Correlation Between Pigment Epithelium-Derived Factor (PEDF) level and Degree of Coronary Angiography and Severity of Coronary Artery Disease in a Chinese Population

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The role of pigment epithelium-derived factor (PEDF) in protection of coronary artery disease (CAD) remains controversial. The aim of this study was to reassess the value of PEDF in predicting the severity and prognosis of newly diagnosed stable CAD in a Chinese population.

Material/Methods: Plasma PEDF levels were measured in 259 stable CAD patients undergoing coronary angiography and 116 age- and sex-matched healthy controls. The severity of coronary atherosclerosis was assessed using Gensini score.

Results: PEDF levels were significantly lower in CAD patients than in healthy subjects (5.856±0.790 *vs.* 6.658±1.070 μg/ml, respectively, p<0.01). Stepwise regression analysis showed a negative correlation between PEDF levels and severity of CAD as quantified by Gensini score value (β=−0.626, p<0.01).

Conclusions: Our study showed that plasma PEDF levels were significantly lower in CAD patients than in controls, and the plasma PEDF levels may be used as a potential predicator for coronary severity.

MeSH Keywords: Angiography • Coronary Artery Disease • Plasma

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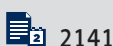
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Background

Coronary artery disease (CAD) remains a leading cause of human mortality. It is an atherosclerotic disease. The role of inflammation in the atherosclerotic process includes inducing a cascade of events that magnify immune cell infiltration, platelet activation and adhesion, arterial occlusion, plaque rupture, unstable angina, and myocardial infarction [1–5]. Pigment epithelium-derived factor (PEDF) is a 50-kDa glycoprotein belonging to the superfamily of serine protease inhibitors [6,7]. PEDF, expressed in various tissues throughout the body, such as the eyes, liver, heart and adipose tissue, was first identified in retinal pigment epithelium cells. It has been reported that PEDF inhibits the expression of various inflammatory factor such as tumor necrosis factor-α (TNF-α), IL-6, vascular endothelial growth factor (VEGF), monocyte chemoattractant factor-1 (MCP-1), and intercellular adhesion molecule-1 (ICAM-1). In addition, the suppression of NAPDH oxidase-mediated reactive oxygen species (ROS) generation can be effectively suppressed. PEDF also inhibits occlusive thrombus formation by blocking platelet activation and aggregation. It has been shown that PEDF has anti-inflammatory, anti-oxidant, anti-angiogenic (Liu, Wang et al. 2014) properties [8–11]. Therefore, this evidence indicates that PEDF has a protective role in atherosclerosis and has been considered to be a therapeutic target in cardiovascular disease [6].

Clinical studies have shown that PEDF is a marker of atherosclerosis in humans [12–14]. PEDF levels are significantly lower in human ischemic hearts than in healthy hearts [8,13,15]. We previously demonstrated that serum PEDF level is significantly decreased in patients with acute coronary syndrome (ACS) [13]. However, it remains unknown whether PEDF level is correlated with CAD severity. In the present study we examined whether serum PEDF level is independently correlated with CAD severity as evaluated by the Gensini score (GS).

Material and Methods

Patients

A total of 375 consecutive patients were studied at the General Hospital of the People's Liberation Army (GHPLA) between October 2016 and June 2017, including 259 patients with coronary heart disease (the CAD group) (CAD was defined as stenosis of single or multiple vessels ≥50%) and 116 age- and sex-matched controls with stenosis <50% as defined by angiography (the non-CAD group) during the same period.

The following patients were excluded from the study: those testing positive on the treadmill exercise test (non-CAD group); patients with previous history of cardiac surgery, percutaneous coronary intervention, or coronary bypass grafting (CABG) and/or acute myocardial infarction (AMI); patients with uncontrolled decompensated heart failure, unstable hemodynamic status, acute coronary syndrome, cardiomyopathy, severe kidney or liver dysfunction, infectious or systematic inflammatory disease, immune disease and/or glucocorticoid therapy; patients with known malignant tumor; and patients with clinical or coronary angiogram (CAG) data unavailable or incomplete. All of the CAD patients were given medical treatments based on the relevant guidelines [16].

