

Original Paper

Relationship between Plasma Proprotein Convertase Subtilisin/Kexin Type 9 and Estimated Glomerular Filtration Rate in the General Chinese Population

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Keywords

Cardiovascular disease · PCSK9 · Estimated glomerular filtration rate · Dyslipidemia

Abstract

Background: Elevated levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) have been reported to be related to dyslipidemia, including patients with kidney dysfunction. However, its association with estimated glomerular filtration rate (eGFR) in individuals with normal serum creatinine (SCr) has not been determined. **Methods:** A total of 2,089 subjects with normal SCr and without lipid-lowering treatment were consecutively enrolled in this study. Plasma PCSK9 levels were measured by ELISA kit and eGFR was evaluated by the Chronic Kidney Disease Epidemiology Collaboration equation. Subjects were divided into a normal eGFR group ($n = 1,205$, ≥ 90 mL/min/1.73 m²) and a decreased eGFR group ($n = 884$, < 90 mL/min/1.73 m²). Baseline characteristics and laboratory findings were compared between the two groups. Spearman's correlation and linear regression were performed to determine the association between PCSK9 and eGFR. **Results:** No significant difference in PCSK9 levels was found between the normal eGFR group and the decreased eGFR group (236.84 ± 67.87 vs. 239.98 ± 68.72 ng/mL, $p = 0.303$). In Spearman's correlation and multivariable linear regression analysis, no association of PCSK9 levels with eGFR was detected in the total cohort ($r = -0.039$, $p = 0.079$; adjusted $\beta = -0.013$, $p = 0.630$). This result remained the same in the subgroups of normal eGFR ($r = -0.038$, $p = 0.190$; adjusted $\beta = -0.031$, $p = 0.367$) and decreased eGFR ($r = -0.054$, $p = 0.109$; adjusted $\beta = -0.034$, $p = 0.319$). **Conclusion:** In this single-center study with moderate sample size, the data showed no relationship of

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PCSK9 levels with normal or decreased eGFR in untreated patients with normal SCr, suggesting that further studies may be needed to understand the relationship between PCSK9 and lipid disorder in different stage of kidney dysfunction. © 2018 S. Karger AG, Basel

Introduction

Evidence to date has shown that dyslipidemia plays a crucial role in the development of atherosclerosis and coronary artery disease (CAD) [1]. Previous studies have indicated that patients with kidney disease also exhibit significant alterations in lipid metabolism and that the progression of kidney disease may lead to severe dyslipidemia [2–4]. Importantly, it is worth noting that disorders in lipid metabolism can also be observed in patients even in the early stage of kidney dysfunction [5, 6]. Recently, proprotein convertase subtilisin/kexin type 9 (PCSK9), a novel protease, has been established as an important regulator in lipid metabolism by regulating low-density lipoprotein receptor expression [7, 8] and its gain of mutation can result in elevated low-density lipoprotein cholesterol (LDL-C) and increased risk of CAD [8, 9]. Hence, considering the effects of PCSK9 and status of kidney function on lipid metabolism, whether PCSK9 is involved in the different stages of the kidney dysfunction needs to be clinically studied.

An increasing number of studies have investigated the potential associations of circulating PCSK9 levels with kidney function. However, the results remained inconsistent. Several studies revealed that plasma PCSK9 levels are influenced by kidney function in severe kidney disease [10–13], whereas other research found that plasma PCSK9 levels are not associated with kidney function [14, 15]. Indeed, this disparity regarding the relationship of PCSK9 with kidney dysfunction in different studies might be due to confounders, including the different state of kidney injury. Thus, further studies are needed to clarify the correlations between PCSK9 levels and kidney function, especially in different stages of kidney function.

In this study, therefore, we consecutively enrolled 2,089 subjects with normal serum creatinine (SCr) and without lipid-lowering treatment and tried to investigate the relationship between plasma PCSK9 levels and early kidney dysfunction.

