Evaluation of Growth Differentiation Factor-15 in Patients with or without Coronary Artery Disease

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Abstract. Background: Growth-differentiation factor-15 (GDF-15) is a distant member of the transforming growth factor-beta cytokine superfamily expressed in human atherosclerotic plaque macrophages. In this study, we sought to compare GDF-15 between patients with coronary artery disease and control group.

Methods: In this cross-sectional study, 176 subjects were enrolled, consisted of 88 coronary artery disease patients (CAD group) and 88 non-CAD participants (control group. Clinical and demographic data, comprising of family history of CAD, history, and lifestyle factors, hypertension, diabetes, and some blood parameters (e.g. glucose, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride, high-sensitivity C-reactive protein (hs-CRP)).

Results: Mean age of the patients was 55.5±11.1 years (age range: 28–80 years). Of all the participants, 91 (51.7%) were male and 85 (48.3%) female. Hs-CRP, LDL-C, and GDF-15 levels were significantly higher in the CAD patients (P=0.091, P=0.008, and P<0.001, respectively). Total cholesterol, hematocrit, and hemoglobin were significantly higher in the controls (P=0.002, P=0.011, and P=0.055, respectively). The area under the receiver operating characteristic curve yielded the satisfactory result of 0.9 (95% CI, 0.8-0.9; P<0.001). The optimum cut-off value of GDF-15 was 1233 ng/L with 71% specificity and 71% sensitivity for CAD diagnosis. Conclusion: These data suggest that serum GDF-15 might be useful in prediction of CAD. (www.actabiomedica)

Keywords: Growth differentiation factor-15, Coronary artery disease, Angiography

Introduction

Coronary artery disease (CAD) is a worldwide health concern with high morbidity and mortality rates. It is a chronic inflammatory atherosclerosis process lead to CAD and acute coronary syndromes (1). Cytokine or growth factors produced in the inflamed intima induce monocytes to enter the plaque to differentiate into macrophages leading to the development of atherosclerosis (2). Effector molecules from immune cells that dominate the early stage of atherosclerotic lesions accelerate lesion progression and further elicit acute coronary syndromes. Inflammatory factors such as C-reactive protein or monocyte chemoattractant protein-1 are attractive biomarkers in order to the prediction of risk for developing coronary artery disease (3, 4). Although these biomarkers are promising, they only have a moderate predictive value and are not widely used in clinical practice (5).
Therefore, there is a growing interest in using blood circulating biomarkers to obtain pathophysiological insight and improve the management of CAD patients.

Microarray analyses have been used to identify downstream targets of nitric oxide (NO) when growth differentiation factor-15 (GDF-15) first came to attention (6). GDF-15 is a distant member of the transforming growth factor beta (TGF-β) cytokine superfamily that was initially cloned from an activated macrophage cell line (7).

Like other TGF-β-related cytokines, GDF-15 is synthesized as a precursor protein that undergoes disulfide-linked dimerization (8). Under physiological circumstances, GDF-15 is weakly produced in most tissues (9), its expression level may increase in response to pathological stress associated with tissue injury or inflammation. Along that line, GDF-15 was detected in macrophages in human carotid atherectomy samples (10).

Cardiomyocytes express and secrete GDF-15 following ischemia or any reperfusion injury, stimulation with reactive oxygen species or pro-inflammatory cytokines, and exposure to mechanical stretch (7). GDF-15 expression in the myocardium has been shown to increase in mouse models of myocardial infarction, aortic stenosis, and dilated cardiomyopathy (11, 12). GDF-15 is also expressed in the myocardium of patients with acute myocardial infarction (11).

However, GDF-15 is not a cardiac-specific cytokine, oxidized low-density lipoproteins and pro-inflammatory cytokines induce GDF-15 are expressed in cultured macrophages (10, 13). Consistent with these in-vitro observations, GDF-15 is expressed in human atherosclerotic plaque macrophages (14). GDF-15 is also upregulated in the endothelial cells exposed to antiangiogenic stress (15, 16) and in vascular smooth muscle cells upon stimulation with triglyceride-rich lipoproteins (17). Adipocytes synthesize and secrete GDF-15 upon exposure to oxidative stress and may release paracrine factors that promote GDF-15 expression in the neighboring cells (17). Hence, GDF-15 is expressed by multiple cardiovascular cell types under stressful circumstances. With this background in mind, in the present study, we aimed to compare GDF-15 between CAD patients and healthy cases.

Materials and Methods

In this cross-sectional study, 176 subjects were enrolled, which consisted of 88 CAD patients (CAD group) and 88 non-CAD participants (control group) recruited from cardiac catheterization lab of Ghaem Hospital, Mashhad, Iran, during January-December 2015.