Written informed consent was obtained from all patients, and the study protocol was approved by the Ethics Committee of the GHPLA.

Clinical examination

The traditional clinical risk factors were: hypertension, blood pressure ≥140/90 mmHg (at least 3 times in different environments in a sitting position for 15 min) or self-reported hypertension and currently taking anti-hypertensive drugs; diabetes, fasting blood glucose ≥7.0 mmol/L or 2-h postprandial blood glucose ≥11.1 mmol/L, or random plasma glucose ≥11.1 mmol/L, or currently taking hypoglycemic drugs; hyperlipidemia, fasting total cholesterol (TC) ≥5.1 mmol/L or triglyceride (TG) ≥1.7 mmol/L; body mass index (BMI), calculated as weight (kg)/height (m^2); and currently smoking (smoking regularly within the last 6 months).

Evaluation of CAD severity

Coronary angiography was blindly evaluated by 3 experienced cardiologists. The coronary stenosis was assessed by coronary angiography. CAD was defined as stenosis of ≥50% in the diameter of the coronary artery. The severity and extent of CAD were valued by GS as the sum of all segment scores. Briefly, stenosis severity of ≤25% stenosis, 26–50% stenosis, 51–75% stenosis, 76–90% stenosis, 90–99% or 100% (total occlusion) were scored as 1, 2, 4, 8, 16, or 32, respectively. The severity of each branch was calculated by multiplying factors according to the functional importance of the given segment (Table 1) [17]. The CAD patients were further divided into 3 subgroups according to their GS score: Sb1, score ≤26; Sb2, GS score 27–45; and Sb3, GS score >45.

Plasma collection and chemistry measurement

Blood samples were collected from each patient after at least 12-h fasting in the morning. Serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), serum Glu, uric acid, Scr, and BUN were all measured using standard laboratory techniques in an automatic biochemical analyzer (Cobas 8000,

Table 1. Gensini score calculation method.

Coronary stenosis	Severity score
1–25%	1 points
26–50%	2 points
51–75%	4 points
76–90%	8 points
91–99%	16 points
100%	32 points
Coronary artery	Multiplication factor
Left main coronary artery	5
Proximal left anterior descending artery	2.5
Proximal circumflex artery	
Mid left anterior descending artery	1.5
Distal left anterior descending artery,	1
Mid or distal circumflex artery	
Right coronary artery	
Other branch	0.5

Roche Diagnostics, USA). The serum concentration of hemoglobin A1c (HbA1c) was analyzed by standard procedures using the VARIANT II hemoglobin testing system (BIO-RAD, USA). The samples were centrifuged 4000 rpm for 15 min at 4°C and stored at –80°C until analysis.

Serum PEDF levels were determined using enzyme-linked immunosorbent assay (ELISA) kits for detection of human PEDF (Cloud-clone Corp, 96T, USA) according to the manufacturer's protocol. The detection range was 1.56–100μg/ml.

Statistical analysis

Statistical analysis was performed by SPSS (Version 22.0, IBM, USA). Data of continuous variables are presented as the mean ± standard deviation (SD), and categorical variables are presented as the percentage (%). Continuous variables were compared using the independent Student's t test between these groups. One-way ANOVA was performed for the subgroups, followed by the LSD t test. Pearson's correlation analysis was used to determine the correlation between serum PEDF level and GS. Independent predictors of coronary lesion severity scored by GS were determined by multivariate linear regression. The P value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

According to the angiography, the 375 participants investigated were initially divided into a CAD and a non-CAD group. The baseline demographics and clinical characteristics of the studied population are presented in Tables 2 and 3. Baseline characteristics were compared between the CAD and non-CAD groups. The CAD group had significantly higher BMI, HBA1c percentage, GLU levels, hypertension, diabetes, hyperlipidemia, smoking, and male sex ratio rate compared to the non-CAD group, but it had significantly lower concentrations of LDL-C, TC, and HDL-C (Table 2, P<0.001). Subgroup analysis revealed that there were no significant differences in hypertension, diabetes, or smoking rate. There were no significant differences in HDL-C, LDL-C, TC, TG, BP, uric acid, ser, or BUN levels. However, the BMI was significantly different among the 3 subgroups (Table 3, P=0.02).

