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Association of Plasma PCSK9 with Hypercholesterolemia in Patients with Nephrotic Syndrome

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Abstract

Background: Hypercholesterolemia poses a significant cardiovascular risk in patients with nephrotic syndrome. Elevated proprotein convertase subtilisin/kexin type 9 (PCSK9) levels in these patients may exacerbate lipid dysregulation, contributing to heightened cardiovascular events.

Objective: To investigate the association between PCSK9 and hypercholesterolemia in patients with nephrotic syndrome.

Methods: This study was conducted at the Department of Nephrology, National Institute of Kidney Diseases and Urology (NIKDU), Dhaka, Bangladesh. A total of 80 patients were enrolled; of them 40 patients were nephrotic syndrome (Group A) and 40 were apparently healthy subjects (Group B). Their detailed clinical history with demographic profile were recorded. Fasting blood samples were taken for lipid profile, serum albumin, serum creatinine, plasma PCSK9 and 24 hours urine sample for protein creatinine ratio. After collection of all required data, analysis was done accordingly.

Results: Mean age of group A patients was 35.40±7.66 years and that was 31.02±9.27 years in group B. Nephrotic syndrome patients have a slightly higher mean BMI than healthy controls (24.84±3.26 kg/m^2 versus 23.53±2.97 kg/m^2, p= 0.067). Majority (25%) of the nephrotic syndrome patients had minimal change disease (MCD) followed by focal segmental glomerulosclerosis. (FSGS), membranous nephropathy (MN). lupus nephritis (LN) and IgA nephropathy (IgAN). Individuals with nephrotic syndrome had markedly elevated levels of TC, LDL cholesterol and TG compared to healthy controls (p<0.001). Mean PCSK9 level was significantly higher (p<0.001) in nephrotic syndrome group (274.87±139.73 ng/mL) compared to healthy controls (82.91±37.41 ng/mL). In individuals with nephrotic syndrome, PCSK9 levels have a significant positive correlation with LDL cholesterol (r= 0.646, p<0.001), total cholesterol (TC) (r= 0.341, p= 0.031) and triglycerides (TG) (r= 0.488, p= 0.001); indicating higher PCSK9 levels correspond to elevated lipid levels, while no significant correlation was found with high-density lipoprotein (HDL) cholesterol (r=0.288, p=0.072).

Conclusion: The plasma PCSK9 level is significantly higher in patients with nephrotic syndrome. High PCSK9 level associated with high total cholesterol, LDL cholesterol and TG levels in nephrotic syndrome.

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Keywords: Correlation; Dyslipidemia; Hypercholesterolemia; Nephrotic Syndrome; Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9).

Introduction

Nephrotic syndrome (NS) is a recognized manifestation of kidney disease. The prevalence of nephrotic syndrome is nearly 16 cases per 100,000 [1]. Nephrotic syndrome is characterized by proteinuria exceeding 3.5g/24 hours, hypoalbuminemia, generalized edema, hyperlipidemia, lipiduria and hypercoagulability [2]. Nephrotic syndrome associated dyslipidemia is believed to be connected to decreased hepatic lipase and lipoprotein lipase activity, a reduced hepatic high-density lipoprotein (HDL) cholesterol uptake, and an increased hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9) production causing decreased low-density lipoprotein (LDL) cholesterol endocytosis and catabolism [3]. Comparison to healthy individuals, patients with NS have higher concentrations of total cholesterol and triglycerides (TG). Low-density lipoprotein (LDL) cholesterol concentrations are up to 4-fold higher in patients with NS [4]. Serum total cholesterol and LDL cholesterol levels are high among patients with NS as because there are heavy losses of protein in urine [4]. Serine protease PCSK9 is mostly produced in the liver and a lesser amount also produced by the kidney and intestine [5]. PCSK9 attaches itself to the LDL receptor (LDL-R) on the surface of hepatocytes, forming a complex that is internalized and inducing its degradation via the lysosome metabolic pathway [6]. The ability of PCSK9 to promote degradation of the LDL- R is not related to its enzymatic activity; instead, PCSK9 acts as a chaperone that facilitates intracellular degradation of the LDL- R [7]. PCSK9 inhibits the LDL-R from recycling to the cell membrane by encouraging its breakdown, which results in a post-translational decrease in LDL- R expression [8]. In fact, loss-of-function mutation of PCSK9 is linked to marked reduction of plasma LDL-cholesterol and a significant decrease in cardiovascular risk [9]. As a result, PCSK9 has come to light as a promising new target of therapy for the control of hypercholesterolemia. Sterol regulatory element binding protein 2 (SREBP-2) is the transcription factor that mainly controls the expression of PCSK9 which is activated when intracellular free cholesterol levels decline and is inhibited when they increase [10]. Several factors tend to reduce hepatocyte free cholesterol concentration and thereby promote activation of SREBP-2 and upregulation of PCSK9 expression [10]. Chief among them is acyl-coenzyme A cholesterol acyltransferase 2 (ACAT- 2; encoded by the SOAT2 gene), which catalyses esterification of free cholesterol. Nephrotic syndrome is associated with a significant increase of hepatic ACAT-2 [11].

