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RESEARCH

Does pathological type of primary nephrotic syndrome affect serum concentrations of proprotein convertase subtilisin/kexin type 9?

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Abstract

Background: Dyslipidemia is a common finding in primary nephrotic syndrome (PNS). Serum PCSK9 level is also increased in PNS and is the main cause of dyslipidemia in such patients. There is a paucity of data on the relation between dyslipidemia and pathological types of PNS. We hypothesized that severity of dyslipidemia varies across different types of PNS, and this variation is due to differences in serum PCSK9 levels.

Methods: Fifty patients recently diagnosed with PNS were included in this cross-sectional study. Serum PCSK9, albumin, creatinine, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), and 24-h urine protein were measured. Comparison of patients' characteristics between pathological types of PNS and correlations between serum PCSK9 and other parameters were assessed.

Results: Serum PCSK9 levels were significantly higher in PNS patients compared with healthy individuals (314.58 ± 73.83 vs 253.42 ± 36.66 ng/ml, $p < 0.001$). No differences found between PNS types regarding serum levels of PCSK9 ($p = 0.571$), TC ($p = 0.806$), LDL-C ($p = 0.950$), HDL-C ($p = 0.844$), VLDL-C ($p = 0.472$), and TG ($p = 0.969$). Serum PCSK9 levels correlated significantly with TC ($p < 0.001$), LDL-C ($p < 0.001$), HDL-C ($p = 0.003$), VLDL-C ($p = 0.008$), TG ($p = 0.005$), 24-h urine protein ($p = 0.005$), and male sex ($p = 0.014$).

Conclusion: The pathological type of PNS does not affect serum levels of PCSK9 and components of lipid profile.

Keywords: Nephrotic syndrome, PCSK9, Dyslipidemia

Introduction

Nephrotic syndrome is a glomerular disease characterized by proteinuria > 3.5 g/dl, hypoalbuminemia < 3 g/dl, and the presence of edema [1]. Hypercholesterolemia is present in 90% of patients with nephrotic syndrome, while 78% have hypertriglyceridemia with a combined prevalence of 74% [2, 3].

Hyperlipidemia in nephrotic syndrome patients is due to increased production and decreased catabolism of lipoprotein particles containing apolipoprotein B and cholesterol [3–7]. The mechanisms contributing to these defects include the following: increased activity of HMG-CoA reductase in the liver [8, 9], increased expression and activity of hepatic acetyl CoA acetyltransferase 2 which leads to enhanced cholesterol esterification and reduction of intracellular free cholesterol [5, 10], decreased activity of hepatic lipase and lipoprotein lipase in peripheral tissues with subsequently decreased clearance of lipoprotein particles [11–16], and elevated plasma levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) [17, 18].

PCSK9 is a serine protease synthesized in the liver, and its main function is to regulate the degradation of LDL-R [2]. Previous studies revealed increased expression of

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PCSK9 in hepatocytes of animal models of nephrotic syndrome [17]. So, it is suggested that it is a major player in the metabolism of LDL-C in nephrotic syndrome patients [19].

To the best of the authors' knowledge, there are no available studies that are conducted with a primary outcome to assess the differences in frequency and severity of dyslipidemia and serum concentrations of PCSK9 in different pathological types of PNS. We hypothesized that dyslipidemia severity varies between PNS types, and this variation is due to differences in serum PCSK9 levels and conducted this study to investigate this hypothesis.

Methods

Study population

Fifty patients were included in this study. Inclusion criteria were adults aged ≥ 18 years with recently diagnosed PNS defined as proteinuria > 3.5 g/day, serum albumin < 3 g/dl, the presence of edema, and the absence of secondary causes such as diabetes mellitus, autoimmune diseases, viral infections, paraproteinemia, and malignancy. Exclusion criteria were serum creatinine > 1.3 mg/dl and the use of lipid-lowering drugs, steroids, and other immunosuppressants. Thirty healthy individuals were also included as a control group for measurement of serum PCSK9 for comparison with PNS patients. The patients signed a written consent before enrollment in the study, and the study protocol was approved by the local ethical committee.

Study design

This was a cross-sectional study. Patients' demographics including age and gender and clinical data including pathological type of PNS and hypertension status were collected and recorded. Serum PCSK9 levels were measured by commercially available ELISA kits according to manufacturer instructions. Serum albumin, creatinine, TC, LDL-C, HDL-C, VLDL-C, TG, and 24-h urine protein were measured by automatic biochemistry analyzers. The estimated glomerular filtration rate (e-GFR) was calculated according to the modification of diet in renal disease (MDRD) formula: $GFR = 186.3 + \text{s.creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742(\text{for women})$. All samples were drawn after fasting for 12 h. Samples for PCSK9 measurement were centrifuged, and serum was stored under $-80\,°C$ until analysis.

