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Association between plasma levels of pigment epithelium-derived factor and renal dysfunction in patients with coronary artery disease

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Abstract

Background: *Although plasma pigment epithelium-derived factor (PEDF) levels have been shown to be significantly correlated with the levels of creatinine (Cr) in type 2 diabetes, little is known about the association between PEDF levels and renal dysfunction in patients with coronary artery disease (CAD).*

Methods: *We enrolled 134 consecutive patients with diagnosed CAD and measured plasma levels of PEDF, serum Cr, uric acid (UA) and high-sensitive C-reactive protein (hsCRP).*

Results: *Plasma PEDF levels were positively correlated with serum Cr ($p < 0.0001$) and UA ($p < 0.0001$) and negatively correlated with the estimated glomerular filtration rate (eGFR) ($p < 0.0001$), whereas there was no association between plasma PEDF and age or hsCRP. When the subjects were divided into five groups (0–4) according to the number of metabolic factors (obesity, diabetes, hypertension and dyslipidemia), PEDF levels in patients with four factors were significantly higher than those in patients without factors. Next, we divided the patients into quartiles according to their plasma PEDF levels (< 9.9 μg/mL, 9.9–12.8, 12.9––15.7, > 15.7). The eGFR in the first group was significantly higher than those in the third and fourth groups. Multivariate logistic analysis indicated that eGFR ($p < 0.0001$) and age ($p = 0.030$) were significant independent variables that correlated with the quartile classification according to PEDF levels.*

Conclusions: *This study revealed that PEDF may play a role in renal dysfunction in CAD patients.* (Cardiol J 2011; 18, 5: 515–520)

Key words: pigment epithelium-derived factor, coronary artery disease

Introduction

Pigment epithelium-derived factor (PEDF) is a glycoprotein with potent neuronal differentiating activity that was purified from the conditioned media of human retinal pigment epithelial cells [1]. PEDF has anti-angiogenic, anti-oxidant, and anti-inflammatory effects [2, 3]. Recent clinical studies have shown that serum levels of PEDF are correlated with adiposity [4, 5], a decreased incidence of cirrhosis [6], and increased incidences of metabolic syndrome (MetS) [5], insulin resistance [7], and renal failure [8].

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The interdependence of cardiac and renal dysfunction (cardio-renal syndrome) has emerged as a focus of intense interest in heart failure management due to the substantial associated morbidity and mortality. Several studies have demonstrated that the risk of subsequent cardiovascular events is higher among patients with chronic kidney disease (CKD) than among subjects with normal renal function [9]. Furthermore, CKD is an independent risk factor for all-cause death or coronary artery disease (CAD) in the general population [9, 10], as well as in high-risk populations [11, 12]. However, little is known about the association between PEDF levels and renal dysfunction in patients with coronary artery disease (CAD). Therefore, we tested the hypothesis that there is also a significant association between plasma levels of PEDF and renal function in patients with CAD.

Methods

Study subjects

The subjects included 134 consecutive patients (101 males and 33 females) who had stable angina pectoris as assessed by coronary angiography at Fukuoka University Hospital between October 2006 and December 2007. The protocol was approved by the Ethics Committee of Fukuoka University Hospital, and all subjects gave their informed consent to participate.

Evaluation of cardiovascular risk factors

In all subjects, body mass index (BMI), systolic blood pressure, diastolic blood pressure, serum levels of triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr), uric acid (UA), fasting plasma glucose, hemoglobin A1c, smoking status (current versus nonsmoker), family history (myocardial infarction, angina pectoris or sudden death) and medication use were collected as cardiovascular risk factors. All blood samples were drawn in the morning after the patients had fasted overnight. Laboratory data was determined using enzymatic methods. Blood pressure was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer.

The patients' characteristics with regard to history of hypertension, dyslipidemia, diabetes mellitus (DM), history of smoking, previous myocardial infarction, and prior coronary intervention were obtained from medical records. Patients who had a current systolic/diastolic blood pressure > or = 140/90 mm Hg or who were receiving antihypertensive therapy were considered to have arterial hypertension. Patients with a LDL-C level of 140 mg/dL or who were receiving lipid-lowering therapy were considered to have hypercholesterolemia. DM was defined using the American Diabetes Association criteria. BMI was calculated as weight (kg)/height $(m)^2$.

Calculation of estimated glomerular filtration rate

Estimated glomerular filtration rate (eGFR) was determined using the abbreviated equation that the Japanese Society of Nephrology modified for Japanese based on the Modification of Diet in Renal Disease study: $194 \times [\text{age (years)}]^{-0.287} \times [\text{serum Cr (mg/dL)}]^{-1.094} \times [0.739 \text{ if female}]$. CKD was defined as an eGFR < 60 mL/min/1.73 m^2.

