Serum platelet-derived growth factor is a novel biomarker for the prediction of vulnerable plaque in patients with NSTEMI-ACS

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Abstract

Objective: To investigate the relationship between serum platelet-derived growth factor (PDGF) and vulnerable plaque in patients with non-ST-elevation acute coronary syndrome (NSTEMI-ACS).

Methods: A total of 65 patients with NSTEMI-ACS were divided into vulnerable plaque group (n=46) and vulnerable plaque and stable plaque group (n=19) according to intravascular ultrasound (IVUS) examinations. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and serum PDGF were measured. Plaque characteristics and components were analyzed using gray-scale and iMap-IVUS. Correlation was performed between plaque characteristics and ACS markers. Logistic regression analysis was applied to determine risk factors. Receiver operating characteristic (ROC) curve was used to evaluate the predictive value.

Results: Patients in vulnerable plaque group had visible higher levels of TG, LDL-C and PDGF ($P < 0.05$). There were significant differences in minimal lumen area (MLA), plaque area, plaque burden, fibrotic (FI), lipidic (LI) and necrotic core (NC) between the two groups ($P < 0.05$). PDGF was weakly correlated with plaque burden ($R=0.428$, $P < 0.05$), as well as moderately correlated with NC ($R=0.669$, $P < 0.05$). Multivariate analysis showed that serum PDGF (OR 4.751, [95% CI 1.534-29.543], $P=0.05$) was an independent risk factor of vulnerable plaque. The area under the curve (AUC) was 0.876 (95% CI 0.804-0.948, $P=0.001$).

Conclusion: Serum PDGF could be used as a novel biomarker for the prediction of vulnerable plaque in patients with NSTEMI-ACS.

Introduction

Non-ST-elevation acute coronary syndrome (NSTEMI-ACS) is a major life-threatening disease worldwide, and the rupture of vulnerable plaque were demonstrated to be associated with ACS in clinic [1]. IVUS could be feasible to characterize the morphology of culprit coronary lesions or satellite lesions in patients undergoing coronary angiography, which provided clues to identify potentially vulnerable plaques [2]. However, it has not been widely used in clinic due to its invasiveness and high expenses. Identifying a novel biomarker may aid detection of vulnerable coronary plaques [3, 4], and such symptomatic and asymptomatic patients would dramatically benefit from intensive antithrombotic therapy or stenting in patients with NSTEMI-ACS [5].

As one of growth factors, platelet-derived growth factor (PDGF) was originally considered to be platelet and serum mitogen that regulated the growth and division of glial cells, smooth muscle cells (SMC) and fibroblasts [6]. Previous researches further unveiled that PDGF was involved in atherosclerosis [7] and tumor growth and metastasis [8]. In a heart-specific transgenic mice model, PDGF-D was demonstrated to contribute to the development of cardiac fibrosis and proliferation of vascular smooth muscle cells (vSMCs) [9]. On the contrary, there were some studies demonstrated that PDGF accelerated the generation of bone marrow-derived cardiac myocytes after acute coronary occlusion [10] and improved

ventricular function after infarction [11]. Moreover, the relationship between PDGF and vulnerable plaque remains poorly elucidated.

Therefore, it is of great significance to identify the relationship between the level of serum PDGF and plaque characteristics in patients with NSTEMI-ACS from the perspective of clinical trials. In this study, the correlation analysis was performed between vulnerable coronary plaques characterized using IVUS in conjunction with the detection of serum PDGF, as well as the predictive value of PDGF for vulnerable plaques was also investigated in NSTEMI-ACS patients.

Methods

Participants

From May 2016 to February 2018, 65 patients diagnosed with NSTEMI-ACS were continuously selected from coronary angiography (CAG) examination in Tianjin Chest Hospital, and the degree of coronary stenosis was between 50% and 90%. Intravascular ultrasound (IVUS) examinations were performed, and the participants were divided into vulnerable plaque group (n = 46) and vulnerable plaque and stable plaque group (n = 19) according to the definition of vulnerable plaque [12]. Patients with bivascular or multivascular disease were divided into vulnerable plaque groups as long as they had vulnerable plaques in any major vessel. NSTEMI-ACS diagnosis was based on the guidelines for the diagnosis and treatment of NSTEMI-ACS [13]. Diabetes mellitus was defined as active use of an antidiabetic agent, or fasting plasma glucose level ≥ 7.0 mmol/L or casual plasma glucose level ≥ 11.1 mmol/L. All participants gave written informed consent and the study was approved by Tianjin Chest Hospital ethics committee.