Statistical analysis

The data were analyzed by SPSS 26.0 software. Continuous variables were presented as mean $\pm$ standard deviation if normally distributed or median and interquartile range if not normally distributed. Categorical variables were presented as numbers and percentages. Comparison of categorical variables between PNS types was done by chi-squared test, while the comparison of continuous variables was performed by one-way ANOVA except for serum creatinine and total cholesterol, and VLDL-C was done by Kruskal–Wallis test. The correlations between serum PCSK9 levels and other parameters were assessed by Spearman's rank correlation. Independent associations with PCSK9 were evaluated by multivariable linear regression analysis. A *p*-value less than 0.05 was considered statistically significant.

Results

Demographics and clinical and laboratory characteristics of patients

The mean age of patients was 33.86 ± 9.61 years; 60% of patients were males, and 18% were hypertensive. Membranous nephropathy (MN) was the main cause of nephrotic syndrome (54%) followed by primary focal and segmental glomerulosclerosis (1ry FSGS) (24%) and then minimal change disease (MCD) (22%). Median 24-h urine protein and serum albumin levels were 6.05 (4.57, 8.20) g and 2.35 (1.90, 2.62) g/dl, respectively. Median serum creatinine was 0.9350 (0.77, 1.20) mg/dl, and median e-GFR by MDRD was 91.70 (71.57, 112.57) ml/min/1.73 m². Median TC and TG levels were 301.50 (238.75, 384.25) mg/dl and 240.50 (199, 310) mg/dl, respectively. The average serum PCSK9 level was 314.58 ± 73.83 ng/ml. Serum PCSK9 concentrations were significantly higher in PNS patients compared with healthy individuals (mean: 314.58 ± 73.83 vs 253.42 ± 36.66 ng/ml, $p < 0.001$). The study population characteristics are summarized in Table 1.

Comparison of patients' characteristics according to pathological types of PNS

Patients were divided into 3 groups according to PNS types. No significant differences were found between different types in terms of age and sex of patients, frequency of hypertension, and laboratory parameters including serum PCSK9 levels and lipids (Table 2).

Relationship between serum PCSK9 levels and other characteristics

Serum PCSK9 correlated significantly with male gender ($\rho = 0.345$, $p = 0.014$), 24-h urine protein ($\rho = 0.391$, $p = 0.005$), TC ($\rho = 0.631$, $p < 0.001$), TG ($\rho = 0.390$, $p = 0.005$), LDL-C ($\rho = 0.668$, $p < 0.001$), VLDL-C ($\rho = 0.371$, $p = 0.008$), and HDL-C ($\rho = 0.415$, $p = 0.003$). No significant correlations were found with other parameters (Table 3).

To determine the independent associations with serum PCSK9, a multivariable linear regression analysis was done (Table 4). In model 1, serum PCSK9 was

Table 1 Characteristics of the total study population ($n = 50$)

Parameter	Value
Age, years	33.86 ± 9.61
Sex (male), *n* (%)	30 (60%)
Hypertension, *n* (%)	9 (18%)
Type of PNS, *n* (%)	
MCD	11 (22%)
FSGS	12 (24%)
MN	27 (54%)
Serum PCSK9, ng/ml	314.58 ± 73.83
24-h urine protein, grams	6.05 (4.57, 8.20)
Serum creatinine, mg/dl	0.93 (0.77, 1.20)
eGFR, ml/min/1.73 m^2	91.70 (71.57, 112.57)
Serum albumin, g/dl	2.35 (1.90, 2.62)
TC, mg/dl	301.50 (238.75, 384.25)
TG, mg/dl	240.50 (199.00, 310.00)
LDL-C, mg/dl	197.00 (160.00, 271.25)
VLDL-C, mg/dl	30.00 (25.75, 42.00)
HDL-C, mg/dl	52.40 ± 17.58

independently associated with male sex and 24-h urine protein. Model 2 included the same variables as in model 1 with the addition of TC and TG. In model 2, only TC remained in a significant independent association with serum PCSK9 ($p = 0.016$). The pathological type of PNS had no independent association with serum PCSK9 levels in both models.

Discussion

This study was conducted to assess the differences in serum PCSK9 levels and lipids in different pathological types of PNS. The results demonstrated no significant differences in serum levels of these variables between the investigated PNS types.