Subjects and Methods

Study Population

From October 2012 until June 2017, a total of 2,204 consecutive patients were enrolled in the study from our database (registry study on individuals without treatments with lipid-lowering drugs for at least 3 months prior to entrance) described in a previous study [16]. The exclusion criteria were (1) patients with abnormal SCr ($\geq 133 \mu\text{mol/L}$) and/or definite kidney disease, (2) patients aged < 18 years, (3) patients with severe infectious or systemic inflammatory disease, and (4) patients with significant hematologic disorders, thyroid dysfunction, or severe liver insufficiency. The study flowchart is shown in Figure 1. Finally, a cohort of 2,089 patients was analyzed.

Hypercholesterolemia was defined as fasting plasma total cholesterol (TC) $\geq 5.2 \text{ mmol/L}$ (200 mg/dL) and/or triglyceride (TG) $\geq 1.7 \text{ mmol/L}$ (150 mg/dL). Type 2 diabetes mellitus was defined as fasting plasma glucose $\geq 7.0 \text{ mmol/L}$ and/or nonfasting plasma glucose $\geq 11.1 \text{ mmol/L}$ in multiple examinations or subjects with hypoglycemic therapy. Hypertension was defined as repeated measurements of blood pressure $\geq 140/90 \text{ mm Hg}$ three times at least or patients with antihypertensive treatments. CAD was defined as 50% diameter stenosis in at least one of the three major coronary arteries assessed by selective coronary angiography. The body mass index was calculated as body weight (kg) divided by body height (m^2). Kidney function was measured as estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: $\text{eGFR} = 141 \times \min(\text{SCr}/\kappa, 1)^\alpha \times \max(\text{SCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ [if female] $\times 1.159$ [if black] [17].

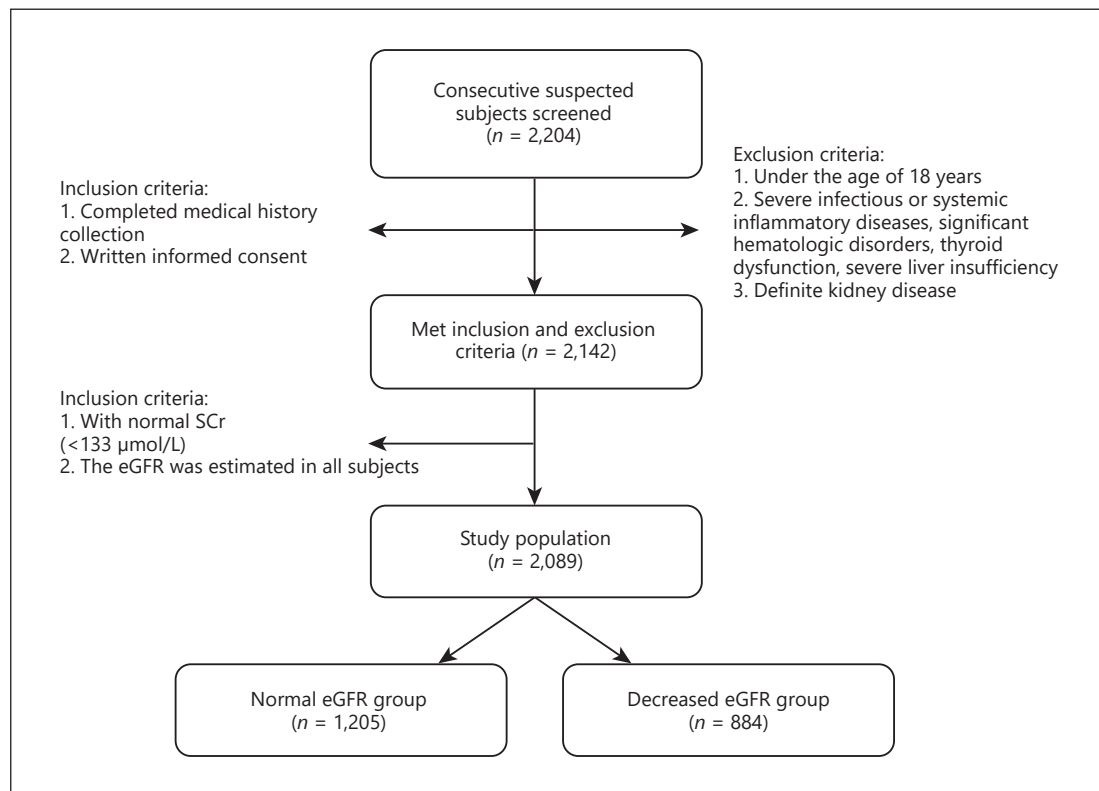


Fig. 1. Flowchart of the present study.

