CLINICAL RESEARCH

Serum Progranulin As a Risk Predictor in Patients with Acute Myocardial Infarction

Authors' Contribution:
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Data Collection B
Statistical Analysis C
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Background: Although progranulin was recently proposed as an adipokine that may be involved in glucose metabolic and inflammatory diseases, the role of serum progranulin in cardiovascular disease is elusive and remains disputed. The aim of our research was to determine the concentration of serum progranulin in Chinese patients with cardiovascular disease, notably in acute myocardial infarction (AMI), and its relationship to other cardiometabolic risk factors.

Material/Methods: This prospective observational study included 342 Chinese AMI patients and 255 healthy control subjects. Serum progranulin concentrations and various cardiometabolic risk factor levels were investigated. We assessed the relationship between progranulin and other cardiometabolic risk factors. Logistic regression analysis was applied to evaluate risk factors in patients with AMI.

Results: Progranulin levels were obviously elevated in AMI patients compared to control subjects (P=0.0001). Correlation analysis showed that progranulin levels were positively associated with coronary artery disease severity (r=0.380, P=0.0001), glucose (r=0.195, P=0.015), and myeloperoxidase (r=0.198, P=0.014). In logistic regression analysis, serum progranulin (Exp(B)=1.104, 95% CI=1.043-1.168, P=0.001), myeloperoxidase (Exp(B)=1.006, 95% CI=1.003-1.008, P=0.0001), and uric acid (Exp(B)=1.020, 95% CI=1.009-1.032, P=0.0001) were independent risk factors in AMI patients.

Conclusions: Patients with AMI had significantly higher serum progranulin concentrations than control subjects. This study suggests that serum progranulin is an independent risk predictor in Chinese patients with AMI.

Keywords: **Coronary Artery Disease • Adipokines • Inflammation**

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Background

Acute myocardial infarction (AMI) remains a leading cause of cardiovascular disease mortality in both males and females, despite our best attempts to manage traditional risk factors with contemporary approaches and increase use of evidence-based therapies in recent years [1-3]. This is largely because atherosclerosis, by far the most common cause of AMI in the general population, is a complex disease process whose pathogenic basis extends far beyond intimal infiltration of cholesterol; systemic and local inflammatory events also mediate all phases of plaque development, and progression, with eventual thrombotic manifestations [4]. In particular, evidence indicates that various adipokines that mediate a number of signaling cascades in the vessel wall that exert pro-inflammatory and/or anti-inflammatory activity can directly affect the process of atherosclerosis [5-10].

Progranulin, a novel adipokine, is involved in regulating glucose metabolism, chronic inflammation, and insulin resistance [6-8,10]. Importantly, progranulin plays a key role in the pathogenesis of atherosclerosis. For instance, progranulin was found to be expressed in human atherosclerotic lesions; its expression mainly reduced inflammation, but its degradation into GRNs enhanced inflammation in atherosclerotic plaques, contributing to the progression of atherosclerosis [9]. The level of serum progranulin was identified as an independent determining risk factor for carotid atherosclerosis in subjects without metabolic syndrome [10]. However, there are only a few reports on the role of progranulin in patients with cardiovascular disease, and their results are controversial. In the short term in acute ischemic stroke patients, progranulin was found to be a serum biomarker that independently predicts all-cause mortality and adverse functional outcome [11]. Additionally, circulating progranulin was proposed as a risk factor for cardiovascular disease in obese subjects with chronic periodontitis and in patients with polycystic ovary syndrome [12]. In contrast, Korean patients with acute coronary syndrome (ACS) and stable angina pectoris (SAP) did not show significant differences in progranulin levels compared to control subjects [13].

In this current study, we aimed to clarify the clinical significance of PGRN in the setting of Chinese patients with AMI. In addition, we assessed relationship of serum PGRN with the severity of coronary artery disease and various cardiometabolic risk factors, such as traditional cardiometabolic indicators and homocysteine, myeloperoxidase, and uric acid, which are tightly linked with cardiovascular disease.

Material and Methods

Subjects

A prospective and observational clinical study was conducted in this research. During November 2018 to November 2019, a total of 342 patients with AMI in the Department of Cardiology of the Second Affiliated Hospital of Xi'an Jiaotong University were consecutively enrolled for this study. The subjects had a typical rise and fall in the level of biochemical markers of myocardial necrosis (cardiac troponin isoforms T and I, creatine kinase-MB, high-sensitivity cardiac troponin T) with at least 1 of the following: ischemic symptoms (eg, chest pain, dyspnea, diaphoresis, nausea, fatigue, or syncope), electrocardiogram (EKG) changes (ST elevation or depression, pathologic Q waves, or imaging evidence of new myocardial injury), and who had finally received percutaneous coronary intervention (PCI), stent placement, and routine antithrombotic therapy. We enrolled 255 control subjects from among people attending a routine health check-up at the Health Examination Center of the Second Affiliated Hospital of Xi'an Jiaotong University in the same time period.