The potential role of upregulation of ACAT-2 is evidenced by the dramatic amelioration of hypercholesterolemia and marked reduction in LDL cholesterol level with administration of ACAT inhibitor in animals with nephrotic syndrome [12]. In addition, by lowering the uptake of LDL and its cholesterol cargo from the circulation, depletion of hepatic LDL- R in nephrotic liver contributes to the reduction in hepatocyte cholesterol, which can increase PCSK9 expression by activation of SREBP-2. Thus, upregulation of PCSK9 and depletion of LDL- R participate in a vicious circuit in which each begets and intensifies the other. It was found that PCSK9 plasma concentrations were 65% higher in patients with NS than healthy controls [4]. It is sometimes necessary to explore alternative solutions when statins are unable to regulate cholesterol levels adequately or result in damage to the liver or muscles.

PCSK9 inhibitors could be a safe and effective alternative for traditional methods of treating hypercholesterolemia linked to refractory nephrotic syndrome [13]. The correlation between PCSK9 and the proteinuria linked to nephrotic syndrome remains largely unexplored in human studies. In addition, most cohorts studied include only a small number of individuals and have no or minimal adjustment for potential confounding factors. Considering the inconsistent findings of earlier research and the possibility that PCSK9 inhibitors could be a potential treatment option for nephrotic syndrome patients, validating the results is essential. In this background, current study was aimed to examine the association between PCSK9 and hypercholesterolemia among patients with nephrotic syndrome.

Methodology

This cross-sectional study was conducted at Department of Nephrology, National Institute of Kidney Diseases and Urology (NIKDU), Dhaka, Bangladesh from August 2022 to February 2024. A total of eighty (80) adults were selected as study population; of them 40 had nephrotic syndrome (Group A) and rest 40 were healthy control (Group B). Adult (age ≥18 years) patients of both genders with nephrotic range proteinuria [urinary protein creatinine ratio (PCR) ≥3.5] and equal number of apparently healthy individuals were included. Patients were on corticosteroid or other immunosuppressive treatment or lipid lowering therapy, patients having chronic liver disease, patients with active malignancy, patients had history of peritonitis within the previous 4 weeks were excluded from the study. A through clinical evaluation was done and relevant information like-demographic data, clinical findings, investigations reports were recorded. The study was approved by the ethical review committee, NIKDU, Dhaka, Bangladesh.

Study procedure

Among total 80 study population; 40 were patients with nephrotic syndrome and 40 were apparently healthy subjects. After selection of the patients the aims/objectives,

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procedures and risk/benefits of this study were explained with understandable language to them. The patients were encouraged for voluntary participation and they were allowed being free to withdraw themselves from the study. Then, informed written consent was taken from each participant. Their height (meter) weight (kilogram) and blood pressure (mm of Hg) were measured. Body mass index (BMI) was calculated from the formula, BMI= Weight in Kg/height in meter^2. Relevant history, physical examination findings and laboratory reports of each participant were recorded in a separate data collection sheet.