PEDF levels

Serum PEDF levels in CAD group (5.856±0.790 μg/ml) were significantly lower than in controls (6.658±1.070 μg/ml, P<0.01; Figure 1).

There were significantly different serum PEDF levels among the 3 subgroups (6.404±0.563, 5.863±0.713, 5.305±0.672, Table 3, Figure 2, P=0.000).

Correlation of serum PEDF with the severity of CAD

The severity of CAD quantified by GS (r=–0.569, p<0.001; Table 4, Figure 3) was negatively correlated with PEDF levels, but positively correlated with age, male sex, and BMI (Table 4).

Multiple linear regression analysis

The correlation between the severity of CAD quantified by GS and the serum PEDF levels was analyzed by multiple linear regression analysis. After controlling for age, male sex ratio, DM history, and BMI, linear regression analysis indicated that the severity of CAD quantified by GS (β=–0.626, p<0.001; Table 5) was independently correlated to PEDF concentration.

Discussion

Atherosclerosis is the primary pathological change involved in CAD. Atherosclerosis is thought to be a chronic inflammatory disease of the coronary artery. Inflammatory factors such as interleukin-6 (IL-6) and TNF-α are involved in all stages of atherosclerosis progression. PEDF has been known to be protective

Table 2. Basic characteristics of the studied population.

	CAD group (n=259)	Non-CAD group (n=116)	P value
Baseline clinical features			
Age, years	62.95±11.09	61.49±11.95	0.250
Male, N (%)	181 (69.9)	84 (72.4)	0.619
Hypertension, N (%)	186 (71.8)	58 (50)	0.000
Diabetes, N (%)	94 (36.3)	11 (9.5)	0.000
Hyperlipidemia, N (%)	70 (27.0)	17 (14.0)	0.009
Current smoking, N (%)	103 (39.8)	21 (18.1)	0.000
Body mass index, kg/m^2 (Mean ±SD)	25.68±3.60	24.28±3.41	0.015
BP, systolic, mmHg (Mean ±SD)	133.29±20.60	133.05±24.32	0.924
BP, diastolic, mmHg (Mean ±SD)	75.02±11.58	75.41±11.65	0.764
Biochemistry parameters (Mean ±SD)			
TC, mmol/L	3.75±1.11	4.36±0.98	0.000
HDL-C, mmol/L	1.04±0.28	1.25±0.45	0.000
LDL-C, mmol/L	2.24±0.81	2.72±0.81	0.000
TG, mmol/L	1.56±0.96	1.60±0.96	0.665
HBA1c, %	6.44±1.43	5.75±0.71	0.000
Uric acid, μmol/L	324.25±96.16	318.08±90.25	0.559
GLU, mmol/L	6.64±0.75	5.33±0.85	0.000
Scr, μmol/L	95.31±95.75	90.75±24.96	0.761
PEDF, μg/ml	5.856±0.79	6.658±1.07	0.000

against atherosclerosis through its anti-inflammatory, anti-oxidant, anti-angiogenic, and anti-thrombotic effects. Many inflammatory factors can be suppressed by PEDF; for example, PEDF can inhibit TNF-α-induced IL-6 expression in endothelial cells by suppressing NADPH oxidase-mediated reactive oxygen species generation [18]. *In vitro* studies have found that hepatic CRP production is stimulated by advanced glycation end-product and receptor of advanced glycation end-product interaction, and that AGE signaling-induced CRP expression is blocked by PEDF [19]. In the progression and development of atherosclerosis, endothelial injury induced by oxidized low-density lipoprotein (ox-LDL) plays a vital role. Our previous research has demonstrated that PEDF can decrease the expression of ox-LDL by suppressing the Wnt/β-catenin pathway and then reducing oxidative stress [20,21]. PEDF has been shown to be protective against atherosclerosis through its anti-inflammatory, anti-oxidant, anti-angiogenic, and anti-thrombotic effects [6–8], and serum PEDF level is independently related to intima-media thickness and vascular inflammation [12].