Laboratory Analysis

Blood samples were obtained from the cubital vein and collected into EDTA-containing tubes after a 12-h overnight fasting. All samples were subsequently stored at -80°C and analyzed after thawing. Plasma PCSK9 levels were measured by a high-sensitivity, quantitative sandwich enzyme immunoassay (Quantikine ELISA, R&D Systems Europe Ltd.) as described in our previous studies [16, 18, 19]. The lowest limit of detection was 0.096 mg/L. The measurement range of this assay is 0.16–10 ng/mL; intra-assay imprecision (coefficient of variation) is 1.5–2.6% and inter-assay imprecision 2.90–7.09%. The biochemical variables were measured by an automatic biochemistry analyzer (Hitachi7150, Japan). SCr, TG, TC, LDL-C, and high-density lipoprotein cholesterol (HDL-C) were measured using an enzymatic assay. The plasma levels of apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) were measured using a turbidimetric immunoassay.

Statistical Analysis

Continuous variables are presented using mean \pm SD and categorical variables as percentages. Comparisons of continuous data between groups were performed with Student *t* test or ANOVA as appropriate. For categorical data, χ^2 test or Fisher's exact test were used. The associations of plasma PCSK9 and lipid levels with eGFR were analyzed using Spearman's correlation and multivariate linear regression. A two-sided *p* value <0.05 was considered as statistically significant. Statistical analysis was performed with the SPSS 21.0 software (Chicago, IL, USA).

Results

Characteristics of the Participants

A total of 2,089 subjects who met the study criteria were finally enrolled. The mean age of the study population was 55.8 ± 10.9 years. Patients with hypercholesterolemia accounted

