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Growth differentiation factor-15 is a prognostic marker in patients with intermediate coronary artery disease

Wei WANG[1], Xian-Tao SONG[1], Yun-Dai CHEN[2], Fei YUAN[1], Feng XU[1], Min ZHANG[1], Kai TAN[1], Xing-Sheng YANG[1], Xian-Peng YU[1], Kong-Yong CUI[1], Shu-Zheng LYU[1,#]

[1]*Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China*
[2]*Department of Cardiology, the First Medical Center of Chinese PLA General Hospital, Beijing, China*

Abstract

Background Growth differentiation factor-15 (GDF-15) is involved in multiple processes that are associated with coronary artery disease (CAD). However, little is known about the association between GDF-15 and the future ischemic events in patients with intermediate CAD. This study was conducted to investigate whether plasma GDF-15 constituted risk biomarkers for future cardiovascular events in patients with intermediate CAD. **Methods** A prospective study was performed based on 541 patients with intermediate CAD (20%–70%). GDF-15 of each patient was determined in a blinded manner. The primary endpoint was major adverse cardiac event (MACE), which was defined as a composite of all-cause death, nonfatal myocardial infarction, revascularization and readmission due to angina pectoris. **Results** After a median follow-up of 64 months, 504 patients (93.2%) completed the follow-up. Overall, the combined endpoint of MACE appeared in 134 patients (26.6%) in the overall population: 26 patients died, 11 patients suffered a nonfatal myocardial infarction, 51 patients underwent revascularization, and 46 patients were readmitted for angina pectoris. The plasma levels of GDF-15 (median: 1172.02 *vs.* 965.25 pg/mL, $P = 0.014$) were higher in patients with ischemic events than those without events. After adjusting for traditional risk factors, higher GDF-15 levels were significantly associated with higher incidence of the composite endpoint of MACE (HR = 1.244, 95% CI: 1.048–1.478, Quartile 4 *vs.* Quartile 1, $P = 0.013$). **Conclusions** The higher level of GDF-15 was an independent predictor of long-term adverse cardiovascular events in patients with intermediate CAD.

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Keywords: Growth differentiation factor-15; Intermediate coronary artery disease; Prognosis

1 Introduction

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β cytokine superfamily and is produced by cardiomyocytes and atherosclerotic lesions under stress conditions.[1–3] Generally, GDF-15 is weakly expressed in most tissues under physiological conditions, while ischemia, mechanical stretch, neurohormones, and proinflammatory cytokines can stimulate the expression in cardiac myocytes.[2,3] By virtue of its potential role in antiapoptotic, antihypertrophic, and antiinflammatory actions, GDF-15 may play a counter regulatory role in the processes of cardiovascular injury.[2] Other cardiovascular cell types, including endothelial cells, vascular smooth muscle cells, and adipocytes, can also produce the biomarker under stressful conditions.[4] Elevated circulating level of GDF-15 is involved in multiple processes that are associated with coronary artery disease (CAD), from chest pain,[5] stable CAD,[6] acute coronary syndrome (ACS)[7,8] to heart failure (HF)[9]. GDF-15 is described as a novel biomarker with a high impact on risk stratification and prognostic value in CAD.[10,11] In the Framingham Heart Study, the concentrations of GDF-15 were strongly associated with the risk of death and HF.[12] A study showed that a single measurement of GDF-15 on admission markedly enhances the predictive value of the GRACE score.[11] In addition, several animal experiments have demonstrated roles for GDF-15 in myocardial infarction (MI),[2,3,13] ischemia/reperfusion injury pressure, overload-induced hypertrophy, and HF.[2,3]

However, little is known about the association between GDF-15 and the future cardiovascular events in patients with intermediate CAD. Many patients with ACS exhibit

[#]**Correspondence to:** Shu-Zheng LYU, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University and Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China. E-mail: shuzheng023@163.com
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not serious stenosis, which is associated with vulnerable plaques.[14,15] Therefore, the aim of the present study was to investigate whether plasma GDF-15 constituted risk biomarkers for future cardiovascular events in a cohort of patients with angiographically intermediate coronary artery stenosis.