These findings suggest that PEDF is associated with atherosclerosis plaque volume.

In the present study, we demonstrate for the first time that serum plasma PEDF levels are inversely correlated with coronary artery disease severity as quantified by GS [17], and it is a precise method for use in estimating coronary artery disease severity in a Chinese cohort with stable CAD. In addition, the severity of coronary artery disease was positively related with the male sex, BMI, diabetes.

To the best of our knowledge, this is the first report to evaluate the relationship between PEDF concentration and coronary artery stenosis in a Han Chinese population with CAD. Our previous study confirmed that serum PEDF expression is significantly decreased in ACS patients compared to healthy controls [13]. However, the PEDF levels in CAD patients are still controversial. Our study results are in agreement with previous research showing that the patients in a CAD group have lower

Table 3. Baseline clinical and demographic features according to Gensini scores in CAD patients.

|	Gensini score category			P value
	≤26 N=85	26–45 N=88	>45 N=86	
Baseline clinical features				
Age, years	62.92±9.92	62.01±9.87	63.95±13.20	0.514
Male, n (%)	50 (58.8)	65 (73.9)	66 (76.7)	0.023
Hypertension, n (%)	60 (70.6)	60 (68.2)	66 (76.7)	0.434
Diabetes, n (%)	27 (31.8)	36 (40.9)	31 (36.0)	0.457
Hyperlipidemia, n (%)	20 (23.5)	29 (33.0)	21 (24.4)	0.302
Current smoking, n (%)	28 (32.9)	40 (45.5)	35 (40.7)	0.238
Body mass index,kg/m^2 (Mean±SD)	24.90±3.42	25.35±2.98	26.31±3.54	0.020
BP, systolic, mmHg (Mean ±SD)	135.08±20.66	131.05±17.05	133.80±23.66	0.420
BP, diastolic, mmHg (Mean ±SD)	75.39±11.53	75.15±11.57	74.53±11.76	0.884
Biochemistry parameters (Mean ±SD)				
TC, mmol/L	3.73±1.20	3.74±0.99	3.77±1.11	0.973
HDL-C, mmol/L	1.06±0.29	1.05±0.31	1.01±0.25	0.431
LDL-C, mmol/L	2.27±0.81	2.20±0.76	2.25±0.96	0.836
TG, mmol/L	1.67±1.20	1.50±0.89	1.50±0.73	0.564
HBA1c, %	6.47±1.52	6.43±1.37	6.43±1.42	0.986
Uric acid, μmol/L	327.62±81.46	319.01±80.99	326.27±121.45	0.819
GLU, mmol/L	6.34±2.33	6.66±2.68	6.92±3.20	0.305
Scr, μmol/L	85.53±48.19	93.14±98.14	107.21±123.97	0.324
PEDF, μg/ml	6.404±0.563	5.863±0.713	5.305±0.672	0.000
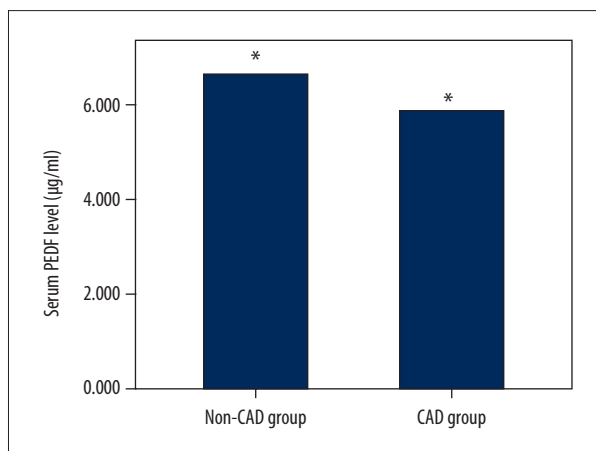
Figure 1. Serum PEDF levels in the CAD and Non-CAD group. CAD – coronary artery disease; PEDF – pigment epithelium-derived factor. * P<0.001.
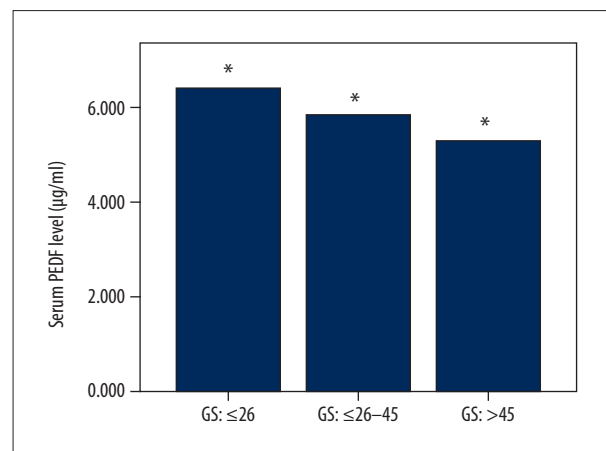