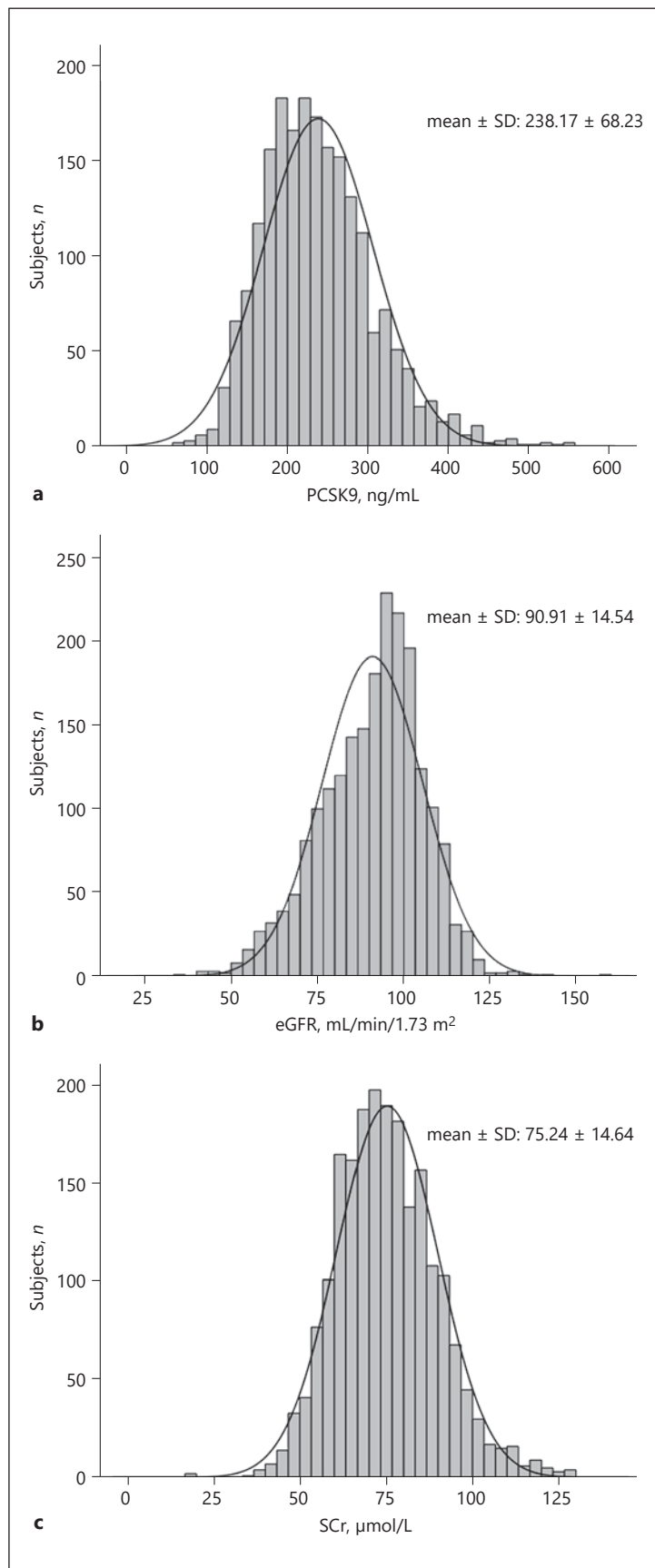


Fig. 2. Distribution of PCSK9 (mean ± SD: 238.17 ± 68.23 ng/mL) **(a)**, eGFR (mean ± SD: 90.91 ± 14.54 mL/min/1.73 m²) **(b)**, and SCr (mean ± SD: 75.24 ± 14.64 μmol/L) **(c)** in the total cohort.

Table 1. Characteristics of the normal (≥ 90 mL/min/1.73 m²) and decreased (< 90 mL/min/1.73 m²) eGFR groups

Variables	Total (n = 2,089)	Normal eGFR (n = 1,205)	Decreased eGFR (n = 884)	p value ¹
<i>Baseline characteristics</i>				
Age, years	55.8±10.9	51.8±9.7	61.4±10.0	<0.001
Male	1,272 (60.9%)	788 (65.4%)	484 (54.8%)	<0.001
Hypertension	1,152 (55.1%)	637 (52.9%)	515 (58.3%)	0.014
Body mass index	25.58±3.27	25.67±3.47	25.60±3.43	0.677
Hypercholesterolemia	1,271 (60.8%)	738 (61.2%)	533 (60.3%)	0.660
Diabetes	398 (19.1%)	222 (18.4%)	176 (19.9%)	0.393
Coronary artery disease	1,234 (59.1%)	651 (54.0%)	583 (66.0%)	<0.001
<i>Laboratory parameters</i>				
Triglyceride, mmol/L	1.84±1.26	1.96±1.38	1.81±1.07	0.005
Total cholesterol, mmol/L	4.82±0.98	4.79±0.98	4.86±0.97	0.112
LDL-C, mmol/L	3.14±0.88	3.09±0.91	3.19±0.85	0.026
HDL-C, mmol/L	1.11±0.34	1.08±0.33	1.13±0.35	0.001
Non-HDL-C, mmol/L	3.72±0.93	3.73±1.04	3.87±1.07	0.644
Apolipoprotein A1, g/L	1.31±0.27	1.33±0.29	1.38±0.30	<0.001
Apolipoprotein B, g/L	1.02±0.26	1.01±0.26	1.04±0.25	0.005
Lipoprotein(a), mg/L	220.44±240.94	217.92±244.83	224.58±237.65	0.534
Hemoglobin A1c, %	6.01±0.98	5.98±1.02	6.06±0.92	0.067
Fasting plasma glucose, mmol/L	5.59±1.51	5.66±1.64	5.48±1.28	0.417
Serum creatinine, μ mol/L	75.24±14.64	81.29±12.97	65.59±11.91	<0.001
Blood urea nitrogen, mmol/L	5.62±1.81	5.58±1.50	6.05±1.51	<0.001
hs-CRP, mg/L	2.33±2.78	2.29±2.77	2.38±2.76	0.425
PCSK9, ng/mL	238.17±68.23	236.84±67.87	239.98±68.72	0.303