2 Methods

2.1 Study population

Patients aged 18–80 years who showed diameter stenosis of 20%–70% in the more than one main coronary branch by coronary angiography[16,17] from February 2007 to November 2009 in Beijing Anzhen Hospital were enrolled. The exclusion criteria were as follows: (1) acute MI; (2) left main coronary disease; (3) cardiogenic shock or left ventricular ejection fraction < 30%; (4) history of coronary revascularization; (5) valvular heart disease, cardiomyopathy, or peripheral vascular disease; (6) systemic inflammatory diseases, such as acute and chronic infection; (7) known immune system or connective tissue disease; (8) baseline creatinine > 2.5 mg/dL (if males) or > 2.0 mg/dL (if females); (9) baseline alanine aminotransferase or aspartate aminotransferase was three times higher than normal; (10) heart transplant recipients; (11) patients with advanced cancer and multiple organ failure; and (12) patients who could not comply with the research program. This research was approved by the Ethics Committee of Beijing Anzhen Hospital and was conducted according to the guidelines of the declaration of Helsinki. Written consent was obtained from all participants, with explicit consent given for linking to healthcare-use databases, and for the storage and future use of blood assays.

2.2 Data collection and GDF-15 analysis

After evaluating the lesions with coronary angiography, demographic, clinical as well as procedural characteristics of patients were recorded in a computerized database. Fasting venous blood samples were collected from the antecubital vein on the morning after the coronary angiography procedure using ethylene diamine tetraacetic acid as an anticoagulant. The blood samples were centrifuged at 1500 r/min for 10 min. The plasma samples were immediately separated into multiple aliquots and stored at –80°C until analyzed. Plasma total cholesterol (TC), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, serum creatinine and the other routine blood biochemical examination were measured in a biochemical analyzer (Hitachi-7600, Tokyo). Plasma high-sensitivity C-reactive protein (CRP) was determined using an enzyme-linked immunosorbent assay. The concentrations of the plasma GDF-15 was analyzed in a blinded manner with respect to clinical information and measured using commercially available protein arrays (RayBiotech, Norcross, GA) following the manufacturer's instructions.

2.3 Follow-up

Follow-up information was obtained by review of hospital charts, clinical visit or telephone interviews, conducted by trained reviewers. Clinical follow-up was performed at 1, 6, and 12 months and then every one year thereafter, which was extended through February 2014. The primary endpoint was major adverse cardiac event (MACE), which was defined as a composite of all-cause death, non-fatal MI, revascularization and readmission due to refractory angina pectoris. Death was defined as death from any cause. The diagnosis of non-fatal MI was assessed by the third universal definition of MI. Revascularization was defined as percutaneous coronary intervention or coronary artery bypass grafting of any vessels. Moreover, all outcomes of interest were carefully adjudicated by the independent group of clinicians.

2.4 Statistical analysis

Categorical variables are reported as percentages and continuous variables as mean ± SD or median (interquartile range), depending on the distribution of the variables. All the patients were divided into four groups according to the GDF-15 quartiles. Analysis of variance, the Kruskal-Wallis H test, or the χ^2 test was used to determine the difference of baseline characteristics among the four groups. The association between GDF-15 and baseline variables was tested using the Spearman rank correlation statistics. The Mann-Whitney U test and the χ^2 test were used to test the difference of baseline data between event and event-free groups. The association of the baseline characteristics with survival was assessed using univariate Cox regression and the Kaplan–Meier method. The hazard ratio (HR) and 95% confidence interval (CI) were reported. Additionally, to evaluate the predictive values of GDF-15 level on the risk of cardiovascular events, multivariate Cox regression models were performed. The Model 1 was adjusted for traditional risk factors age, gender, body mass index (BMI), systolic blood pressure (SBP), diabetes, smoking, and TC. The Model 2 was additionally adjusted for CRP. In addition, further adjustment was performed for medication use (statin and aspirin) in the Model 3.

The statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA). All statistical tests were two-sided, with P-value < 0.05 considered statistically significant.

3 Results

3.1 Baseline characteristics of study population and GDF-15

A total of 541 patients were recruited between February 2007 and November 2009 in Beijing Anzhen Hospital. The median age was 60.1 years and 67.5% of the patients were men. Baseline characteristics and medication use of the patients according to GDF-15 quartiles are shown in Table 1. Besides, GDF-15 quartiles of patients with different clinical presentations are also shown (supplemental material, Table 1S). Overall, 504 patients (93.2%) received complete clinical follow-up with a median of 64 months. The combined endpoint appeared in 134 patients (26.6%): 26 patients died, 11 patients suffered a nonfatal MI, 51 patients underwent revascularization, and 46 patients were readmitted for angina pectoris.

Using Spearman's correlation analysis, we found a significant correlation between the levels of GDF-15 and age (r = 0.357, P < 0.001), smoking (r = –0.156, P < 0.001), and SBP (r = 0.134, P = 0.002). The plasma GDF-15 levels showed very weak correlations with diabetic (r = 0.099, P = 0.022) and creatinime (r = 0.095, P = 0.028), but no association was observed with other cardiovascular risk factors as shown in Table 2.