Hypercholesterolemia and/or hypertriglyceridemia are common complications of nephrotic syndrome [2, 3]. Previously, it was believed that the mechanism of dyslipidemia is the increased synthesis of lipoproteins by hepatocytes in response to hypoproteinemia [2]. But later, studies suggested that the main cause of hypercholesterolemia is decreased expression of LDL-R in hepatocytes due to elevated plasma levels of PCSK9, with subsequently decreased uptake of LDL-C from the circulation [17, 18].

The present study showed a significant difference in serum PCSK9 levels between PNS patients and healthy individuals. This result is consistent with earlier reports [20]. Induction of nephrotic syndrome in a mice model led to increased plasma PCSK9 7- to 24-fold, which appeared to be due to increased hepatic secretion and decreased removal of PCSK9 [21].

We did not find significant differences in serum levels of TC, LDL-C, HDL-C, VLDL-C, TG, and PCSK9 between pathological types of PNS. Other investigators [20] reported similar findings when comparing serum PCSK9 levels in Chinese patients with MCD and MN. From this result, we can speculate that the investigated types of PNS had a similar stimulatory and inhibitory effect on hepatic synthesis and clearance of PCSK9, respectively.

Significant positive correlations between serum PCSK9 levels and TC and LDL-C were observed in our study, and these results are in line with earlier reports [17, 20–22]. Kwakernaak et al. demonstrated that changes in TC, LDL-C, and non-HDL-C in response to antiproteinuric treatment correlated with changes in serum PCSK9 levels [23]. Haas et al. studied a cohort of nephrotic syndrome

Table 2 Characteristics of the study population according to PNS types

Parameter	MCD ($n = 11$)	FSGS ($n = 12$)	MN ($n = 27$)	*p*-value
Age, years	31.18 ± 9.57	37.50 ± 7.97	33.33 ± 10.12	0.270
Sex (male), *n* (%)	59 (10%)	7 (14%)	18 (36%)	0.476
Hypertension, *n* (%)	1 (2%)	2 (4%)	6 (12%)	0.627
Serum PCSK9, ng/ml	301.36 ± 84.81	333.17 ± 81.82	311.70 ± 66.58	0.571
24-h urine protein, grams	6.07 ± 1.79	6.12 ± 1.71	6.68 ± 2.34	0.624
Serum creatinine, mg/dl	0.88 ± 0.24	0.95 ± 0.21	0.96 ± 0.25	0.612
eGFR, ml/min/1.73 m^2	100.40 ± 32.08	89.69 ± 28.35	96.06 ± 31.74	0.705
Serum albumin, g/dl	2.27 ± 0.55	2.38 ± 0.43	2.19 ± 0.48	0.531
TC, mg/dl	321.27 ± 112.04	325.25 ± 79.75	305.48 ± 80.61	0.806
TGs, mg/dl	249.27 ± 70.63	258.25 ± 87.00	253.37 ± 90.35	0.969
LDL-C, mg/dl	219.64 ± 97.71	222.83 ± 74.51	214.89 ± 63.13	0.950
VLDL-C, mg/dl	37.18 ± 15.77	43.25 ± 24.65	33.85 ± 14.56	0.472
HDL-C, mg/dl	51.55 ± 10.52	56.00 ± 26.59	51.15 ± 15.27	0.844

Table 3 Univariate correlations between serum PCSK9 levels and other parameters

Parameter	Spearman's ρ	*p*-value
Age	− 0.129	0.371
Sex (male)	0.345	**0.014**
Hypertension	− 0.115	0.424
24-h urine protein	0.391	**0.005**
Serum creatinine	0.010	0.945
e-GFR	− 0.078	0.592
Serum albumin	− 0.188	0.191
TC	0.631	**< 0.001**
TG	0.390	**0.005**
LDL-C	0.668	**< 0.001**
VLDL-C	0.371	**0.008**
HDL-C	0.415	**0.003**

patients during active disease and remission. During active disease, serum PCSK9 correlated significantly with serum levels of TC, LDL-C, and HDL-C, and after remission, hyperlipidemia resolved, and in parallel, serum PCSK9 levels decreased significantly, and the changes in serum PCSK9 correlated with the changes in TC, LDL-C, and HDL-C [21]. Jatem et al. [24] reported a series of 12 patients with refractory nephrotic syndrome and hypercholesterolemia who were treated with PCSK9 inhibitors. A significant correlation between serum PCSK9 and LDL-C was found before treatment, and after treatment, the significant reduction of LDL-C was associated with a significant reduction in serum PCSK9 levels. The significant correlation between serum levels of PCSK9 and cholesterol can be explained by the fact that high serum PCSK9 levels cause more degradation of LDL-R with subsequently decreased clearance of LDL-C from the circulation and finally high serum levels of TC and LDL-C [17].