Values are expressed as mean \pm SD or n (%). Bold indicates statistical significance ($p < 0.05$). eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SD, standard deviation. ¹ p values from ANOVA or Kruskal-Wallis test as appropriate for continuous variables and from χ^2 test for categorical variables.

for 60.8% of the total cohort, and none of them received any lipid-lowering drug treatment. As shown in Figure 2, the mean levels of PCSK9, eGFR, and SCr in the total cohort were 238.17 ± 68.23 ng/mL, 90.91 ± 14.54 mL/min/1.73 m², and 75.24 ± 14.64 μ mol/L, respectively. Furthermore, subjects were divided into a normal eGFR group (≥ 90 mL/min/1.73 m², $n = 1,205$) and a decreased eGFR group (< 90 mL/min/1.73 m², $n = 884$). As established in Table 1, the subjects were older and the prevalence of hypertension and CAD were higher in the decreased eGFR group compared with the normal eGFR group ($p < 0.001$, $p = 0.014$, and $p < 0.001$, respectively). In addition, the levels of LDL-C, HDL-C, ApoA1, and ApoB were higher in the decreased eGFR group ($p = 0.026$, $p = 0.001$, $p < 0.001$, and $p = 0.005$, respectively). However, no significant difference in circulating PCSK9 levels was found between the two groups (236.84 ± 67.87 vs. 239.98 ± 68.72 ng/mL, $p = 0.303$).

Relationship between Plasma Lipid Levels and Renal Function

As shown in Table 2, we found a slightly negative correlation of concentrations of LDL-C, HDL-C, ApoA1, and ApoB with eGFR ($r = -0.064$, $p = 0.014$; $r = -0.082$, $p < 0.001$; $r = -0.080$, $p < 0.001$; and $r = -0.080$, $p < 0.001$, respectively) in the total cohort. However, no significant correlations were found between these variables in the subgroup of decreased eGFR ($p > 0.05$, respectively).

Table 2. Associations among eGFR, PCSK9, and lipids in the normal (≥ 90 mL/min/1.73 m²) and decreased (<90 mL/min/1.73 m²) eGFR groups

	Total		Normal eGFR		Decreased eGFR	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
PCSK9	-0.039	0.079	-0.038	0.190	-0.054	0.109
Total cholesterol	-0.035	0.110	0.002	0.938	-0.025	0.450
Triglyceride	0.043	0.062	0.043	0.139	-0.005	0.880
LDL-C	-0.064	0.014	-0.027	0.553	-0.031	0.421
HDL-C	-0.082	<0.001	-0.069	0.295	0.020	0.560
Apolipoprotein A1	-0.080	<0.001	-0.040	0.168	-0.016	0.628
Apolipoprotein B	-0.080	<0.001	-0.038	0.182	-0.045	0.178
Lipoprotein(a)	-0.057	0.179	-0.034	0.234	-0.015	0.655

Bold indicates statistical significance ($p < 0.05$). eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Table 3. Correlations between PCSK9 and lipids in the normal (≥ 90 mL/min/1.73 m²) and decreased (<90 mL/min/1.73 m²) eGFR groups

	Total		Normal eGFR		Decreases eGFR	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
Total cholesterol	0.238	<0.001	0.275	<0.001	0.187	<0.001
Triglyceride	0.085	<0.001	0.069	0.017	0.109	0.001
LDL-C	0.217	<0.001	0.252	<0.001	0.169	<0.001
HDL-C	0.131	<0.001	0.173	<0.001	0.072	0.034
Apolipoprotein A1	0.138	<0.001	0.155	<0.001	0.110	0.001
Apolipoprotein B	0.209	<0.001	0.229	<0.001	0.181	<0.001
Lipoprotein(a)	0.059	0.009	0.084	0.004	0.016	0.647

Bold indicates statistical significance ($p < 0.05$). eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Relationship between Plasma Lipid Levels and PCSK9 Levels

Spearman's correlation of PCSK9 and lipids in different level of eGFR is shown in Table 3. In the total cohort, PCSK9 levels were positively correlated with TC ($r = 0.238$, $p < 0.001$), LDL-C ($r = 0.217$, $p < 0.001$), ApoA1 ($r = 0.138$, $p < 0.001$), and ApoB ($r = 0.209$, $p < 0.001$). In the subgroup with different eGFR levels, the positive relationship between plasma lipid levels and PCSK9 levels remained significant ($p < 0.05$, respectively).