Figure 2. Serum PEDF levels in the 3 subgroups of CAD. CAD – coronary artery disease; PEDF – pigment epithelium-derived factor. * P<0.001.

Table 4. Correlation between severity of Gensini scored – coronary artery disease and clinical variables.

	Correlation coefficient	p Value
Age, years	0.148	0.017
Male, n (%)	0.171	0.006
BMI (kg/m²)	0.180	0.004
SBP (mmHg)	0.033	0.596
DBP (mmHg)	−0.014	0.823
PEDF (µg/ml)	−0.569	0.000
TC (mmol/L)	−0.03	0.634
TG (mmol/L)	−0.067	0.280
HDL-c (mmol/L)	−0.112	0.073
LDL-c (mmol/L)	−0.030	0.636
Diabetes, n (%)	0.055	0.038
Current Smoking, n (%)	0.088	0.161
HBA1c, %	0.041	0.525
Uric acid, µmol/L	0.011	0.854
Hypertension, n (%)	0.095	0.127

Table 5. Stepwise multiple linear regression analysis of clinical characteristics and the Gensini scores in CAD patients.

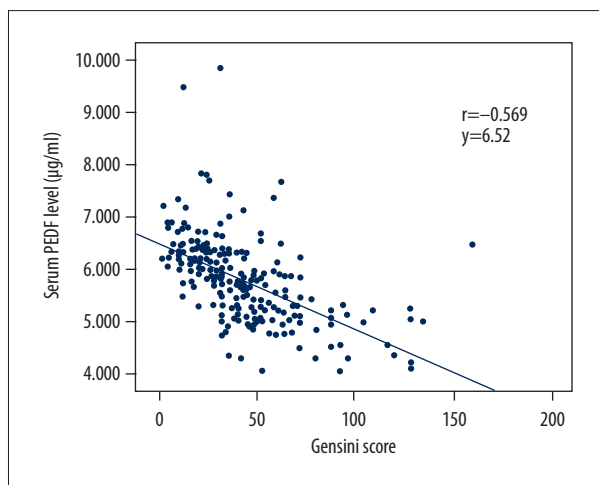|	Correlation coefficient	p Value
Age, years	0.072	0.164
Male, n (%)	−0.088	0.092
BMI (kg/m²)	0.064	0.219
SBP (mmHg)	0.069	0.218
DBP (mmHg)	0.005	0.926
PEDF (µg/ml)	−0.626	0.000
TC (mmol/L)	−0.039	0.443
TG (mmol/L)	−0.032	0.531
HDL-c (mmol/L)	−0.069	0.179
LDL-c (mmol/L)	−0.025	0.634
Diabetes, n (%)	0.151	0.002
Current Smoking, n (%)	0.096	0.063
HBA1c, %	0.038	0.512
Uric acid, µmol/L	0.052	0.315
Hypertension, n (%)	0.094	0.073