NSTEMI-ACS patients aged > 18 years old, who were first diagnosed with NSTEMI-ACS; who had diameter stenosis > 50% in two or more major vessels and had not recently been heavily exposed to antiplatelet and anticoagulant drugs were eligible for enrollment. Exclusion criteria: (1) Acute STEMI or previous history of old myocardial infarction; (2) Serum creatinine > 2.5 mg/dl; (3) Heart failure decompensation stage, combined with cardiac valvular disease, severe arrhythmia, pacemaker implantation and previous history of revascularization, and history of cardiac surgery; (4) Severe allergic reactions to drugs used throughout the trial process; (5) Contraindications for CAG examination or IVUS; (6) Combined with malignant tumors, autoimmune diseases, hematological diseases, etc. (7) Coronary artery bypass surgery is planned after coronary angiography; (8) Vascular anatomical characteristics make it impossible to perform IVUS examination, such as severe calcification, tortuosity, chronic occlusive lesions and thrombosis.

Laboratory evaluation

4 ml of peripheral venous blood was taken from the fasting state, placed in a sodium citrate anticoagulant tube, centrifuged at 3000 r/min for 10 min at room temperature, and the serum samples

were stored at -80°C . Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and glycated hemoglobin (HBA1c) were measured. The serum PDGF level was detected by ELLSA (Wuhan Elabscience Biotechnology Co., Ltd) according to the manufactures' instructions.

CAG and IVUS procedure and analysis

Coronary angiography was performed using single-arm digital subtraction angiogram (DSA, Boston Scientific, Natick, MA, USA) and digital imaging system together with standard Judkins method. Visual measurement was used to estimate the stenosis degree of reference vessel diameter and lesion location diameter, and the angiographic results were evaluated by at least two experienced cardiologists.

IVUS imaging was then performed in patients with NSTEMI-ACS with a degree of coronary stenosis between 50% and 90% (*Fig 1A*). The catheter was advanced sufficiently distal to the culprit lesion, and then automated pullback was performed at a speed of 0.5mm/s. Real-time image acquisition and continuous input and storage, followed by localization analysis were further applied using QIVUS iMap BasicViewer 3.0 (Medis medical imaging systems, Leiden, the Netherlands). After identifying the external elastic membrane (EEM) and the boundary of each layer (0.4mm thickness), the following parameters were measured: EEM cross-sectional area (EEM CSA), lumen area and minimal lumen area (MLA). Plaque area = EEM CSA - lumen area, and plaque burden = plaque area / EEM CSA. The plaque components were quantitatively analyzed by using different colors to represent different plaque components, and the plaque components were fibrotic (FI), lipidic (LI), necrotic core (NC) and dense calcium (DC) (*Fig 1B and 1C*).

Statistical analysis

SPSS 20.0 statistical software (SPSS Inc, Chicago, IL) was utilized for all statistical analysis. The continuous variables were exhibited as mean $\pm$ SD. ANOVA was utilized for comparison between multiple groups, following Tukey's multiple comparison tests. Data were expressed as frequencies and percentages for category variables, using Chi-square test. Correlation was evaluated by using Pearson analysis. Logistic regression analysis was applied to determine risk factors. ROC curve was used to evaluate the predictive value. The level of statistical significance was 0.05.

Results

Patient characteristics

A total of 65 consecutive patients with NSTEMI-ACS were enrolled in the study. The participants for inclusion were divided into stable plaque group (n = 19) and vulnerable plaque group (n = 46). As shown

in *Table 1*, there were significant differences in sex, smoking history and diabetes mellitus history between the two groups ($P < 0.05$). Patients in vulnerable plaque group had visible higher levels of TG and LDL-C than those in stable plaque group ($P < 0.05$). In addition, elevated level of PDGF was observed in vulnerable plaque group ($P < 0.05$).

Plaque characteristics and components analysis

Plaque characteristics and components in vulnerable plaque group and stable plaque group were then examined using gray-scale and iMap-IVUS. The findings showed that there were significant differences in MLA, plaque area, plaque burden, FI, LI and NC between the vulnerable plaque and stable plaque groups ($P < 0.05$), while no statistic differences were found in EEM CSA and DC (*Table 2*).

Correlation analysis between plaque characteristics and ACS markers

Variables with $P < 0.05$ including TG, LDL-C and PDGF in *Table 1* were selected to analyze the correlation with plaque characteristics. The results showed that TG and LDL-C were not correlated with plaque burden. In addition, PDGF was weakly correlated with plaque burden ($R = 0.428$, $P < 0.05$), as well as moderately correlated with NC ($R = 0.669$, $P < 0.05$) (*Table 3*).