The diagnosis of CAD was confirmed by coronary angiography performed with Judkins technique using quantitative coronary angiographic system. CAD diagnosis was defined by angiography with at least one main coronary vessel > 50% luminal narrowing. The control group was defined as angiography with no or < 50% luminal narrowing. All the CAD patients were new case.

Inclusion and exclusion criteria

The inclusion criteria were being candidate for angiography and aged 20-80 years old; the exclusion criteria comprised of history of myocardial infarction and history of using statin drugs.

Data collection

Demographic information, family history of CAD, history, and lifestyle factors were obtained through interview and recorded in a questionnaire. Hypertension was diagnosed in individuals with systolic blood pressure at or above 140 mmHg, diastolic blood pressure at or above 90 mmHg, and/or consumption of anti-hypertension medication. Diabetes mellitus was defined as fasting blood sugar (FBS) of ≤126 mg/dl or consumption of oral hypoglycemic agents or insulin. Blood samples (10 cc) were collected in the morning of the angiography day after an overnight fast from the femoral artery of the angiographic catheter insertion site. Serum and plasma were separated by centrifugation at 1500 g for 15 min and stored at -80°C until testing. The GDF-15 assay was constructed using Human GDF-15 Duoset Kit (Biotechne, R&D, Minneapolis, United states) by ELISA method.

Statistical analysis

Statistical analyses were performed in SPSS, version 16. The normal distribution assumptions were as-
Assessed by Kolmogorov-Smirnov test. Mean±standard deviation was applied for quantitative normally distributed variables, median (plus range) for quantitative non-parametric data, and number (plus percentage) for qualitative variables. Quantitative normally distributed variables were compared using the independent samples t-test, and quantitative non-parametric variables were compared by performing the Mann–Whitney test. P-value less than 0.05 was considered statistically significant. Serum GDF-15 concentrations were used to draw receiver operating characteristic (ROC) curve, and the specificity, sensitivity, and area under the ROC curve (AUC) were determined.

**Ethical consideration**

Written informed consent was obtained from each participant. The confidentiality of the subjects the study was approved by the Ethics Committee of Mashhad University of Medical Sciences (ethical code: IR.MUMS.REC.1391.23). Peripheral blood sample was obtained from each participant.

**Results**

Mean age of the patients was 55.52±11.10 years (range: 28–80 years). We also compared women with the age-matched men. The mean age of the male patients was 61.66±7.94 years, while it was 61.92±9.67 years in females (P=0.846). Other demographic data are presented in Table 1.

As presented in Table 1 there were significant differences in height and weight between males and females (P<0.001 and P=0.033, respectively). Other variables including age, body mass index (BMI), hypertension, diabetes, high sensitivity-C reactive protein (hs-CRP), total cholesterol (TC), total triglyceride (TG), low density lipoprotein-C (LDL-C), high density lipoprotein-C (HDL-C), fasting blood sugar (FBS), hematocrit (HCT), height/weight, hemoglobin (Hb), and GDF-15 were not significantly different between the two genders.

The mean heights of the patients were 163.23±11.56 and 155.21±6.89 cm in male and female patients, respectively. The mean weights of the patients

| Characteristics | Male (n=91) | Female (n=85) | P-value |
|-----------------|------------|--------------|---------|
| Age (years)     | 61.66±7.94 | 61.92±9.67   | 0.846   |
| Height          | 163.23±11.56 | 155.21±6.89 | <0.001  |
| Weight          | 71.47±11.85 | 67.02±13.55 | 0.033   |
| BMI (kg/m²)     | 25.70±3.64  | 25.16±3.31   | 0.306   |
| Hypertension n (%) | 32(40.0%) | 35 (44.9%)  | 0.536   |
| Diabetes n (%)  | 23(28.8%)  | 19(23.8%)    | 0.472   |
| hs-CRP (mg/dl)  | 3.14(1.50-8.81) | 2.85(1.19-6.66) | 0.324   |
| TC (mg/dl)      | 182.66±63.27 | 187.48±66.77 | 0.623   |
| TG (mg/dl)      | 190.23±64.82 | 201.86±63.44 | 0.231   |
| LDL-C (mg/dl)   | 126.38±38.36 | 127.62±3369 | 0.820   |
| HDL-C (mg/dl)   | 47.89±15.85  | 44.41±13.26  | 0.129   |
| FBS (mg/dl)     | 114.43±56.03 | 107.48±41.37 | 0.594   |
| HCT             | 39.53±5.27  | 39.49±4.90   | 0.960   |
| Height/Weight   | 0.43±0.08   | 0.42±0.08    | 0.356   |
| Hb              | 13.10±1.90  | 13.06±1.68   | 0.883   |
| GDF-15 (ng/l)   | 923.49±665.09 | 873.79±538.39 | 0.920   |

