Evaluation of Arterial Stiffness Parameters and Growth Differentiation Factor-15 Level in Patients with Premature Myocardial Infarction

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Article

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Abstract: Background: Myocardial infarction is increasing at a young age. New tools are needed to evaluate the risk population of young patients. GDF-15 has been implicated in several key mechanisms of atherogenesis and also is associated with increased mortality and cardiovascular events in patients with coronary artery disease. Arterial stiffness parameters, including pulse wave velocity, can also be measured using peripheral arterial tonometry and can indicate the presence or progression of atherosclerotic changes. The aim of this study is to evaluate the GDF-15 level and arterial stiffness parameters in patients with premature myocardial infarction. **Method:** Thirty patients who recovered from a myocardial infarction were consecutively included. Fifteen age-sex-matched subjects were included as controls. The patients' serum GDF-15 concentration levels were measured using relevant kits. Measurements of arterial stiffness [pulse-wave velocity (PWV) and augmentation index (AIx)] were performed using a Mobil-O-Graph arteriography system. **Results:** GDF-15 concentration levels were significantly higher in the patients with premature myocardial infarction when compared to controls. PWV and AIx were similar between the groups. GDF-15 level was negatively correlated with high-density cholesterol (HDL) and positively correlated with uric acid levels in all study populations. **Conclusions:** GDF-15 levels may be a risk factor for patients with premature myocardial infarction. This pilot study may trigger further studies to elucidate the central role of GDF-15 in the pathophysiology of early atherosclerosis in the young population.

Keywords: GDF-15; arterial stiffness; premature myocardial infarction and PWV

Introduction

The leading cause of death in the world is coronary heart disease (CHD). Acute myocardial infarction is among the most common causes of death in developing countries[1]. The prevalence of acute myocardial infarction in young patients ranges from 6-10% [2]. Most registries and studies use an age range of 40-45 years to define "young" individuals with coronary artery disease or acute myocardial infarction [3]. While acute coronary syndrome (ACS) rates have dropped among older individuals, younger men experiencing acute myocardial infarction (MI) haven't seen comparable reductions in cardiovascular events [4].

Arterial stiffness measures, including pulse wave velocity (PWV), represent a significant predictor for upcoming cardiovascular ailment. This holds true regardless of widely recognized cardiovascular risk elements. Elevated arterial stiffness is linked to unfavorable cardiovascular results, regardless of established risk factors like high blood pressure, abnormal lipid levels, diabetes, obesity, advancing age, and tobacco use. [5]. However, the data on the effectiveness of arterial stiffness in young patients is not enough.

Over time, researchers studied various biomarkers and signaling molecules tied to the development of atherosclerosis. An attention-grabbing molecule is GDF-15 (Growth Differentiation Factor 15), a member of the transforming growth factor-beta superfamily[6]. Previous studies have demonstrated that increased GDF-15 level is also related to CVD and CHD [7]. Recent studies have shown that GDF-15 is a strong predictor of mortality and recurrent MI in patients with acute coronary syndrome [8].

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The aim of this study is to investigate the association between plasma GDF-15 levels and arterial stiffness parameters in patients with premature myocardial infarction.

Patients and Methods

Study population

Fourty consecutive patients admitted to the cardiology clinics with the diagnosis of acute myocardial infarction were invited to participate in the study. The diagnosis of myocardial infarction was confirmed with coronary angiography. Patients were evaluated for the presence of CVD risk factors including hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM), family history, and cigarette smoking. Patients with other inflammatory conditions including systemic lupus erythematosus (SLE), typical rheumatoid arthritis (RA), thrombophilia, gout, chronic kidney disease, left ventricular (LV) systolic dysfunction, cardiomyopathy, valvular heart disease, , arrhythmias, were excluded from the study. After exclusion criteria, the remaining 30 patients with premature myocardial infarction were included in the study. As a control group, 15 age-/sex-matched healthy volunteers were included in the study. Volunteers were excluded if they had systemic connective tissue disease, any evidence of systemic infection, arrhythmias, or conduction disorders. The investigation complies with the principles outlined in the Declaration of Helsinki. The study was approved by the ethics committee of the Marmara University School of Medicine, and all participants gave written informed consent before participating.