Statistical analysis

Statistical analysis was performed using the Stat View statistical software package (Stat View 5; SAS Institute Inc., Cary, NC, USA) at Fukuoka University. Data is shown as mean ± standard deviation. Categorical and continuous variables were compared among groups by χ^2 analysis and analysis of variance (ANOVA), respectively. A value of $p < 0.05$ was considered significant. Multivariate analysis was performed by a logistic regression analysis for independent variables that were related to values of PEDF.

Results

Patient characteristics

Table 1 shows the baseline clinical characteristics of the 134 subjects. The percentages of hypertension, dyslipidemia, DM, and CKD were 81%, 80%, 43%, and 34%, respectively. The mean age was 65 ± 2 years, BMI was 24 ± 1 kg/m^2, Cr was 0.89 ± 0.05 mg/dL and eGFR was 66 ± 3 mL/min/ /1.73 m^2. Patients with CKD showed mild renal dysfunction because the stage in CKD was 3, but not 4 or 5 [13]. The frequencies of 1 vessel disease (VD), 2 VD and 3 VD were 47%, 29% and 24%, respectively.

Levels of plasma PEDF

Plasma levels of PEDF in all patients were 13.3 ± ± 4.8 μg/mL. There were no differences in the levels of PEDF between groups categorized according to sex, the presence or absence of hypertension, DM and dyslipidemia, the number of VD or target lesion (Table 2). The levels of PEDF in patients with β-blocker(+) were significantly higher than those in patients with β-blocker(–).

Table 1. Characteristics of patients.

Age (years)	65 ± 2
BMI [kg/m^2]	24 ± 1
Gender (male)	101 (75%)
Diabetes mellitus	44%
Hypertension	81%
Dyslipidemia	80%
Chronic kidney disease	34%
SBP [mm Hg]	129 ± 2
DBP [mm Hg]	71 ± 2
Biochemical parameters:	
Cr [mg/dL]	0.9 ± 0.05
eGFR [mL/min]	66 ± 3
LDL-C [mg/dL]	114 ± 6
HDL-C [mg/dL]	47 ± 2
TG [mg/dL]	147 ± 14
HbA1c (%)	6.3 ± 0.4
UA [mg/dL]	5.5 ± 0.2
LDL/HDL ratio	2.6 ± 0.2
Coronary angiographic analysis	
Number of VD:	
1 VD	47%
2 VD	29%
3 VD	24%
Target lesion:	
LMT	1%
LAD	55%
Cx	18%
RCA	26%
Complex lesion	51%
Medication:	
ARB	72%
ACE-I	1%
CCB	52%
NG	16%
Beta-blocker	10%
Diuretics	5%
Statin	75%
SU	13%
Insulin	10%

BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; Cr — creatinine; eGFR — estimated glomerular filtration rate; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglycerides; HbA1c — hemoglobin A1c; UA — uric acid; VD — vessel disease; LMT — left main tract; LAD — left anterior descending; Cx — circumflex; RCA — right coronary artery; ARB — angiotensin II receptor blocker; ACE-I — angiotensin converting enzyme inhibitor; CCB — calcium-channel blocker; NG — nitroglycerin; SU — sulfonyl urea

Association between levels of plasma PEDF and number of metabolic factors

When the subjects were divided into five groups (0–4) according to the number of metabolic factors (obesity, DM, hypertension and dyslipidemia) (Fig. 1), PEDF levels in patients with four factors were significantly higher than those in patients without these factors.

Association between the levels of plasma PEDF and eGFR

Next, we divided the patients into quartiles according to plasma PEDF levels (< 9.9 μg/mL, 9.9––12.8, 12.9–15.7, > 15.7) (Fig. 2). The eGFR in the first group was significantly higher than those in the third ($p = 0.0091$) and fourth groups ($p < 0.0001$).

Correlation between plasma levels of PEDF and parameters

As shown in Figure 3, PEDF was positively correlated with Cr ($r = 0.482$, $p < 0.0001$) and UA ($r = 0.367$, $p < 0.0001$), and negatively correlated with eGFR ($r = –0.422$, $p < 0.0001$). There were no correlations between PEDF and age or high-sensitive C-reactive protein (hsCRP).

Next, we analyzed predictors for PEDF levels using independent variables (age, gender, BMI, eGFR, DM, hypertension and dyslipidemia) by multiple regression analysis (Table 3). PEDF levels were significantly associated with age ($p = 0.030$) and eGFR ($p < 0.0001$).