Relationship between Plasma PCSK9 Levels and Renal Function

As shown in Figure 3, there were no associations between PCSK9 levels and eGFR in the total cohort ($r = -0.039$, $p = 0.079$). Moreover, in the subgroups of normal or decreased eGFR, no significant relationship was found between PCSK9 levels and eGFR ($r = -0.038$, $p = 0.190$; $r = -0.054$, $p = 0.109$, respectively). As shown in Table 4, we further investigate their relationship in the decreased eGFR group using multivariate linear regression adjusted for age, sex, hypertension, diabetes, history of CAD, and hypercholesterolemia, and again no associa-

Table 4. Linear regression analysis of the association between eGFR and PCSK9 levels in the decreased eGFR group (<90 mL/min/1.73 m²)

	Unadjusted		Adjusted ¹	
	β	<i>p</i> value	β	<i>p</i> value
Total cholesterol	-0.017	0.613	-0.008	0.812
LDL-C	-0.016	0.628	-0.011	0.737
Apolipoprotein B	-0.051	0.131	-0.068	0.054
PCSK9	-0.069	0.071	-0.034	0.319

eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9. ¹ Adjusted for age, sex, hypertension, diabetes, history of coronary artery disease and hypercholesterolemia.

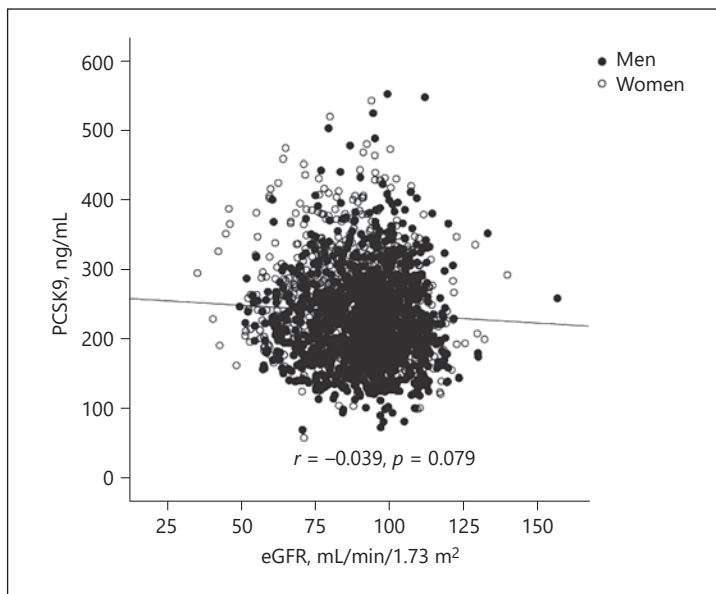


Fig. 3. Relationship between PCSK9 levels and eGFR in the total cohort ($r = -0.039$, $p = 0.079$).

tions between PCSK9 levels and eGFR were found (unadjusted $\beta = -0.069$, $p = 0.071$; adjusted $\beta = -0.034$, $p = 0.319$). In addition, we found a weakly negative correlation between PCSK9 and SCr levels in the total cohort ($r = -0.127$, $p < 0.001$; unadjusted $\beta = -0.147$, $p < 0.001$). However, this relationship disappeared after adjusting for the established confounders (adjusted $\beta = -0.024$, $p = 0.252$).

Discussion

It has been reported that there are significant lipoprotein disorders in patients with kidney dysfunction, but the mechanism is not fully understood. PCSK9 is a key regulating protein of lipid metabolism, and we hypothesized that PCSK9 might be involved in the lipid changes of kidney dysfunction even in the early stage. We decided to study the relationship between circulating PCSK9 levels and kidney function in a Chinese cohort without lipid-lowering therapy. We used the CKD-EPI equation to evaluate kidney function, which takes into account sex, age, ethnicity, and SCr concentration [17]. Importantly, it has lower bias,

especially at a eGFR >60 mL/min/1.73 m² [17]. Interestingly, the data showed that although elevated LDL-C levels were found in subjects with decreased eGFR, there was no significant increment of circulating PCSK9 levels. Apparently, our study may provide meaningful information with regard to the association among PCSK9, kidney function, and dyslipidemia in subjects with clinically normal SCr.