Figure 3. The relationship between serum PEDF levels and Gensini score (r=−0.569; P<0.001) in CAD group. CAD – coronary artery disease; PEDF – pigment epithelium-derived factor.

PEDF levels compared to the non-CAD group patients [8,12,15]. In the present prospective study of new-onset patients undergoing CAG, we found that baseline plasma PEDF levels were inversely correlated with the severity of CAD in a Chinese cohort with stable CAD. Our results show that there is a linear relationship between PEDF and GS. PEDF levels were significantly higher in patients with GS >45 compared with patients with scores of 26–45 or ≤26. These results indicate that PEDF may be a valuable biomarker of coronary artery stenosis. Our results may help develop a new method for predicting the severity or stenosis of coronary artery disease.

Recently, diabetes has been noted as a new independent risk factor of coronary heart disease [22]. Many researchers have demonstrated that diabetes is an independent risk factor for the prevalence and severity of significant angiographic CAD [23–25]. Research in Chinese populations has also demonstrated that GS correspondingly increased with FPG (fasting blood glucose) levels [23]. Our stepwise multiple linear regression analysis showed that the diabetes prevalence rate in these subgroups are significantly different, and the diabetes

prevalence rate was significantly higher in patients with GS >45 compared with patients with scores of 26–45 or ≤26. Our study shows that coronary heart disease comorbid with diabetes in patients with coronary heart disease is more likely to be a multivessel disease, and the mechanisms are activation of inflammation, blood lipid metabolism, and vascular endothelial cell injury [26]. Our study may provide a new approach to estimate the severity of coronary artery disease. Some research showed that current smoking is related to the severity of coronary artery disease [27], but we did obtain a similar result, probably because of the small population of our study.

The inflammatory process initiated by myocardial tissue necrosis is related to an increase of nonspecific serum markers such as C-reactive protein (CRP) peripheral white blood cell count (WBC) and erythrocyte sedimentation rate above normal limits. Severity of CAD is optimally assessed by means of coronary angiography, demonstrates the number of epicardial coronary vessels affected, the anatomical distribution of critical stenotic lesions, and the extent of vascular flow impairment. Coronary angiography remains the standard method for assessment of anatomic coronary disease, because no other currently available test can accurately define the extent of coronary luminal obstruction [28,29].

By comparing the CAD group with the non-CAD group, we observed that there were considerable differences in the proportion of males, individuals with hypertension, diabetes, hyperlipidemia, smoking, and BMI levels. These are in agreement with previous studies reporting that male sex, hypertension, diabetes, hyperlipidemia, smoking, BMI levels are major risk factors for CAD.

There are certain limitations to our study that need to be considered. First, this was a cross-sectional study, and no follow-up analysis was performed. Our previous study showed that after 6-month follow-up, patients with lower PEDF levels had more adverse cardiac outcomes after ACS [13]. Second, our sample size was small, and the study was performed at a single center. Finally, it has been noted that PEDF contributes to plaque stability, and is thus involved in the pathogenesis of ACS [30,31]; unfortunately, we did not have CT images for all of the patients in this study, so future studies investigating the relationship between PEDF levels and plaque instability in patients with CAD are needed. Further research with and larger sample sizes will help determine the exact function of PEDF in atherosclerosis.

Conclusions

We found that plasma PEDF levels were significantly lower in CAD patients than in non-CAD patients, and PEDF concentration can be considered a potential predictor of coronary artery disease severity.

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