A significant positive correlation was found between serum PCSK9 and TG in univariate analysis. But significance disappeared in multivariable analysis after adjustment for other variables. Consistent with our results, a significant correlation between serum PCSK9 and TG was noticed in a cohort of proteinuric patients before and after antiproteinuric treatment [23]. On the other side, other investigators did not find a significant correlation between TG and serum PCSK9 [20] or the changes in these variables after remission of nephrotic syndrome [21]. An inconsistent correlation between TG and serum PCSK9 indicates that there are other players involved in the development of hypertriglyceridemia in nephrotic patients [4, 25, 26].

Another important finding in this study is the positive correlation between daily protein excretion and serum PCSK9 levels which remained in model 1 of multivariable analysis. In line with this result, other researchers reported similar correlation results between plasma PCSK9 and urine protein-to-creatinine ratio before and after maximal antiproteinuric treatment for proteinuric patients [23]. Similarly, results of another study [21] showed a significant reduction in serum PCSK9 levels after remission of nephrotic syndrome. In the same study, induction of nephrotic syndrome in mice was associated with a significant increase in serum PCSK9 levels.

The male sex correlated significantly with serum PCSK9 levels ($p = 0.014$), and serum levels of PCSK9 were higher in males compared with females (347.80 ± 82.59 vs 292.43 ± 58.933, $p = 0.008$). The relation between serum PCSK9 and sex is variable as another study [27] reported higher serum levels of PCSK9 in females compared with males. The explanation for sex difference is unknown. It is largely not related to estrogen status as the levels were not different in postmenopausal females who received estrogen and those who were not treated with estrogen [27]. The contradictory results from different reports are mostly due

Table 4 Multivariable linear regression analysis with serum PCSK9 levels as the dependent variable

Predictor	Model 1 ($R^2 = 0.287$, $p = 0.019$)				Model 2 ($R^2 = 0.457$, $p = 0.002$)			
	B	SE	Beta	*p*-value	B	SE	Beta	*p*-value
24-h urine protein	11.660	4.883	0.328	**0.021**	7.225	4.704	0.203	0.132
Serum albumin	− 5.119	21.359	− 0.034	0.812	13.611	21.396	0.089	0.528
e-GFR	− 0.117	0.323	− 0.048	0.720	− 0.148	0.294	− 0.061	0.617
Sex (male vs female)	− 57.083	19.877	− 0.383	**0.006**	− 37.354	20.395	− 0.250	0.074
PNS type								
MCD vs MN	37.862	28.230	0.221	0.187	− 17.066	22.367	− 0.097	0.450
FSGS vs MN	14.439	24.421	0.098	0.557	12.623	21.715	0.074	0.564
TC					0.332	0.132	0.390	**0.016**
TG					0.106	0.120	0.120	0.383

B Unstandardized coefficient, *SE* Standard error, *Beta* Standardized coefficient

to differences in patients' characteristics, e.g., patients in the previously mentioned study were not nephrotic.

This study has some limitations. The sample size was small, and the number of patients in the different pathological types of PNS was not equal; thus, it may be claimed that these are the causes of the lack of difference in serum PCSK9 levels noticed in our study. The biochemical tests done for PNS patients were not performed for the control group except for serum PCSK9 which was measured to compare levels with nephrotic patients. This study included only 3 types of PNS, and despite these being the main types, the results cannot be generalized.

Conclusions

Our study showed that pathological type of PNS does not affect serum levels of lipid profile and PCSK9.

Abbreviations

PNS: Primary nephrotic syndrome; PCSK9: Proprotein convertase subtilisin/kexin type 9; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; VLDL-C: Very low-density lipoprotein cholesterol; TG: Triglycerides; HMG-CoA reductase: 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase; e-GFR: Estimated glomerular filtration rate; MN: Membranous nephropathy; MCD: Minimal change disease; 1ry FSGS: Primary focal and segmental glomerulosclerosis; MDRD: Modification of diet in renal disease.

Authors' contributions

HE, MS, and AM designed the research and participated in the analysis and interpretation of the data; AM participated by acquisition of data; and MS wrote the manuscript. The authors read and approved the final manuscript.

Availability of data and materials

The datasets of the study are not publicly available as it is private data but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

It was done in accordance with the ethical standards of the Ain Shams University, Faculty of Medicine ethical committee, reference number MS 671/2021, date 14 November 2021. Informed verbal and written consent was obtained.

Consent for publication

Participants provided a consent for the study findings to be published.

Competing interests

The authors declare that they have no competing interests.

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