All values are mean±standard deviation for quantitative normal distribution variables and median (range) for quantitative non-parametric data; also number (percentage) for Qualitative variables. BMI (body mass index), hs-CRP (high sensitivity-C reactive protein), TC (total cholesterol), TG (total triglyceride), LDL-C (low-density lipoprotein cholesterol), HDL-C (high-density lipoprotein cholesterol), FBS (fasting blood sugar), HCT (hematocrit), Height/Weight, Hb (hemoglobin) and GDF-15 (Growth Differentiation Factor-15)
were 71.47±11.85 and 67.02±13.55 kg in male and female patients, respectively. Also, the mean BMI of the patients were 25.70±3.64 and 25.16±3.31 kg/m² in male and female patients, respectively. Further, 32 (40%) and 35 (44.9%) of the male and female patients were hypertensive, respectively, and 23 (28.8%) and 19 (23.8%) of the male and female patients were diabetic, respectively. The mean TC levels of the patients were 182.66±63.27 and 187.48±66.77 mg/dl in male and female patients, respectively.

The mean ranges of TG in the male and female patients were 190.23±64.82 and 201.86±63.44 mg/dl, respectively. In addition, the mean ranges of LDL-C in male and female patients were 126.38±38.36 and 127.62±33.69 mg/dl, respectively. The mean ranges of HDL-C in male and female patients were 47.89±15.85 and 44.41±13.26 mg/dl, respectively. The mean FBS levels were 114.43±56.03 and 107.48±41.37 mg/dl in male and female patients, respectively. The mean ranges of HCT in the male and female patients were 39.53±5.27 and 39.49±4.90 mg/dl, respectively. Finally, the mean ranges of GDF-15 in male and female patients were 923.49±665.09 and 873.79±538.39 mg/dl, respectively.

According to Table 2, hs-CRP, LDL-C, and GDF-15 levels were significantly higher in the CAD patients compared to the non-CAD group (P=0.091, P=0.008, and P<0.001, respectively); besides, TC, HCT, and Hb levels were significantly higher in the control group (P=0.002, P=0.011, and P=0.055, respectively).

The other parameters including age (years), height, weight, BMI, hypertension, diabetes, TG, HDL-C, FBS, and height/weight were not significantly different between the CAD and non-CAD groups. The mean heights of the patients were 160.52±10.44 and 157.45±9.91 cm in the case and control groups, respectively. The mean weights were 69.89±12.26 and 68.37±13.95 kg in the case and control groups, respectively. Moreover, 44 (50%) and 47 (53.4%) of the patients in the case and control groups were male, respectively.

### Table 2. Baseline clinical and laboratory data according to coronary artery disease

| Characteristics | Case (n=88) | Control (n=88) | P-value |
|-----------------|------------|---------------|---------|
| Age (years)     | 61.07±8.42 | 62.50±9.15    | 0.281   |
| Height          | 160.52±10.44 | 157.45±9.91  | 0.065   |
| Weight          | 69.89±12.26 | 68.37±13.95   | 0.472   |
| Female n (%)    | 44 (50.0%) | 41 (46.6%)    | 0.651   |
| Male n (%)      | 44 (50.0%) | 47 (53.4%)    |         |
| BMI (kg/m²)     | 25.33±3.47 | 25.55±3.51    | 0.680   |
| Hypertension n (%) | 42 (45.7%) | 25 (37.9%)   | 0.330   |
| Diabetes n (%)  | 28 (30.4%) | 14 (20.6%)    | 0.162   |
| hs-CRP (mg/dl)  | 3.16 (1.54-8.48) | 2.54 (0.99-6.63) | 0.091 |
| TC (mg/dl)      | 169.69±64.14 | 200.28±62.22 | 0.002   |
| TG (mg/dl)      | 201.90±61.20 | 189.80±66.94 | 0.212   |
| LDL-C (mg/dl)   | 134.10±37.02 | 119.86±33.85 | 0.008   |
| HDL-C (mg/dl)   | 46.10±15.46 | 46.32±14.03   | 0.832   |
| FBS (mg/dl)     | 115.49±55.35 | 106.66±42.67 | 0.279   |
| HCT             | 38.64±4.50  | 40.37±5.50    | 0.011   |
| Height/Weight   | 0.42±0.08   | 0.42±0.08     | 0.992   |
| Hb              | 12.82±1.69  | 13.34±1.86    | 0.055   |
| GDF-15 (ng/l)   | 1069.58±677.46 | 729.40±470.36 | <0.001   |