Assessment of Arterial Stiffness Parameters

The assessment of arterial stiffness took place while the subjects were lying down in a tranquil, temperature-regulated room during the early hours of the morning. Mobil-O-Graph arteriograph system (Mobil-O-Graph NG, Stolberg, Germany) used for arterial stiffness parameters measurement and PWV were calculated according to current guidelines [9]. We performed arterial stiffness measurements once for each study patient.

Assessment of Plasma GDF-15 Levels

Plasma was collected using EDTA-Na2 as an anticoagulant. Samples were centrifuged for 15 min at 1000×g at 2-8°C within 30 min of collection. Supernatants were collected to carry out the assay. Plasma GDF-15 concentration levels were measured using relevant Human GDF15 (Growth Differentiation Factor 15) ELISA Kit (catalog number: E-EL-H0080, Elabscience Biotechnology Inc. USA).

Statistical Analysis

All statistical tests were performed by a statistical analysis program (SPSS 21.0 for Windows, Chicago, IL). The distribution of data was tested using a one-sample Shapiro-Wilk test. Categorical variables were defined as a percentage, and comparisons were made using the Chi-square test. Continuous data were expressed as mean ± standard deviation and Student's t-test was used to compare the normally distributed continuous variables while the Mann-Whitney U test was used to compare the nonparametric continuous variables. Correlation analysis was performed by the Pearson or Spearman test. A significance level was set at $p<0.05$

Results

Thirty patients (mean age: 39 ± 5 years, 23 male) with premature myocardial infarction were consecutively included in the study. Characteristics of the study population are shown in Table 1. There were no significant differences in age, sex, or comorbidities between the groups. Laboratory parameters of the groups are shown in Table 2. Total cholesterol and low-density lipoprotein (LDL) levels did not show a significant difference between the patient and control groups. While HDL was found to be significantly lower in the patient group compared to the controls, triglyceride and uric

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acid levels were found to be significantly higher. GDF-15 level was statistically higher in the patient group.

Table 1. Characteristics of the study population.

	Patients (n=30)	Controls (n=15)	p
Age (years)	39.6±5.3	40.2±3.4	0.694
Gender (male) (n-%)	23 (76.7)	11(73.7)	1
BMI (kg/m²)	28.6±5.3	27.2±3.9	0.350
Coronary heart disease (n-%)	7 (21.1)	0	0.77
Hypertension (n-%)	6 (20)	1 (6.7)	0.395
Diabetes mellitus (n-%)	11 (36.6)	3 (20)	0.255
Hyperlipidemia (n-%)	4 (13.3)	0	0.285
Smoker (n-%)	10 (33.3)	6 (40)	0.660
Family history (n-%)	4 (13.3)	2 (13.3)	1
Clinical presentation			
Anterior STEMI (n-%)	12 (40)	-	
Inferior STEMI (n-%)	9 (30)	-	
NSTEMI/USAP (n-%)	9 (30)	-	

BMI: Body mass index; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction; USAP: unstable angina pectoris;.

Table 2. Laboratory parameters of the study population.

	Patients (n=30)	Controls (n=15)	P
Hemoglobin (g/dL)	14.5±2	14.4±2	0.838
Hematocrit (%)	41.8±5	43±5.3	0.470
Creatinin (mg/dL)	0.82±0.15	0.77±0.11	0.323
Total cholesterol (mg/dL)	173±42	185±25	0.159
Triglycerides (mg/dL)	155±56	126±68	**0.020**
LDL cholesterol (mg/dL)	111±32	112±30	0.885
HDL cholesterol (mg/dL)	37±13	51±12	**<0.001**
Uric acid (mg/dL)	5.9±1.4	4.8±1	**0.007**
NT-ProBNP (ng/mL)	0.22±0.03	0.19±0.03	**0.004**
GDF-15, (Pg/mL)	105.9±196	25.9±10	**0.002**

LDL: low-density lipoprotein; HDL: high-density lipoprotein; NT-ProBNP: N-terminal pro-B-type natriuretic peptide; GDF-15: Growth Differentiation Factor-15.

The arterial stiffness parameters and hemodynamic parameters of the patients are listed in Table 3. There were not any significant differences in PWV and AIx of the patients with premature myocardial compared to controls. Patients with premature myocardial infarction had significantly lower peripheral pulse pressure and heart rates compared to controls.