Indeed, PCSK9 is a serine protease mainly produced and released in the circulation by the liver and also expressed by the intestine and kidney partly. Besides, PCSK9 is also cleared from extrahepatic tissues, including the kidneys [20]. Therefore, the progression of kidney dysfunction may influence the expression or clearance of circulating PCSK9 levels, or in other words contribute to the change in plasma concentrations of PCSK9. Previous studies have reported that elevated PCSK9 concentrations are strongly associated with increased LDL-C levels and the development of atherosclerosis [8, 16, 18, 19]. Consequently, PCSK9 inhibitors have become a novel therapeutic target for the therapy of hypercholesterolemia, which has been demonstrated to reduce the risk of cardiovascular disease [21, 22]. Given the possible interactions among plasma levels of PCSK9, lipids, and kidney function, studies might be of clinical interest.

Notably, in recent years, several clinical and experimental studies have examined the relationship between circulating PCSK9 levels and kidney function. A study conducted by Konarzewski et al. [10] revealed that plasma PCSK9 and lipids levels in CKD patients were higher compared with those in the control group, and a strong negative correlation between PCSK9 levels and eGFR was found. Moreover, Abujrad et al. [11] showed that hemodialysis treatment could significantly reduce LDL-C and PCSK9 levels in CKD patients. The data from Jin et al. [13] also indicated that there were higher plasma PCSK9 concentrations in patients with nephrotic syndrome. Another research demonstrated that PCSK9 was correlated with hypercholesterolemia in nephrotic syndrome [12]. In addition, considering that circulating PCSK9 concentrations may be influenced by lipid-lowering treatments [23], Tecson et al. [24] did not find any association between PCSK9 and LDL-C in a mixed population of statin-treated and nontreated patients. Morena et al. [14] conducted a study in CKD patients without statin treatment. Unfortunately, they found that plasma PCSK9 levels did not vary significantly between different CKD stages and that PCSK9 levels were not associated with eGFR. Another study conducted by Rogacev et al. [15] in 729 patients who received statins showed that no correlation between eGFR and PCSK9 levels existed. Based on the disparity of studies, it is necessary to further examine the relationship between PCSK9 and kidney function at different stages in different populations.

It has also been demonstrated that patients with impaired kidney function show significant alterations in lipoprotein metabolism. These changes could be observed in the early stages of kidney disease [25, 26], and serious kidney dysfunction led to the development of severe dyslipidemia [2, 3, 27]. In our study, we found a higher LDL-C level in the decreased eGFR group compared to the normal eGFR group. However, no difference in PCSK9 levels was found, which suggests that dyslipidemia in patients with mild kidney dysfunction may not be involved in the PCSK9 pathway in our present study on 2,089 Chinese untreated individuals. However, we could not reach a definite conclusion, but the data suggested that more studies might be needed to further examine the relationship between PCSK9 and the early lipid abnormality in kidney dysfunction.

There were some limitations to the present study. Firstly, it was a single-center study, and selection bias might have been present. Besides, we did not enroll patients with severely decreased eGFR levels. Whether the results are consistent in such a population needs to be further studied. Finally, the relatively small sample size and the single measurement of circulating PCSK9 levels may also be limitations.

Conclusions

In this cohort study on 2,089 Chinese subjects without lipid-lowering treatment and with normal SCr, we did not find an association between circulating PCSK9 concentrations and mildly decreased eGFR. Our data suggest that PCSK9 might not be involved in the development of dyslipidemia in patients with mild kidney dysfunction but normal SCr. Further studies are needed to confirm our findings.

Acknowledgments

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Statement of Ethics

The protocol of this study complied with the Declaration of Helsinki. The study was approved by the hospital ethics review board (Fu Wai Hospital and National Center for Cardiovascular Diseases, Beijing, China). Informed consent was obtained from all enrolled subjects.

Disclosure Statement

The authors state that no conflict of interest exists in this paper.

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