Blood sample collection and analysis

With all aseptic precaution 6 ml fasting blood sample was drawn from peripheral vein of each study subjects. Each blood sample was collected in two separate test tubes for biochemical and immunological investigations. All collected blood samples were centrifuged at 3000 rpm for 15 minutes in room temperature (22°C-24°C), then serum and plasma were separated. These samples were labeled accordingly. Plasma samples were stored in ultra-deep freezer (-20°C) until analysis and serum samples were assayed immediately. Serum creatinine, serum fasting lipid profile, serum albumin and urinary PCR were measured by turbidity method using fully automated bio-chemistry analyzer Erba-XL-200. Plasma PCSK9 was measured using "The RD 191473200R Human PCSK9 ELISA" kit, an enzyme immunoassay.

Statistical analysis of data

After collection, all data were cross-checked, verified and compiled. Statistical analysis was performed using Windows based software program Statistical Packages for Social Sciences (SPSS) version -25. The quantitative data were expressed as mean with standard deviation (SD), but qualitative data were indicated by frequencies and percentages. Unpaired t-test was conducted to observe the mean differences. Pearson's correlation was done to observe the relationship between different variables. A p value less than 0.05 was considered as statistically significant.

Results

The purpose of this cross-sectional study was to evaluate the relationship between PCSK9 and hypercholesterolemia in individuals with nephrotic syndrome. Total 80 participants were included following selection criteria. Among them; 40 patients were nephrotic syndrome (Group A) and 40 were apparently healthy subjects (Group B). In terms of age, individuals with nephrotic syndrome exhibit a lower mean age compared to healthy controls (31.02±9.27 years versus 35.40±7.66 years, p= 0.024). Nephrotic syndrome patients have a slightly higher mean BMI than healthy controls (24.84±3.26 kg/m^2 versus 23.53±2.97 kg/m^2, p= 0.067) (Table 1). This suggests potential variations in metabolic profiles among these populations, with implications for understanding disease progression and management.

Table 1: Age and BMI of the study participants (N=80)

Variable	Nephrotic syndrome (n=40)	Healthy control (n=40)	p-value
	Mean±SD	Mean±SD	
Age (years)	31.02±9.27	35.40±7.66	0.024^s
BMI (kg/m^2)	24.84±3.26	23.53±2.97	0.067^{ns}

Among the study population; in Group-A (Nephrotic syndrome) 28 (70%) were male and 12 (30%) were female, while in Group-B (Healthy controls) 15 (37.5%) were male and 25 (62.5%) were female (Figure 1).

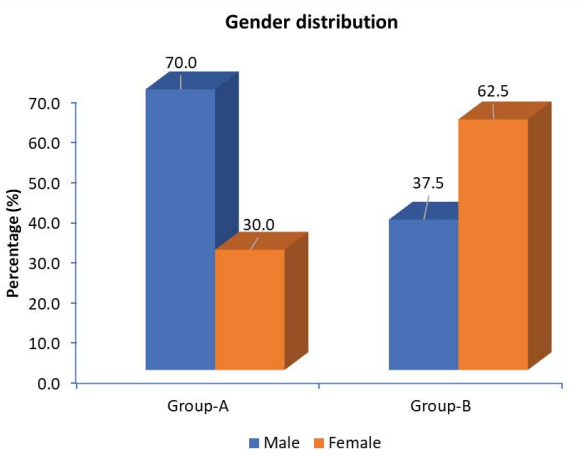

Figure 1: Distribution of study participants according to gender (N= 80)

Regarding etiologies of nephrotic syndrome; 10 (25%) participants had minimal change disease (MCD), 9 (22.5 %) participants had focal segmental glomerulosclerosis (FSGS), another 9 (22.5 %) participants had membranous nephropathy (MN). 8 (20%) participants had lupus nephritis (LN) and 4 (10%) participants had IgA nephropathy (IgAN) (Figure 2).

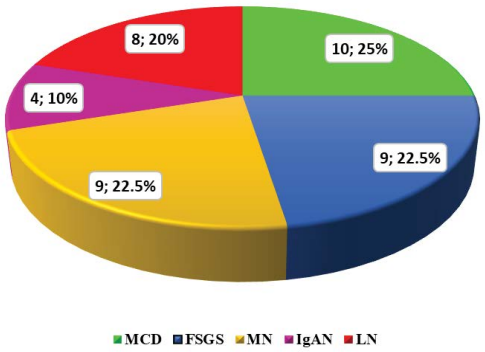

Figure 2: Distribution of primary diseases among the patients with nephrotic syndrome (n= 40)

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Nephrotic syndrome patients had mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 129.25±8.28 mmHg and 84.5±5.34 mmHg respectively, while in healthy controls these levels were 117.25±7.50 mmHg and 74.50±5.03 mmHg. Nephrotic syndrome patients had a significant elevated blood pressure (BP) compared to healthy controls (p<0.001) (Table 2).