3.2 Follow-up and cardiovascular events

As shown in Table 3, patients with cardiovascular events had significantly higher GDF-15 levels than those in the event-free survival group (1172.02 *vs.* 965.25 pg/mL, P = 0.014). Besides, patients with cardiovascular events were older, were more likely to have hypertension or be current smokers compared with those in the event-free group.

Table 4 shows the results of the Cox proportional hazards analysis and the HR for GDF-15 was 1.251 (95% CI: 1.074–1.456, P = 0.004, Quartile 4 *vs.* Quartile 1). After adjustment for age, sex, BMI, SBP, diabetes, smoking, and TC, the HR for GDF-15 was 1.228 (95% CI: 1.041–1.447, P = 0.015, Quartile 4 *vs.* Quartile 1) in the Model 1. After further adjustment for CRP in the Model 2, GDF-15 showed the same statistically significant relationship with the outcome (HR = 1.227, 95% CI: 1.041–1.447, P = 0.015, Quartile 4 *vs.* Quartile 1). For the Model 3, which was additionally adjusted for aspirin and statin, the HR for GDF-15 was 1.244 (95% CI: 1.048–1.478, P = 0.013, Quartile 4 *vs.* Quartile 1). However, we found that the risks of MACE were not significantly different when comparing the patients in the Quartile 2 or Quartile 3 versus that in the Quartile 1 (supplemental material, Table 2S & Table 3S).

Figure 1 showed Kaplan-Meier plots for the incidence of MACE as functions of the levels of GDF-15. There was a clear increase in the incidence of MACE during the follow-up for the patients with high levels of GDF-15 (P = 0.025).

Table 1. Baseline characteristics and medication use of the patients according to GDF-15 quartiles.

Variable	Quartile 1 (n = 135)	Quartile 2 (n = 135)	Quartile 3 (n = 135)	Quartile 4 (n = 136)	P-value
GDF-15, pg/mL	≤ 694.97	695.90–1005.45	1006.01–1458.25	≥ 1462.29	
Age, yrs	54.4 ± 9.4	58.3 ± 9.0	61.7 ± 9.2	63.5 ± 9.5	< 0.001
Male	94 (69.6%)	91 (67.4%)	95 (70.4%)	85 (62.5%)	0.506
Hypertension	79 (58.5%)	80 (59.3%)	85 (63.0%)	88 (64.7%)	0.682
Diabetic mellitus	24 (17.8%)	27 (20.0%)	39 (28.9%)	29 (21.3%)	0.139
Smoking	59 (43.7%)	55 (40.7%)	39 (28.9%)	35 (25.7%)	0.003
SBP, mmHg	130 (120–140)*	130 (120–140)*	130 (120–140)*	131 (120–140)*	0.051
BMI, kg/m^2	26.08 ± 2.93	25.68 ± 3.15	25.59 ± 3.18	25.51 ± 3.17	0.282
TC, mmol/L	4.64 ± 0.89	4.44 ± 0.99	4.44 ± 1.00	4.66 ± 1.07	0.060
HDL-C, mmol/L	1.08 ± 0.30	1.05 ± 0.31	1.01 ± 0.33	1.03 ± 0.28	0.288
LDL-C, mmol/L	2.95 ± 0.84	2.74 ± 0.88	2.83 ± 0.88	2.91 ± 0.86	0.093
Creatinine, μmol/L	78.9 ± 18.5	81.14 ± 18.31	85.36 ± 25.99	84.92 ± 21.04	0.076
C-reactive protein, mg/L	3.47 (1.20–8.34)*	3.60 (1.67–7.87)*	3.27 (0.93–9.80)*	3.10 (1.07–7.75)*	0.840
Hypertension treatment	73 (54.1%)	90 (66.7%)	80 (59.3%)	92 (67.6%)	0.068
Statin medication	68 (50.4%)	77 (57.0%)	65 (48.1%)	78 (57.4%)	0.313
Aspirin medication	87 (64.4%)	86 (63.7%)	80 (59.3%)	88 (64.7%)	0.770

Data are presented as means ± SD or n (%). *Presented as median (interquartile range). BMI: body mass index; GDF-15: growth differentiation factor-15; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol.

Table 2. Correlation between GDF-15 and baseline characteristics.

Variable	Correlation coefficient	*P*-value
Age	0.357	< 0.001
Smoking	–0.156	< 0.001
SBP	0.134	0.002
Diabetic mellitus	0.099	0.022
Creatinine	0.095	0.028
BMI	–0.051	0.232
Hypertension	0.046	0.288
HDL-C	–0.040	0.353
C-reactive protein	–0.012	0.783
LDL-C	–0.007	0.872
TC	< 0.001	0.997

BMI: body mass index; GDF-15: growth differentiation factor-15; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol.