Univariate logistic regression analysis for vulnerable plaque

Univariate logistic regression analysis was established with vulnerable plaque as dependent variables and variables with $P < 0.05$ in *Table 1* as independent variables in this study, yielding that there were significant differences in smoking, diabetes mellitus and PDGF (*Table 4*).

Multivariate logistic regression analysis for vulnerable plaque

Then variables with $P < 0.05$ in univariate analysis were further analyzed. Multivariate analysis showed that the level of serum PDGF (OR 4.751, [95% CI 1.534–29.543], $P = 0.05$) was independent risk factor of vulnerable plaque (*Table 5*).

To indicate PDGF in ROC analysis, a cut-off value had 76.2% sensitivity, 43.7% specificity, 62.9% positive predictive value (PPV) and 59.4% negative predictive value (NPV) for prediction of vulnerable plaque. The area under the curve (AUC) was 0.876 (95% CI 0.804–0.948, $P = 0.001$) (*Fig 2*).

Discussion

The proportion of patients manifesting with NSTEMI-ACS is increasing and remain a major cause of death worldwide [14]. Plaque instability and subsequent thrombus formation are the leading causes of ACS. Although IVUS has ability to characterize the culprit lesions, it is attractive to noninvasively characterize morphology and composition of vulnerable plaques in culprit and stable lesions in the future, especially in patients with ACS at low risk or in patients with suspected ACS. Therefore, the aim of this study was to find a novel biomarker to noninvasively predict vulnerable plaque in patients with NSTEMI-ACS. The results showed a higher level of serum PDGF in vulnerable plaque group; correlation analysis showed that PDGF was weakly correlated with plaque burden and moderately correlated with NC; Logistic regression analysis revealed that serum PDGF was independent risk factor of vulnerable plaque; ROS analysis demonstrated that PDGF could be used as a predictor to indicate plaque instability.

Gray-scale IVUS is commonly used to characterize coronary plaques in the clinical setting; however, it is insufficient for accurate assessments of plaque characteristics due to its lower resolution. iMap-IVUS, make up for shortcomings of Gray-scale IVUS, could more intuitively classify and quantify plaques. Trusinskis K [15] revealed a comparatively higher proportion of necrotic tissue in the culprit lesions detected by iMap IVUS than that in non-culprit lesions. Araki T [16] characterized coronary plaque using a 40 MHz iMAP-IVUS, and increased lipidic amount and necrotic plaque volume were found in type 2 diabetes mellitus patients. In the present study, gray-scale IVUS combined with iMAP-IVUS technique was used to characterize coronary plaque in patients with NSTEMI-ACS critical lesions; patients in vulnerable plaque group had elevated MLA, plaque area, plaque burden, FI, FF and NC.

Ohayon J and colleagues [17] studied the changes in plaque instability with size of necrotic core and plaque morphology, yielding that a combination of cap thickness, necrotic core thickness and the arterial remodeling index played pivotal roles in determining plaque stability. Previous studies conducted by Araki T et al [18] confirmed that increased percentages of lipidic, necrotic, and large plaque burdens seemed to be implicated in plaque vulnerability. In addition, Liu et al [19] believed that the absolute necrotic area, percentages of fibrotic and necrotic tissues, and plaque burden were relevant predictors of plaque instability. In the current study, PDGF was weakly correlated with plaque burden, as well as moderately correlated with necrotic core. Based on these previous studies, it was verified that PDGF could be a predictor of vulnerable plaque in patients with NSTEMI-ACS.

Compelling studies have shown that PDGFs and their receptors contribute to the cardiovascular diseases [20]. Gallini R et al [21] demonstrated that all PDGF isoforms induced cardiac hypertrophy and fibrosis in transgenic mice, in which abundant PDGF-A led to an severe fibrotic reaction, while overexpression of PDGF-B resulted in focal fibrosis and moderate cardiac hypertrophy. Pontén A [9] overexpression of PDGF-D in transgenic mice promoted proliferation of cardiac interstitial fibroblasts and vSMCs, which led to cardiac fibrosis and dilated cardiomyopathy followed by subsequent cardiac failure. In this study, elevated level of serum PDGF was observed in patients with vulnerable plaques, and PDGF was proved to

be an independent risk factor of vulnerable plaque. Further analysis suggested that PDGF could be used to predict vulnerable plaque in patients with NSTEMI-ACS.

In this study, in order to eliminate confounding factors caused by platelets, the patients who were first diagnosed with CHD, had not recently been heavily exposed to antiplatelet and anticoagulant drugs, and had no blood diseases were selected in this study. There are some limitations in this study. Firstly, the present study comprised a relatively small sample size which may introduce selection bias. Secondly, this single-center study lacks external validation. Finally, the follow-up time was missing. Therefore, more multi-center, longer term follow-up and large-sample clinical studies are urgent to be performed in the future.