All values are mean ± standard deviation for quantitative normal distribution variables and median (range) for quantitative non-parametric data; also number (percentage) for Qualitative variables. BMI (body mass index), hs-CRP (high-sensitivity C reactive protein), TC (total cholesterol), TG (total triglyceride), LDL-C (low-density lipoprotein cholesterol), HDL-C (high-density lipoprotein cholesterol), FBS (fasting blood sugar), HCT (hematocrit), Height/Weight, Hb (hemoglobin) and GDF-15 (Growth Differentiation Factor-15),
Also, the mean BMIs were 25.33±3.47 and 25.55±3.51 kg/m² in the case and control groups, respectively. Additionally, 42 (45.7%) and 25 (37.9%) of the case and control patients were hypertensive, respectively, 28 (30.4%) and 14 (20.6%) of the case and control patients were diabetic, respectively. The medians and quartile ranges of Hs-CRP in the case and control groups were 3.16 (1.54-8.48) and 2.54 (0.99-6.63), respectively. The mean TCs were 169.69±64.14 and 200.28±62.22 mg/dl in the case and control groups, respectively. The mean ranges of TG in the case and control groups were 201.90±61.20 and 189.80±66.94 mg/dl, respectively. The mean levels of LDL-C in the case and control groups were 134.10±37.02 and 119.86±33.85 mg/dl, respectively. The mean ranges of HDL-C in the case and control groups were 46.10±15.46 and 46.32±14.03 mg/dl, respectively. The mean FBS levels were 115.49±55.35 and 106.66±42.67 mg/dl in the case and control patients, respectively. The mean ranges of HCT in the case and control patients were 38.64±4.50 and 40.37±5.50 mg/dl, respectively. The mean ranges of Hb in the case and control patients were 12.82±1.69 and 13.34±1.86 mg/dl, respectively. Finally, the mean ranges of GDF-15 in the case and control patients were 1069.58±677.46 and 729.40±470.36 mg/dl, respectively.

To determine the diagnostic predictive value of GDF-15 for CAD, ROC curve analysis was performed. As shown in Figure 1, the area under the ROC curve yielded a satisfactory result of 0.912 (95% CI, 0.866-0.959; P<0.001). The optimum cut-off value of GDF-15 was 1233 ng/L with 71% specificity and 71% sensitivity for CAD diagnosis.

Discussion

According to our results, LDL-C and GDF-15 were significantly higher in the CAD patients compared to the controls. TC and HCT levels were significantly higher in the control group. The optimum cut-off value of GDF-15 was 1233 ng/L with 71% specificity and 71% sensitivity for CAD diagnosis. These data suggest that serum GDF-15 can predict CAD.

In a study conducted by Khan et al. in 2009 in the UK, GDF-15 was found as a prognostic marker of death and heart failure (HF) in patients with acute myocardial infarction. According to the ROC analysis, NT-pro BNP and GDF-15 were of similar accuracy in the prediction of death or HF (18). According to previous studies, GDF-15 rapidly increases in response to cardiovascular injury, hypertension, HF, ischemia, and atherosclerosis (7, 19, 20). Also, GDF-15 is strongly correlated with age in both healthy and unhealthy adults (21, 22). Ho et al. showed that GDF-15 is significantly higher in healthy elderly than younger adults (23). Additionally, GDF-15 is positively associated with diabetes, CAD (21, 22, 24, 25), and chronic kidney disease (26, 27).

Recent studies also exhibited that GDF-15 is correlated with inflammatory biomarkers such as C-reactive protein and N-terminal pro b-type natriuretic peptide, suggesting a link between GDF-15 and inflammation (19, 28, 29).
Prospective investigation of the vasculature in Uppsala Seniors study reported that GDF-15 is related to the male gender, current smoking, and diabetes. In this study observed an independent relationship between GDF-15 and TG level, low LDL, and low HDL, supporting a link between GDF-15 and lipid metabolism (30).

Notably, GDF15 could predict cardiovascular events, even after correction for the Framingham risk score, endothelium-dependent vasodilation, and intima-media thickness (IMT), emphasizing the strong and independent relation of this biomarker with cardiovascular diseases (30).

Conclusion

GDF-15 was significantly higher in CAD patients relative to the controls. The optimum cut-off value of GDF-15 was 1233 ng/L with 71% specificity and 71% sensitivity for CAD diagnosis. These data suggest that serum GDF-15 has a good capability in predicting CAD.

Limitations

This study has some limitations. First, this was a cross-sectional study and had no follow-up; thus, we could not clearly establish a causal relationship between GDF-15 and development of CAD. Second, this study only included Iranian subjects; therefore, our results may not fully apply to the general population. Third, the sample size was limited, and further larger studies are required in this regard.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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