Table 3. Difference between event group and event-free group.

Variable	Event (*n* = 134)	Event-free (*n* = 407)	*P*-value
GDF-15, pg/mL	1172.02 (757.84–1655.02)*	965.25 (670.93–1405.37)*	0.014
Age, yrs	58.9 ± 9.9	61.4 ± 9.8	0.019
Male	95 (70.9%)	270 (66.3%)	0.329
Hypertension	92 (68.7%)	240 (59.0%)	0.046
Diabetic mellitus	32 (23.9%)	85 (20.9%)	0.465
Smoking	61 (45.5%)	127 (31.2%)	0.003
SBP, mmHg	130 (120–140)*	130 (120–140)*	0.951
BMI, kg/m^2	25.49 ± 2.92	25.79 ± 3.17	0.545
TC, mmol/L	4.64 ± 0.89	4.56 ± 1.00	0.531
HDL-C, mmol/L	1.02 (0.88–1.18)*	1.01 (0.88–1.18)*	0.814
LDL-C, mmol/L	2.72 (2.22–3.44)*	2.76 (2.31–3.41)*	0.663
Creatinine, μmol/L	78.00 (71.00–94.25)*	80.00 (68.00–93.00)*	0.663
C-reactive protein, mg/L	3.47 (1.12–7.67)*	3.33 (1.06–8.94)*	0.863

Data are presented as means ± SD or *n* (%). *Presented as median (interquartile range). BMI: body mass index; GDF-15: growth differentiation factor-15; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol.

Table 4. Associations between GDF-15 quartiles and MACE during the follow-up.

	HR	95% CI	*P*-value
Unadjusted	1.251	1.074–1.456	0.004
Adjusted for multiple covariates*	1.228	1.041–1.447	0.015
Adjusted for multiple covariates#	1.227	1.041–1.447	0.015
Adjusted for multiple covariates†	1.244	1.048–1.478	0.013

*Refer to adjust for age, gender, body mass index, systolic blood pressure, diabetes, smoking, and total cholesterol. #Refer to adjust for age, gender, body mass index, systolic blood pressure, diabetes, smoking, total cholesterol, and C-reactive protein. †Refer to adjust for age, gender, body mass index, systolic blood pressure, diabetes, smoking, total cholesterol, C-reactive protein, and medication use (statin and aspirin). CI: confidence index; GDF-15: growth differentiation factor-15; HR: hazard ratio; MACE: major adverse cardiac event.

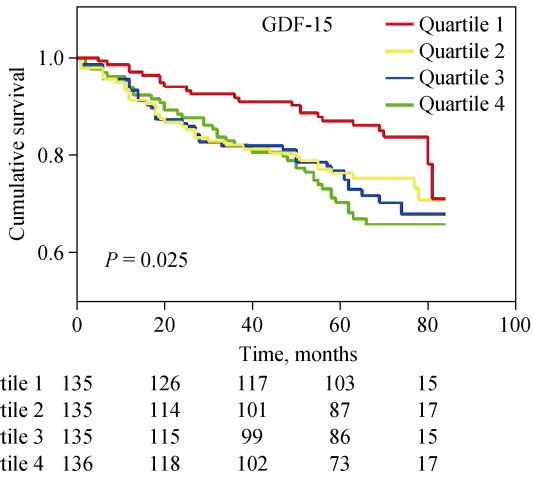

Figure 1. Cumulative survival curve for composite endpoint according to GDF-15 quartiles. GDF-15: growth differentiation factor-15.

4 Discussion

In this study involving the long-term follow-up of patients with intermediate coronary artery lesions, we found that the circulating levels of GDF-15 are related to subsequent cardiovascular events that persisted after adjustment for established risk factors.