Discussion

In this cross-sectional study, we assessed the association between PEDF levels and renal dysfunction in patients with CAD. To the best of our knowledge, this is the first report to show that PEDF may play a role in renal dysfunction in CAD patients.

PEDF has both anti-atherogenic and anti-inflammatory properties. There is increasing evidence that PEDF plays an important role in the development of renal dysfunction in patients with diabetic retinopathy [14] and end-stage renal disease (ESRD) [15]. Our findings also indicated that PEDF was associated with renal dysfunction, because PEDF was positively correlated with Cr or UA and negatively correlated with eGFR. In addition, PEDF levels were most closely associated with eGFR by a multiple regression analysis. Although the characteristics of the subjects in the present study differed from those in previous studies, the important point is that we specifically analyzed CAD patients, rather than patients with diabetes retinopathy or ESRD.

A recent study reported a significant association between PEDF levels and metabolic disorder [5]. Although the study enrolled subjects without

Table 2. Plasma levels of PEDF in each factor.

Factors	PEDF [μg/mL]		P
Gender (male/female)	12.1 ± 4.4 (n = 33)/13.7 ± 4.8 (n = 101)		0.119
DM (–/+)	13.3 ± 4.3 (n = 76)/13.4 ± 5.3 (n = 53)		0.900
Hypertension (–/+)	12.1 ± 3.9 (n = 25)/13.6 ± 4.9 (n = 109)		0.192
Dyslipidemia (–/+)	12.6 ± 4.4 (n = 27)/3.5 ± 4.9 (n = 107)		0.364
Coronary angiographic analysis			
Number of VD			
1 VD	13.3 ± 4.6 (n = 63)	1 VD *vs* 2 VD	0.846
2 VD	13.5 ± 5.6 (n = 39)	1 VD *vs* 3 VD	0.947
3 VD	13.2 ± 4.0 (n = 32)	2 VD *vs* 3 VD	0.820
Target lesion			
LMT	16.0 (n = 1)	LMT *vs* LAD	0.501
LAD	12.8 ± 4.2 (n = 72)	LMT *vs* Cx	0.637
Cx	13.7 ± 5.3 (n = 24)	LMT *vs* RCA	0.701
RCA	14.1 ± 5.4 (n = 35)	LAD *vs* Cx	0.407
		LAD *vs* RCA	0.161
		Cx *vs* RCA	0.725
Complex lesion (–/+)	13.5 ± 4.8 (n = 66)/13.1 ± 4.7 (n = 68)		0.672
Medication			
ARB (–/+)	13.7 ± 4.8 (n = 38)/13.2 ± 4.8 (n = 96)		0.546
ACE-I (–/+)	13.3 ± 4.8 (n = 133)/15.2 (n = 1)		0.692
CCB (–/+)	12.5 ± 4.5 (n = 65)/14.1 ± 4.9 (n = 69)		0.056
NG (–/+)	13.3 ± 4.7 (n = 113)/13.3 ± 5.2 (n = 21)		0.990
Beta-blocker (–/+)	13.0 ± 4.5 (n = 121)/16.0 ± 6.4 (n = 13)		0.036
Diuretic (–/+)	13.3 ± 4.8 (n = 128)/13.0 ± 3.9 (n = 6)		0.865
Statin (–/+)	12.7 ± 4.9 (n = 33)/13.5 ± 4.7 (n = 101)		0.405
SU (–/+)	13.2 ± 4.8 (n = 120)/14.2 ± 4.7 (n = 14)		0.462
Insulin (–/+)	13.4 ± 4.7 (n = 116)/12.9 ± 5.0 (n = 18)		0.707

DM — diabetes mellitus; VD — vessel disease; LMT — left main tract; LAD — left anterior descending; Cx — circumflex; RCA — right coronary artery; ARB — angiotensin II receptor blocker; ACE-I — angiotensin converting enzyme inhibitor; CCB — calcium-channel blocker; NG — nitroglycerin; SU — sulfonyl urea