All patients with coronary artery disease severity were quantitatively evaluated by the Gensini Scoring system, which is based on coronary angiography. Briefly, each coronary artery lesion is scored for stenosis diameter (1-25%=1, 26-50%=2, 51-75%=4, 76-90%=8, 91-99%=16, and complete occlusion=32). This score is multiplied by a predefined factor according to the functional relevance of the diseased vascular segment. Thus, according to the final Gensini scores, the experimental subjects were divided into 4 subgroups: 1-8 points for group I, 8-15 points for group II, 15-49.75 points for group III, and ≥49.75 points for group IV.

Exclusion criteria of the patients were as follows: severe respiratory insufficiency, stroke, type 1 and type 2 diabetes, hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90), malignancy, renal or hepatic failure, inflammatory disease, use of systemic steroids and NSAIDs, and pregnant and lactating women. The study was approved by the Ethics Committee of Xi'an Jiaotong University, and signed informed consent was obtained from all participants enrolled in this study.

Clinical and Laboratory Measurements

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Before routine and invasive medical treatment, all overnight fasting blood samples with patients and healthy subjects were collected and immediately stored at -80°C for subsequent assays. The levels of serum triglyceride, cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density

Table 1. Baseline characteristics of the study participants.

Characteristics	Experiment (n=342)	Control (n=255)	P
Gender (M: F)	240: 102	174: 81	0.611
Age (years)	61.38±9.18	61.85±10.37	0.778
BMI (kg/m²)	24.92±3.03	24.18±2.43	0.285
Progranulin (ng/mL)	145.19±11.10	134.38±13.99	0.0001
Glucose (mmol/L)	4.98±2.27	4.43±0.49	0.106
Cholesterol (mmol/L)	3.81±0.99	4.41±0.73	0.0001
Triglyceride (mmol/L)	1.51±0.72	1.11±0.32	0.0001
HDL-cholesterol (mmol/L)	0.99±0.27	1.20±0.26	0.0001
LDL-cholesterol (mmol/L)	2.87±0.54	2.41±0.77	0.0001
Homocycteine (mmol/L)	20.59±12.29	14.44±4.59	0.001
Myeloperoxidase (mmol/L)	1014±325	585±324	0.0001
Uric Acid (mmol/L)	347.77±88.18	299.19±54.26	0.001

lipoprotein cholesterol (LDL-C), and uric acid, homocysteine and myeloperoxidase were measured enzymatically using an automated analyzer (Beckman Coulter Analysers; Lismeehan, O'Callaghan's Mill's Co., Clare, Ireland). The plasma glucose levels were tested by glucose oxidase method (Beckman Coulter Analysers; Ireland).

Measurement of Serum PGRN Concentration

Serum PGRN concentration was determined by enzyme-linked immunosorbent assays (ELISA) according to the manufacturers' instructions (Boster Biology Technology, Ltd, China). All samples were run in duplicate and repeated if there was a ≥15% difference between duplicates. No significant cross-reactivity or interference was observed.

Statistical Analysis

Statistical analysis was performed using SPSS software version 20.0. Data are presented as the mean±standard deviation (SD). Before statistical analysis, normally distributed parameters were logarithmically transformed to approximate a normal distribution. The independent-samples t test was used to compare continuous variables between 2 groups, and differences in categorical variables were analyzed using the chi-square test. Differences between groups were tested using a one-way ANOVA test, followed by a post hoc LSD test. Spearman's partial correlation analysis was performed to assess the relationships between PGRN and other variables. Logistic regression analysis was used to determine the independent predictors of AMI. A P value less than 0.05 was considered statistically significant.

Results

Clinical Characteristics

The anthropometric and biochemical characteristics of this study subjects are summarized in **Table 1**. Between normal healthy subjects and patients with AMI, there were no statistically significant differences in sex, age, BMI, or glucose (P>0.05). Compared to the normal healthy group, subjects with AMI exhibited higher levels of progranulin (P=0.0001), homocysteine (P=0.001), triglyceride (P=0.0001), LDL-cholesterol (P=0.0001), myeloperoxidase (P=0.0001) and uric acid (P=0.001), whereas cholesterol (P=0.0001) and HDL-cholesterol (P=0.0001) levels were obviously lower in the AMI group.

In the study of coronary artery disease severity subgroups (**Table 2**), HDL-cholesterol (F=5.005, P=0.003) and myeloperoxidase (F=2.729, P=0.047) levels were obviously different with a gradually increase in the Gensini scores, but progranulin levels had no change in different subgroups (P>0.05). On the other hand, the differences in BMI, homocysteine, glucose, cholesterol, triglyceride, LDL-cholesterol, and uric acid among different subgroups of AMI patients were not significant (p>0.05).