Table 2: Distribution of study participants according to blood pressure (N=80)

Blood pressure (mmHg)	Nephrotic syndrome (n=40)	Healthy control (n=40)	p-value
	Mean±SD	Mean±SD	
SBP	129.25±8.28	117.25±7.50	<0.001[s]
DBP	84.5±5.34	74.50±5.03	0.001[s]

Data presented as Mean±SD, p-value reached through unpaired t-test, s= significant

Individuals with nephrotic syndrome had markedly elevated levels of TC, LDL cholesterol and TG compared to healthy controls. [426.30±137.62 mg/dL versus 190.86±29.41 mg/dL, p<0.001; 365.12±128.29 mg/dL versus 112.75±26.87 mg/dL, p<0.001; and 403.65±123.04 mg/dL versus 205.65±96.41 mg/dL, p<0.001]. However, HDL cholesterol level was not significantly different between the groups (36.30±9.66 mg/dL versus 37.04±5.91 mg/dl, p= 0.681) (Table 3).

The table 4 delineates significant differences in crucial biochemical parameters between individuals with nephrotic syndrome and healthy controls. Notably, individuals with nephrotic syndrome exhibit markedly reduced serum albumin level compared to healthy controls (2.25±0.58 g/dl versus 4.75±0.43 g/dl, p<0.001). Nephrotic syndrome patients had significant higher serum creatinine level compared to healthy controls (1.63±0.86 mg/dl versus 0.81±0.14 mg/dl, p<0.001). Moreover, nephrotic syndrome patients had significant higher urinary protein creatinine ratio (UPCR) compared to healthy controls (4.15±0.92 versus 0.21±0.11, p<0.001) (Table 4).

In this study, individuals with nephrotic syndrome exhibited significantly higher concentration of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) compared to healthy controls (274.87±139.73 ng/mL versus 82.91±37.41 ng/mL, p<0.001) (Figure 3).

In individuals with nephrotic syndrome, there was a positive correlation between PCSK9 level with TC (r=0.341, p=0.031), LDL cholesterol (r=0.646, p<0.001), and TG (r=0.488, p=0.001) levels, indicating that higher PCSK9 levels are associated with higher levels of these lipids. But there was no significant correlation observed between PCSK9 and HDL cholesterol (r=0.288, p=0.072) in this group. Among healthy controls, there was no significant correlation between PCSK9 and any of these lipid parameters, as indicated by the non-significant p-values for TC, LDL cholesterol, TG, and HDL cholesterol (Table 5).

Table 3: Lipid profile of the study participants (N= 80)

Lipids (mg/dl)	Nephrotic syndrome (n=40)	Healthy control (n=40)	p-value
	Mean±SD	Mean±SD	
TC	426.30±137.62	190.86±29.41	<0.001[s]
LDL cholesterol	365.12±128.29	112.75±26.87	<0.001[s]
TG	403.65±123.04	205.65±96.41	<0.001[s]
HDL cholesterol	36.30±9.66	37.04±5.91	0.681[ns]

Data presented as Mean±SD, p-value reached through unpaired t-test, s= significant, ns= not significant

Table- 4: Crucial biochemical parameters of the study population (N= 80)

Variables	Nephrotic syndrome (n=40)	Healthy control (n=40)	p-value
	Mean±SD	Mean±SD	
S. Albumin (g/dl)	2.25±0.58	4.75±0.43	<0.001[s]
S. Creatinine (mg/dl)	1.63±0.86	0.81±0.14	<0.001[s]
UPCR	4.15±0.92	0.21±0.11	<0.001[s]

Data presented as Mean±SD, p-value reached through unpaired t-test, s= significant