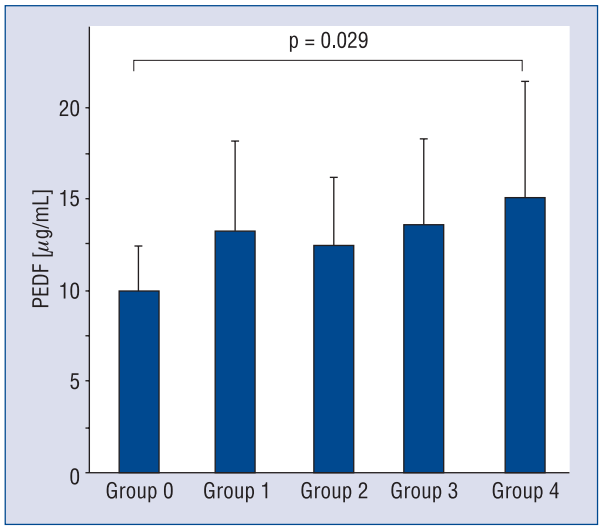

Figure 1. Association between levels of PEDF and the number of metabolic factors. Patients were divided into five groups (0–4) according to the number of metabolic factors (obesity, diabetes, hypertension and dyslipidemia).

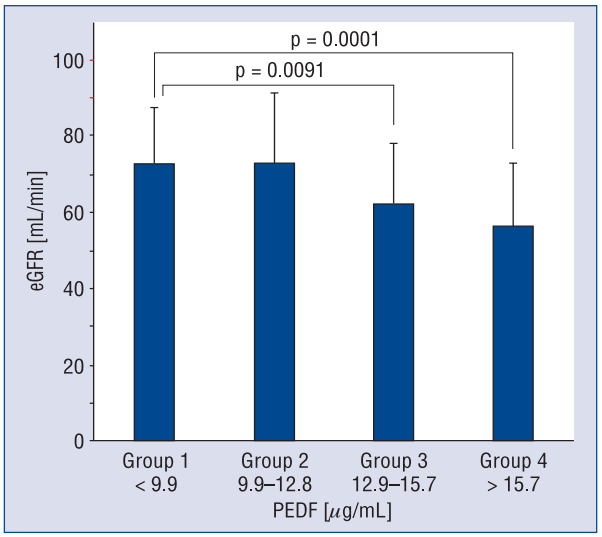

Figure 2. Association between plasma levels of PEDF and eGFR. Patients were divided into quartiles according to plasma PEDF levels (< 9.9 μg/mL, 9.9–12.8, 12.9–15.7, > 15.7).