In conclusion, we demonstrated that the serum PDGF was independent risk factor of vulnerable plaque in patients with NSTEMI-ACS. Our findings suggested that serum PDGF might become a novel biomarker for the prediction of vulnerable plaque in patients with NSTEMI-ACS.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

Concept/design, Ying Zhan; Data collection, data analysis/interpretation and drafting article, Hong Zhang; Data collection and statistics, Yujie Liu and Kejing Ma; Critical revision of article, Jia Zhou and Jingjing Guan

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Availability of data and materials

The dataset supporting the conclusions of this article is available in the Tianjin Chest Hospital repository

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Tables

Table 1 Baseline characteristics of the study population

Variables	stable plaque group (n=19)	vulnerable plaque group (n=46)	P value
Male (%)	6 (33.33)	21 (51.22)	0.013
Age (years)	61.82±10.235	62.28±4.33	0.163
Smoking (%)	8 (44.44)	29 (70.73)	0.002
Diabetes mellitus (%)	3 (16.67)	15 (36.59)	0.035
TC (mmol/L)	4.355±0.963	4.762±1.063	0.091
TG (mmol/L)	1.467±0.434	1.909±0.913	0.031
HDL-C (mmol/L)	1.092±0.225	0.907±0.150	0.064
LDL-C (mmol/L)	3.427±0.775	4.231±0.775	0.028
PDGF (pg/mL)	1.989±0.276	2.378±0.391	0.001

Data are presented as number (percentage) of patients or mean±SD. TC, Total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PDGF, platelet-derived growth factor.

Table 2 Plaque characteristics and components in the vulnerable plaque and stable plaque groups

Variables	stable plaque group (n=19)	vulnerable plaque group (n=46)	P value
EEM CSA/mm ²	13.169±2.668	14.133±4.498	0.474
MLA/mm ²	5.423±1.251	3.593±1.586	0.001
Plaque area/mm ²	7.747±2.585	10.540±3.802	0.004
Plaque burden (%)	57.610±11.533	73.841±8.915	0.001
FI (%)	86.833±4.119	52.275±17.805	0.001
LI (%)	5.667±2.944	10.255±3.463	0.001
NC (%)	6.667±1.852	35.764±11.656	0.001
DC (%)	0.833±0.353	2.255±0.957	0.338

Data are presented as number (percentage) of patients or mean±SD. FI, Fibrotic tissue; LI, clipidic; NC, necrotic core; DC, dense calcium.

Table 3 Correlations between plaque characteristics and ACS markers

Variables	TG	LDL-C	PDGF
MLA	R=0.132	R=0.478	R=0.244
Plaque area	R=0.101	R=0.430	R=0.251
Plaque burden	R=0.226	R=0.235	R=0.428*
FI	R=0.184	R=0.118	R=0.197
LI	R=0.186	R=0.226	R=0.017
NC	R=0.129	R=0.115	R=0.669*
DC	R=0.081	R=0.113	R=0.001

**P* < 0.05. FI, Fibrotic tissue; LI, clipidic; NC, necrotic core; DC, dense calcium; PDGF, platelet-derived growth factor.

Table 4 Univariate logistic regression analysis for vulnerable plaque

Variables	β	Wald	<i>P</i> value	OR	95% CI
Male	0.773	1.184	0.206	2.147	(1.538, 8.725)
Smoking	1.092	2.093	0.003	3.221	(2.876, 4.351)
Diabetes mellitus	0.758	1.006	0.028	2.133	(1.485, 9.479)
TG	1.147	3.617	0.057	1.662	(1.082, 2.647)
LDL-C	2.035	2.58	0.064	2.654	(1.325, 4.531)
PDGF	2.036	6.947	0.008	3.375	(1.009, 5.486)

FI, Fibrotic tissue; LI, clipidic; NC, necrotic core; DC, dense calcium; PDGF, platelet-derived growth factor.

Table 5 Multivariate logistic regression analysis for vulnerable plaque

Variables	B	Wald	<i>P</i> value	OR	95% CI
Smoking	0.962	1.54	0.087	3.384	(1.847, 9.524)
Diabetes mellitus	0.929	4.357	0.056	2.532	(1.534, 12.515)
PDGF	2.531	5.481	0.005	4.751	(1.534, 9.543)

PDGF, platelet-derived growth factor.

Figures

Figure 1

CAG and IVUS examinations. A, CAG showed 70% coronary stenosis; B, Gray-scale IVUS image; C, iMap-IVUS image. CAG, coronary angiography; IVUS, intravascular ultrasound.

Figure 2

PDGF receiver operating curve (ROC) curve. ROS, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.