Correlation of Progranulin Concentration with AMI Cardiometabolic Risk Factors

Spearman correlation analysis (**Table 3**) revealed that progranulin concentration had a significant positive relationship with the severity of coronary artery disease (r=0.362, P=0.0001) and levels in glucose (r=0.195, P=0.038) and myeloperoxidase (r=0.198, P=0.014). However, circulating progranulin levels were not correlated with other laboratory indicators, including

Table 2. Progranulin and other cardiometabolic indicators levels in different coronary artery disease severity subgroups evaluated by Gensini Scoring system.

Characteristics	Group I (n=84)	Group II (n=78)	Group III (n=81)	Group IV (n=99)	F	P
BMI (kg/m²)	24.19±3.41	25.56±3.04	25.04±2.44	25.24±3.06	0.993	0.400
Progranulin (ng/mL)	144.26±9.39	142.9±14.24	147.93±10.00	146.15±10.28	0.996	0.398
Glucose (mmol/L)	4.75±1.49	4.33±1.16	5.75±3.53	5.16±2.24	1.977	0.122
Cholesterol (mmol/L)	4.01±0.99	3.88±0.85	3.48±1.07	3.83±1.03	1.472	0.226
Triglyceride (mmol/L)	1.37±0.67	1.61±0.86	1.70±0.79	1.42±0.54	1.390	0.250
HDL-cholesterol (mmol/L)	1.11±0.35	1.02±0.23	0.88±0.15	0.91±0.21	5.005	0.003
LDL-cholesterol (mmol/L)	2.50±0.76	2.44±0.66	2.17±0.82	2.50±0.83	1.105	0.360
Homocycteine (mmol/L)	18.20±7.99	24.21±14.07	16.94±6.56	23.22±16.83	2.467	0.066
Myeloperoxidase (mmol/L)	1034±325	921±315	1154±193	955±392	2.729	0.047
Uric acid (mmol/L)	333.5±88.18	347.8±74.33	345.49±87.32	365.6±98.38	0.667	0.547

Table 3. Spearman correlation of serum progranulin with coronary artery disease severity and various cardiometabolic risk factor levels.

Parameter	Correlation coefficients for progranulin	
	r	P
BMI (kg/m²)	0.077	0.390
Severity of coronary artery disease (Gensini scores)	0.380	0.0001
Glucose (mmol/L)	0.195	0.015
Cholesterol (mmol/L)	-0.021	0.800
Triglyceride (mmol/L)	0.085	0.294
HDL-cholesterol (mmol/L)	-0.151	0.060
LDL-cholesterol (mmol/L)	-0.006	0.937
Homocycteine (mmol/L)	0.110	0.173
Myeloperoxidase (mmol/L)	0.198	0.014
Uric acid (mmol/L)	0.011	0.890

homocysteine, cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, myeloperoxidase, and uric acid (*P*>0.05).

Determinant Factors in Subjects with AMI

Logistic regression analysis was used to determine whether progranulin and other cardiometabolic indicators were independent risk factors in AMI patients. The results demonstrated that progranulin (Exp(B)=1.104, 95% CI=1.043-1.168,

P=0.001), myeloperoxidase (Exp(B)=1.006, 95% CI=1.003-1.008, *P*=0.0001), and uric acid (Exp(B)=1.020, 95% CI=1.009-1.032, *P*=0.0001) were independent predictive factors in patients with AMI (**Table 4**).

Discussion

The current study demonstrated that progranulin levels are significantly higher in patients with AMI compared to control subjects. Serum progranulin concentrations mainly have significant positive correlations with coronary artery disease severity and levels of glucose and myeloperoxidase. Moreover, we observed that serum progranulin level is an independent risk factor in subjects with AMI.

In our study, we demonstrated that conventional cardiometabolic risk factors, including triglyceride and LDL-cholesterol levels, were higher, while cholesterol and HDL-cholesterol concentrations were lower, in patients with AMI compared to control subjects, which is consistent with other previous reports [14]. Moreover, multiple studies have investigated an association between elevated myeloperoxidase levels and cardiovascular disease and a dose-response relationship between myeloperoxidase levels and cardiovascular disease severity [15-17]. This is similar to our present study, in which the serum myeloperoxidase concentration of AMI patients increased in a coronary artery stenosis severity-dependent manner according to the Gensini scores, and myeloperoxidase was identified as a risk factor for AMI. In addition, recent observational studies and clinical data have confirmed that homocysteine is a risk factor for cardiovascular disease due to its involvement in the promotion of the intracellular production of free oxygen species,

Table 4. Logistic regression analysis for determinant factors in subjects with AMI.