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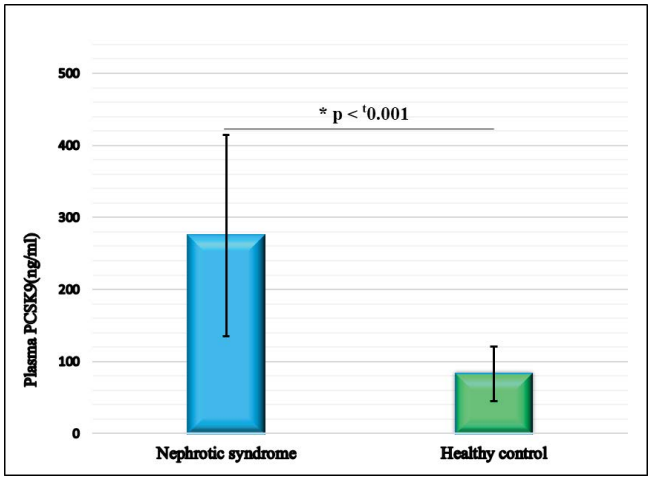

Figure 3: Comparison of PCSK9 between nephrotic syndrome and control group (N=80)

Table 5: Correlation between serum cholesterol levels and plasma PCSK9 concentration in nephrotic syndrome patients and healthy controls (N= 80)

Variables	PCSK9	
	r	p-value
Nephrotic syndrome		
TC (mg/dl)	0.341	**0.031**
LDL cholesterol (mg/dl)	0.646	**<0.001**
TG (mg/dl)	0.488	**0.001**
HDL cholesterol (mg/dl)	0.288	0.072
Healthy Controls		
TC (mg/dl)	0.084	0.608
LDL cholesterol (mg/dl)	0.231	0.151
TG (mg/dl)	-0.253	0.115
HDL cholesterol (mg/dl)	0.176	0.276

Discussion

Nephrotic syndrome (NS) is one of the commonest presentations of kidney disease [1]. Patients with nephrotic syndrome frequently have hypercholesterolemia due to significant protein loss in their urine [2]. Nephrotic syndrome associated dyslipidemia is believed to be linked to a decreased lipoprotein lipase and hepatic lipase activity, a reduced hepatic high-density lipoprotein (HDL) cholesterol uptake, and an increased hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9) production causing decreased low-density lipoprotein (LDL) cholesterol endocytosis and catabolism [3]. Hypercholesterolemia is a major risk factors of cardiovascular disease and is linked to higher mortality in these people [13]. It was reported that, plasma PCSK9 levels are higher in patients having nephrotic syndrome [14]. On this regards this study analyzed plasma PCSK9 and its association with hypercholesterolemia among patients of nephrotic syndrome over nineteen months period in a cross-sectional observational study.

In this study, individuals diagnosed with nephrotic syndrome display markedly elevated levels of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and triglyceride (TG) in comparison to healthy controls. Specifically, the mean TC levels for nephrotic syndrome and healthy controls were 426.30±137.62 mg/dL and 190.86±29.41 mg/dL. Similarly, the mean LDL cholesterol levels were 365.12±128.29 mg/dL and 112.75±26.87 mg/dL in nephrotic syndrome and healthy controls respectively. Additionally, the mean TG levels were 403.65±123.04 mg/dL and 205.65±96.41 mg/dL, in nephrotic syndrome and healthy controls. In this study, nephrotic syndrome individuals consistently exhibiting substantially higher TC, LDL cholesterol and TG levels compared to healthy controls. Notably, no significant differences in high-density lipoprotein (HDL) cholesterol levels were found between the groups. Overall, these findings underscore the significant dyslipidemia associated with nephrotic syndrome and emphasize the necessity of monitoring lipid profiles and implementing targeted interventions to mitigate cardiovascular risk in affected individuals. These results were in line with related previous studies [4, 15].

In this study, plasma PCSK9 concentrations was significantly higher in nephrotic syndrome patients compared to healthy controls ($p<0.001$), with mean value of PCSK9 was 274.87 ng/mL in nephrotic syndrome group compared to 82.91 ng/mL in healthy controls.