4.1 The relationship between circulating GDF-15 concentrations and CAD

The associations between GDF-15 and CAD have largely been reported in previous studies. The first paper published in this field by Brown, *et al*.[18] in 2002. This nested case-control study found that women with increased baseline plasma concentration of GDF-15 had the higher risk to experience a cardiovascular event during the four-year follow-up. Wallentin, *et al*.[19] reported that GDF-15 is an independent marker of the long-term risk for both cardiovascular disease and cancer morbidity beyond clinical and biochemical risk factors from 940 elderly men. For people aged 30–65 years, a high GDF-15 level was associated with older age, black race, hypertension, diabetes, smoking, left ventricular mass/body surface area, and worse renal function and was independently related to all-cause death and cardiovascular mortality during seven years follow-up.[20] In the Framingham Heart Study, the concentrations of GDF-15 were strongly associated with the risk of death and HF. This study aimed at a Framingham offspring cohort of 3428 people with average age of 59 years, followed them 11 years, GDF-15 appeared the strongest prognostic marker for death and HF although several other biomarkers (troponin I, soluble ST2 and B-type natriuretic peptide) were equally prognostic concerning all cardiovascular events.[12]

In accordance with the classification of diseases, elevated circulating level of GDF-15 is involved in multiple CADs. Eggers, *et al*.[5] explored the usefulness of GDF-15 for early risk stratification in 479 unselected patients with acute chest pain. The patients with markedly elevated levels of GDF-15 on admission appeared more CAD event. By multivariable analysis that included clinical characteristics, electrocardiogram findings, peak cardiac troponin I levels within 2 h, N-terminal pro-B-type natriuretic peptide, CRP, and cystatin C, GDF-15 remained an independent predictor of the composite endpoint. A recent study measured plasma GDF-15 and cardiac disease severity in 984 patients with stable CAD. During the average of 8.9-year follow-up, they found that participants who had GDF-15 levels in the highest tertile had higher mortality compared with those in the lowest tertile.[6] GDF-15 is highly expressed in the infarcted myocardium in patients with acute MI,[2] and has emerged as a biomarker of increased mortality and recurrent MI in patients with ACS.[7,8] Meanwhile, GDF-15 was involved in the cardiovascular risk stratification system as a new biomarker.[16,17] Widera, *et al*.[11] showed that a single measurement of GDF-15 on admission markedly enhances the predictive value of the GRACE score.

However, whether GDF-15 has an impact on risk prognostic value in patients with angiographically proven intermediate coronary artery stenosis remains unclear. A recent study showed that increased GDF-15 concentrations were associated with subclinical atherosclerosis. It suggested the role of GDF-15 for screening and management of patients with subclinical atherosclerosis are warranted in future studies.[21] In our study, GDF-15 showed a significant correlation with age, smoking, diabetes, SBP and creatinine. Moreover, similar patterns were observed in other trials. Older patients showed higher levels of GDF-15, because aging is also a chronic inflammatory process.[22] A study showed that the level of GDF-15 was increased in the impared fasting glucose and type 2 diabetes groups, and had a positive correlation with insulin resistance indepdent of age and BMI.[23]

4.2 The possible mechanism of GDF-15 on CAD

Several mechanisms might explain the association between the GDF-15 level and cardiovascular events. GDF-15 is expressed by many cell types in response to oxidative stress and inflammation, and involved in the regulation of apoptosis, cell proliferation and cellular repair. These biological processes are key components of cardiovascular pathobiology.[1–4,24] Meanwhile, GDF-15 is weakly expressed in most tissues under physiological conditions, while ischemia, mechanical stretch, neurohormones, and proinflammatory cytokines can stimulate the expression in cardiac myocytes.[2,3] Human GDF-15 expression is controlled by the protein 53.[25] Proinflammatory cytokines, such as tumor necrosis factor α or interleukin 6, induce the mRNA expression of GDF-15 in activated macrophages, which suggests that GDF-15 could come into play as an autocrine inhibitor during the inflammatory response.[1,4]

De Jager, *et al*.[26] showed that GDF-15 expression is upregulated as disease progresses in murine atherosclerosis and primarily colocalizes with plaque macrophages. Hematopoietic GDF-15 deficiency in low density lipoprotein receptor$^{-/-}$ mice led to initial vascular injury and increased collagen in later lesions. They thought GDF-15 deletion has a beneficial effect both in early and later atherosclerosis by inhibition of CCR2-mediated chemotaxis and by modulating cell death.

A study reported the association between GDF-15 gene

polymorphism and CAD in the Chinese population.[27] They investigated whether GDF-15 −3148C>G variant (SNP, rs4808793) is associated with the predisposition of CAD and its severity in the Chinese population. But the data did not support their hypothesis.

4.3 Limitations

There were several limitations that can not be ignored in this study. Firstly, although rigorous multivariate Cox regression analysis was performed, unmeasured confounders may not have been identified. Secondly, about seven percent of the patients lost to follow-up during the seven-year study period, which might have influenced the results. Last but not least, genetic predisposition to higher GDF-15 levels might be associated with CAD, which was not investigated in the current study.

4.4 Conclusions

In conclusion, GDF-15 played a very important role in predicting the long-term prognosis in patients with intermediate coronary artery lesions in the Chinese population.

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