R=0.403, p=0.001), and VLDL (R=0.313, p=0.015). This suggests that higher Hs-CRP levels are associated with elevated levels of these lipid components. However, no significant correlation is observed between Hs-CRP and HDL levels (R=0.083, p=0.531). The findings indicate a potential relationship between inflammation (hs-CRP) and lipid metabolism in nephrotic children, but further investigation is required to comprehend the underlying mechanisms and clinical implications of these associations.

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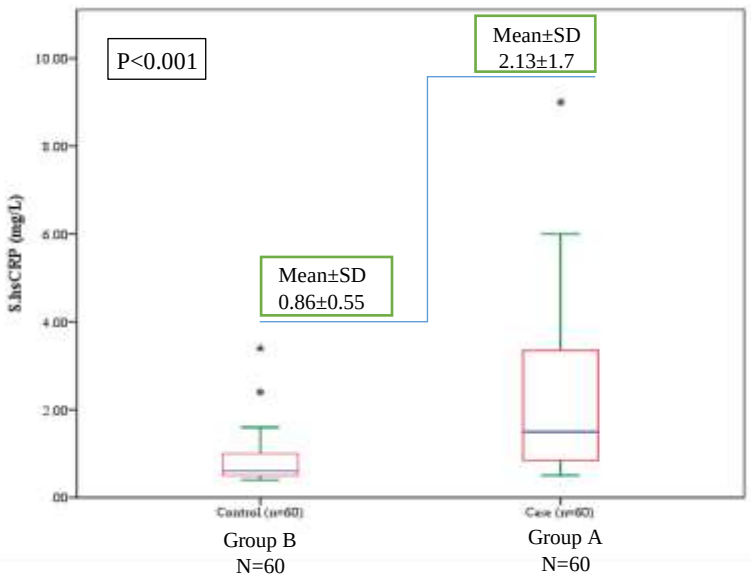

Figure 3: Box-plot distribution of serum Hs-CRP among cases and controls (n=120).

The mean±SD (median) of serum High sensitivity C-reactive protein (hs-CRP) were higher in children with nephrotic syndrome than healthy children [2.13±1.70, (1.50) vs 0.86±0.55, (0.60) mg/L, P < 0.001].

DISCUSSION

Over the last decades, several researches have revealed that systemic inflammatory activity has a key pathogenic role in vascular atherosclerosis which can be induced by hyperlipidemia. Among emerging biomarkers that reflect this inflammatory process, the chronic low-level rise of the Hs-CRP is one of the predictive markers of atherosclerosis and promotes the development of cardiovascular complications. This study was conducted with an aim to measure the level of high-sensitivity C-reactive protein

(hs-CRP) and to find out the association between Hs-CRP and serum lipid profile (total cholesterol, triglyceride, low-density lipoprotein, very low-density lipoprotein, high-density lipoprotein) in children with nephrotic syndrome. The mean age of all study children was 6.44±3.29 years (range: 2-12 years). The highest percentage of children from both group A and group B were aged less than 6 years (55% and 51.67% respectively). Besides, that male was the predominant gender in both NS and healthy group (63.33 and 60%, respectively). However, there were no significant differences between the two groups of children regarding both age and gender distribution. Previous studies also reported similar age-gender distribution among children with nephrotic syndrome [15-17]. Minimal change disease (MCD) was found in 55 cases (91.67%), among the rest (8.33%) other than MCD patients three patients had focal segmental glomerulosclerosis (FSGS) and two patients had membranoproliferative glomerulonephritis (MPGN). This finding is not similar to previous study done by Begum et al.(2017) where MesPGN was the most common histological finding followed by MCD [18]. This maybe we didn‘t include nephrotic syndrome due to secondary causes and most of our patients were not biopsy-proven MCD, rather from clinical and some laboratory parameters. In this study, nephrotic children had significantly higher mean of total platelet count (4.45±1.69 vs 3.24±1.58 lacs/mm^3) and lower albumin level (2.09±0.75 vs 4.25±0.52 mg/dL, p<0.001) than healthy children. Similar to our study, Wasilewska et al. (2007)(16) found increased platelet counts and reduced albumin levels in their nephrotic patients compared to control. Atherosclerosis along with hyperreactive platelets increases the risk of thrombosis among these children with hypoalbuminemia which can be further aggravated by dyslipidemia (Jackson and Calkin, 2007) [19]. In our study, children with NS had significantly higher mean of total cholesterol, triglyceride, LDL, VLDL, and HDL compared to healthy children. Abnormal lipid metabolism is common in patients with NS demonstrated in several previous studies [15, 20-22]. Similar to our study findings, Patel et al. (2017) also found significantly higher serum cholesterol levels in children with NS than in controls (344.35 vs 14 mg/dL) Furthermore, Fadol et al. (2019) also reported that mean total cholesterol (249.6±107.4 mg/dl), LDL (114.4±69.09 md/dl) and HDL (65.87±23.23 mg/dl) were significantly higher in nephrotic children than in control group (139.7±28.52), (46.90±12.33) and (53.58±19.98) respectively [15, 23]. Similarly, a study by Prescott et al. (2014), also found that subjects with NS had total cholesterol levels> 200 mg/dL [21]. We found mean HDL was (57.89±34.65 vs 46.45±11.20 mg/dL) significantly higher in nephrotic children compared to that of healthy children. Astuti et al.(2015a), found that though the level of mean total cholesterol and LDL were high in children with NS, however, mean of HDL was normal, which was not similar to our study finding [9]. A previous study illustrated by Fadol et al. (2019) reported that, although HDL level is usually normal in NS patients, but can be increased or decreased. The difference may be due to differences in demographic data of the subject‘s characteristics. The mean±SD (median) of serum High sensitivity C-reactive protein (hs-CRP) was significantly higher among nephrotic children than healthy children [2.13±1.70, (1.50) vs 0.86±0.55, (0.60) mg/L]. This Hs-CRP among nephrotic patients were at average risk (1-3) whether healthy had Hs-CRP below the level of

mild risk for cardiovascular disease (<1). Comparable to our findings, Patel et al. (2017) also found significantly higher serum Hs-CRP level in children with NS compared to healthy controls (1.92 vs 0.5 mg/L) [15]. Similarly, Astuti et al. (2015), also found high level of Hs-CRP in children with NS [9]. Besides, Fadol et al. (2019)(23) also observed that NS children had higher mean of Hs-CRP (5.28±3.95 mg/L) than in control (0.31±0.24 mg/L). In our study, Pearson correlation analysis showed serum Hs-CRP had significant moderate positive correlation with total cholesterol and LDL; whereas, significant weak positive correlation found with triglyceride and VLDL among children with NS (p value <0.05).

Limitation of the Study

Doses, duration and intensity of drugs therapy given to the nephrotic patients were not taken into account.

CONCLUSION

Serum hsCRP levels were significantly elevated in children with nephrotic syndrome compared to healthy subjects, indicating the presence of low-grade systemic inflammation. In nephrotic patients, hsCRP was approximately 2.5 times higher than in healthy children. These increased hsCRP levels showed a significant positive correlation with total cholesterol, LDL, triglycerides, and VLDL, suggesting a potential risk for atherothrombosis and future cardiovascular events.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

RECOMMENDATION

Regular monitoring of lipids, hsCRP, and platelet count is essential for all children with nephrotic syndrome, particularly those without minimal change disease (MCD). Prolonged follow-up is necessary to identify high-risk patients and implement timely interventions for effective management. Early monitoring and appropriate measures can significantly improve outcomes in these children.

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