Data analysis revealed that, individuals diagnosed with nephrotic syndrome have a significant positive correlation between PCSK9 concentration with total cholesterol (TC) ($r=0.341$, $p=0.031$), low-density lipoprotein (LDL) cholesterol ($r=0.646$, $p<0.001$), and triglycerides (TG) ($r=0.488$, $p=0.001$). This suggests that higher plasma PCSK9 concentrations are associated with elevated levels of these lipids. However, no significant correlation was observed between plasma PCSK9 level and high-density lipoprotein (HDL) cholesterol ($r=0.288$, $p=0.072$) in this group. Overall, the relationships between PCSK9 concentration and lipid parameters vary across different patient groups. These findings suggest potential disparities in the metabolism of lipids and PCSK9 regulation among individuals with nephrotic syndrome. In accordance, Jin K et al. stated that, plasma PCSK9 concentration exhibited positive correlations with total cholesterol and LDL cholesterol concentrations, while showing a negative correlation with serum albumin concentration in patients with nephrotic syndrome [4]. Multiple regression analysis demonstrated a significant correlation between plasma PCSK9 concentration and serum total cholesterol and LDL cholesterol concentrations in nephrotic syndrome. Shen H et al. indicated that plasma

PCSK9 concentration in patients with nephrotic syndrome (PNS) exhibited positive linear correlations with total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol with correlation coefficients (r) of 0.246 ($p = 0.008$), 0.183 ($p = 0.049$), and 0.186 ($p = 0.047$), respectively; however, there were no significant linear correlations observed with very-low-density lipoprotein (VLDL) cholesterol and triglycerides (TG) [16]. Significant direct correlation between plasma PCSK9 and LDL cholesterol levels in the general population have been shown in a number of investigations [17-19].

Patients diagnosed with nephrotic syndrome exhibited a significant high plasma PCSK9 concentration, that was found to be linked with hypercholesterolemia and higher level of LDL cholesterol, which are defining characteristics of the condition. Our investigation shows that patients with nephrotic syndrome had a significant higher plasma PCSK9 concentration, which is in line with a study by Liu S and Vaziri ND on rodents with nephrotic syndrome [20].

Prior research conducted on animals has observed that NS models experience significant increases in serum TC and LDL levels, concomitant with a substantial up-regulation of hepatic PCSK9 expression [14, 20]. Additionally, one previous study revealed a significant rise in plasma PCSK9 levels in nephrotic patients whose TC and LDL cholesterol concentrations are directly correlated with plasma PCSK9 levels [4]. Another longitudinal study found that, during remission of their disease; patients with NS have lower levels of plasma PCSK9 and serum cholesterol [14]. Moreover, alterations in PCSK9 are associated with alterations in TC and LDL cholesterol during NS remission. These findings suggested that NS-associated hypercholesterolemia and PCSK9 in humans are consistently related. In accordance with previous research, we observed a linear positive correlation between elevated levels of plasma PCSK9 in newly diagnosed NS patients and the abundance of TC and LDL cholesterol [4, 14, 20]. These findings indicated that PCSK9 might play a significant role in hypercholesterolemia associated with the NS. Furthermore, an investigation carried out on rodents with NS revealed a substantial decrease in the expression of PCSK9 while hepatic LDL- receptor (LDL- R) was significantly diminished [20]. This finding provides an explanation for the depletion of the receptor in NS. In patients with NS, elevated plasma PCSK9 may play a key role in the pathogenesis of hypercholesterolemia by mediating the degradation of LDL-R. These findings suggested that, PCSK9 might emerge as a novel therapeutic target for the management of hypercholesterolemia related to NS.

Conclusion

This study concluded that, plasma PCSK9 level is significantly higher in patients with nephrotic syndrome compared to healthy controls. There is a positive linear correlation between plasma PCSK9 level with total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and triglycerides (TG) levels: suggesting that PCSK9 may have a role in modifying lipid profile in NS patients. Notably, there is no significant association between PCSK9 and high-density lipoprotein (HDL) cholesterol levels, indicating that these lipid components may be regulated differently.

Limitations of the study

It was a single center study, sample size was relatively small and sample was taken purposively, so randomization was not done which may have lower statistical power. Moreover, this study was conducted at a short period of time.

Recommendations

Further multicenter studies with larger sample size and longer follow up periods are recommended. Strategies aimed at lowering plasma PCSK9 levels may be effective in attenuating hypercholesterolemia and the associated risk in patients with nephrotic syndrome.

Conflicts of interest

The authors disclose that there is no conflict of interest regarding this publication.

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