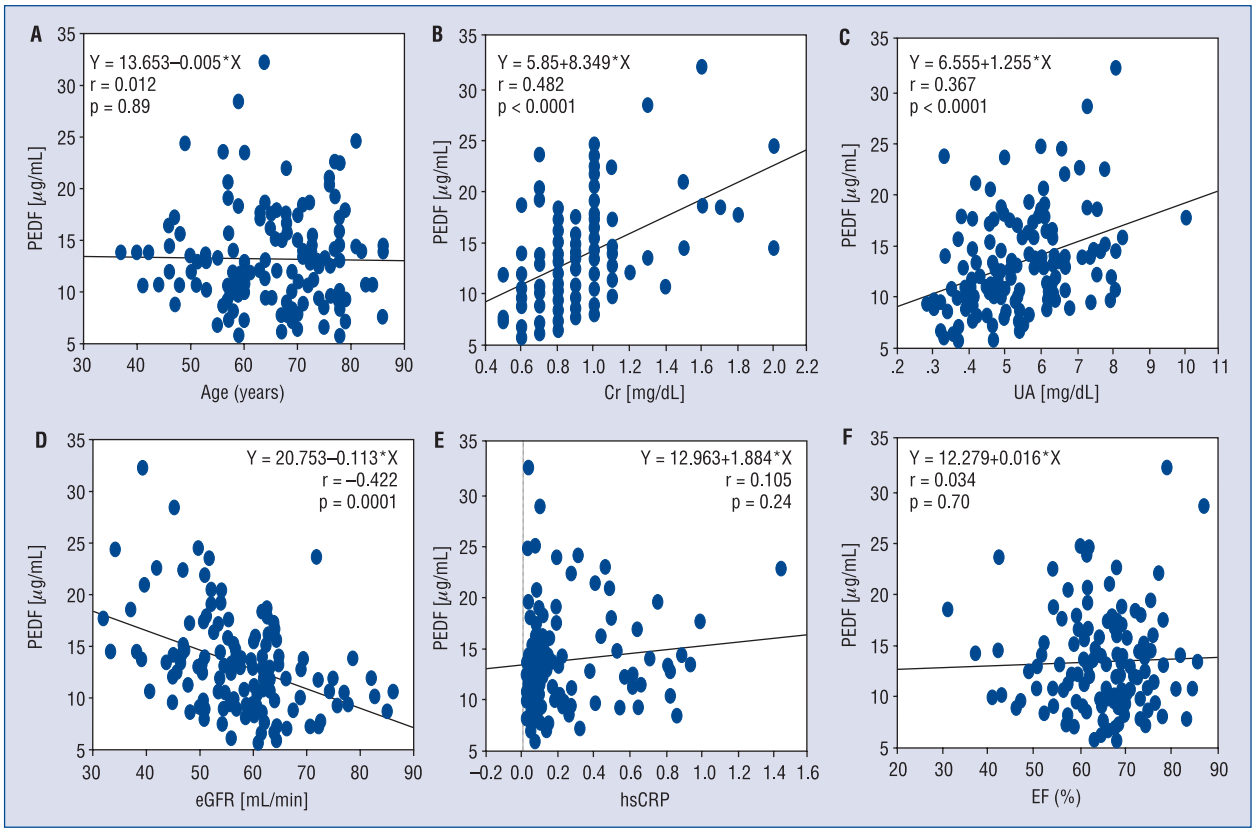

Figure 3. Correlations between plasma levels of PEDF and age (**A**), creatinine (Cr) (**B**), uric acid (UA) (**C**), estimated glomerular filtration rate (eGFR) (**D**), high-sensitive C-reative protein (hsCRP) (**E**) and ejection fraction (EF) (**F**).

Table 3. Predictors for PEDF.

	OR (95% CI)	p
Age	0.93 (0.87–0.99)	0.030
Gender	2.20 (0.57–8.53)	0.252
BMI	1.19 (0.99–1.43)	0.059
eGFR	0.90 (0.86–0.94)	< 0.0001
DM	2.59 (0.77–8.67)	0.123
HT	1.75 (0.29–10.6)	0.544
DL	0.93 (0.18–4.74)	0.930

OR — odds ratio; CI — confidence interval; BMI — body mass index; eGFR — estimated glomerular filtration rate; DM — diabetes mellitus; HT — hypertension; DL — dyslipidemia

clinical evidence of CAD, we also found a significant association between PEDF levels and the number of metabolic factors in CAD patients because PEDF levels in patients with four factors were significantly higher than those in patients without these factors. PEDF is synthesized in adipose tissue and its level is downregulated during the process of differentiation to mature adipocytes [16]. Adiponectin is also known to play an important role in the development of MetS. We previously reported that plasma adiponectin levels significantly decreased as the number of metabolic factors increased [17]. Since adiponectin has multiple functions including anti-atherogenic, insulin-sensitizing, lipid-oxidation enhancing, and vasodilatory activities, both adiponectin and PEDF have similar anti-atherosclerotic functions. Decreased plasma levels of adiponectin may play a significant role in the development of MetS, whereas increased plasma levels of PEDF may play a significant role in the prevention of MetS.

PEDF levels were significantly associated with age and eGFR, but not gender or diabetes by a multiple regression analysis in this study. Although PEDF levels in males were significantly higher than those in females [5], gender was not associated with PEDF levels in CAD patients. In addition, there were no differences in PEDF levels between DM and non-DM. There are contradictory reports regarding PEDF levels in diabetes: one showed that the plasma levels of PEDF increased in proliferative diabetic retinopathy, but not in the absence of, or only mild to moderate, non-prolife-

rative diabetic retinopathy [14], whereas another showed that the plasma PEDF level was low in a rat model of diabetic nephropathy [18]. The subjects with DM in our study may have only had mild to moderate DM.

Serum hsCRP level is an independent predictor of future cardiovascular events and is elevated in patients with CAD [19]. Umei et al. [20] found a positive association between serum levels of PEDF and hsCRP in apparently healthy unmedicated subjects. PEDF levels may be elevated as a compensatory effect against inflammation. However, this study and a previous report [5] indicated that serum hsCRP levels were not correlated with serum levels of PEDF. It is well known that statin and angiotensin II receptor blocker decrease serum levels of hsCRP [21, 22]. In the present study, the percentages of medications, such as statin and angiotensin II receptor blocker, were relatively high (75% and 72%, respectively). Among the patient characteristics, the use of medications could account for the discrepancies regarding the association between PEDF and hsCRP levels.

Limitations of the study

This study was a retrospective analysis of a limited number of patients. Thus, the results represent only a selected group of patients and the sample size was relatively small, which limited our ability to determine the significance of associations. To confirm the results of this study, a larger population needs to be examined.

Conclusions

PEDF may play a role in renal dysfunction in CAD patients. In addition, our study suggests that there is a significant association between PEDF levels and the number of metabolic factors in CAD patients.

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