	Variable	B	Exp (B)	P	95% CI	
					Lower	Upper
Step1a	Myeloperoxidase	0.004	1.004	0.0001	1.003	1.006
	Constant	-1.980	0.138	0.001		
Step2b	Uric acid	0.015	1.015	0.001	1.006	1.025
	Myeloperoxidase	0.005	1.005	0.0001	1.003	1.007
	Constant	-7.551	0.001			
Step3c	Progranulin	0.099	1.104	0.001	1.043	1.168
	Uric acid	0.020	1.020	0.0001	1.009	1.032
	Myeloperoxidase	0.005	1.006	0.0001	1.003	1.008
	Constant	-23.11	0.0001	0.0001		

Variable(s) entered on step 1a: Myeloperoxidase; Variable(s) entered on step 2b: Uric acid; Variable(s) entered on step 3c: Progranulin.

inhibition of nitric oxide synthesis, activation of thrombosis, endothelial dysfunction, hyperuricemia, monocyte activation, and production of inflammatory mediators [18]. Similarly, our present results showed that serum homocysteine levels in subjects with AMI were significantly higher than in control subjects, further indicating that increased homocysteine levels play a role in the context of cardiovascular disease. In addition to the classical recognition of uric acid as the cause of gout and arthritis, recent studies have proposed that it is linked or even provokes cardiovascular disease. Neogi et al demonstrated a clear association between cardiovascular disease and uric acid [19], while Krishnan et al [20] and De Luca et al [21] did not find this association, suggesting that no definitive conclusion can be drawn as to whether uric acid is an independent predictor of cardiovascular disease. In this regard, the present study shows that uric acid levels were higher in patients with AMI than in control subjects, and indicated that it is an independent predictor of cardiovascular disease.

Progranulin, namely acrogranin or proepithelin, is secreted by a broad range of tissues and expressed by a wide variety of cell types; it consists of 593 amino acids and has a molecular weight of 68.5 kDa [22]. It is involved in a diverse array of biological activities, such as cell growth, modulation of immune responses, and neuronal effects [23]. In pathological processes, progranulin has emerged as an endogenous regulator of TNF-α-activated intracellular signaling and has anti-inflammatory actions [24]. However, owing to its complicated biological structure, not all actions of progranulin exert an inhibitory role. Progranulin was recently identified as a novel adipokine mediating high-fat diet-induced insulin resistance through upregulation of interleuin-6 (IL-6) expression in adipose tissue [25]. In type 2 diabetes and its microvascular complications, serum

progranulin levels were significantly higher in patients and was associated with macrophage infiltration [26,27]. Moreover, PGRN levels were found to be significantly higher in the patients with overweight hypertensive and early renal damage [28,29]. In the present study, the serum pragranulin concentration in AMI patients was found to be obviously increased and was an independent risk factor in patients with AMI, which is in contrast to the results of Choi et al [13], who reported that patients with ACS had no significant alteration in progranulin levels, although it tended to be elevated. The observation of discrepancies in progranulin levels could be mainly explained by the use of different recruited patients with confirmed cardiovascular disease criteria and the populations with different ethnicities. Furthermore, in agreement with a previous study on the influence of progranulin on atherosclerosis processes [9], our correlation analysis showed that serum progranulin was positively associated with coronary artery disease severity, as quantitatively assessed by the Gensini method. In patients with nonalcoholic fatal liver disease and ACS and SAP, proganulin levels were associated with traditional cardiometabolic risk factors [13,30], which was in line with our findings that serum progranulin concentration showed a positive correlation with glucose. Interestingly, the present study demonstrated that progranulin concentration had a significant positive association with myeloperoxidase, which may be seen as a mediator or a mechanism by which inflammation promotes cardiovascular disease at the molecular and cellular levels [31]. These results suggest that the concentrations of serum progranulin influence the process of AMI, which may be related to classical cardiovascular factors as well as inflammation.

There are some limitations in our study that require emphasis. Given that the sample size is small, the nonsignificant

correlation between progranulin and some other factors may become statistically significant if the sample size is larger. Additionally, this is a cross-sectional and observational clinical analysis that restricts us from drawing causal conclusions. It is not clear whether serum progranulin and myeloperoxidase levels are causative factors in the pathogenesis of AMI, and further studies are needed to explore the association between progranulin and myeloperoxidase in the setting of cardiovascular disease.

Conclusions

In summary, the present study clearly shows that Chinese patients with AMI had significantly elevated serum progranulin levels, which were closely associated with the degree of coronary stenosis, classical cardiometabolic risk factors, and other cardiometabolic risk factors, such as myeloperoxidase and uric acids, indicating that serum progranulin is an independent predictor for AMI.

Conflicts of Interest

None.

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