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Table 3. Comparison of arterial stiffness parameters and hemodynamic parameters among groups.

	Patients (n=30)	Controls (n=15)	P
Peripheral systolic blood pressure (mmHg)	115±16	123±11	0.115
Peripheral diastolic blood pressure (mmHg)	77±13	78±11	0.656
Peripheral mean blood pressure (mmHg)	95±11	98±11	0.455
Peripheral pulse pressure (mmHg)	38±9	44±9	**0.037**
Heart rate (beat/min)	75±12	83±10	**0.023**
Cardiac output (l/min)	5±0.6	4.9±0.8	0.419
Cardiac index (l/min/m²)	2.6±0.4	2.6±0.5	0.762
Central systolic blood pressure (mmHg)	107±15	113±11	0.094
Central diastolic blood pressure (mmHg)	78±13	80±11	0.515
Central pulse pressure (mmHg)	29±8	33±7	0.088
Reflecting magnitude (%)	61±11	61±6	0.819
Augmentation index (%)	14±10	18±8	0.117
PWV (m/s)	6.04±0.8	6.09±0.7	0.700

PWV: Pulse wave velocity.

GDF-15 was significantly positively correlated with triglyceride (r= 0.296, p: 0.048) and uric acid levels (r= 0.376, p: 0.011) and negatively correlated with HDL (r= -0.368, p: 0.013) as shown in Table 4.

Table 4. Correlation of GDF-15 levels with uric acid, HDL and triglyceride levels.

GDF-15	Uric acid	HDL	Triglyceride
P	**0.011**	**0.013**	**0.048**
R²	0.376	-0.368	0.296

GDF-15: Growth Differentiation Factor-15; HDL: high-density lipoprotein;.

Discussion

In our study, we found that GDF-15 was significantly higher in patients with premature myocardial infarction compared to controls, but PWV was not increased. To the best of our knowledge, the association between plasma GDF-15 levels and arterial stiffness has not been assessed in patients with premature myocardial infarction.

GDF-15 stands as a stress-reactive cytokine which is discharged by diverse cell categories, encompassing endothelial cells, smooth muscle cells, and macrophages. Its function spans over several biological and pathological mechanisms, encompassing inflammation, oxidative stress, and cellular growth. [10]. GDF-15 has shown diagnostic and prognostic value in atherosclerosis [11]. Eggers et al. showed that GDF-15 could be used for early risk stratification in patients with acute chest pain [12]. Wang et al. found that elevated GDF-15 levels were associated with increased mortality and cardiovascular events in patients with CAD [13]. In addition, higher GDF-15 levels were associated with an increased risk of recurrent events in patients stabilized after ACS [14]. Furthermore, another study demonstrated that GDF-15 predicts all-cause mortality and morbidity in stable CHD [15].

There are various hypotheses regarding the relation between plasma GDF-15 level and CVD. GDF-15 induces endothelial dysfunction by impairing nitric oxide synthesis and promoting endothelial cell apoptosis[16]. This contributes to the initiation and progression of atherosclerotic lesions[16] . Also, GDF-15 promotes the recruitment and activation of immune cells, particularly

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macrophages, leading to the formation of foam cells and the development of fatty streaks [10]. Additionally, GDF-15 is involved in promoting inflammation and oxidative stress within the arterial wall, exacerbating the atherosclerotic process[16].

Arterial stiffness serves as a gauge of the elasticity of arteries and the proportional influence of collagen and elastin[17]. Research has indicated that oxidative stress and inflammation are the primary culprits behind the stiffening of blood vessels [18]. Pulse wave velocity (PWV), the most extensively employed gauge of arterial stiffness, has surfaced as a valuable instrument for both diagnosing and categorizing the risk associated with cardiovascular disease (CVD). [19]. The measurement of PWV is a simple, non-invasive, and reproducible marker [20]. Many clinical studies and meta-analyses have shown the association between PWV and CVD [21]. Also, a follow-up study showed that high baseline PWV was significantly associated with the progression of CAD [22]. On the other hand, a few studies show that reduced traditional risk factors such as anti-hypertensive medications, regular exercise, statin use, and smoking cessation improve arterial stiffness and decrease PWV value [23]. The prognostic efficacy of arterial stiffness is more pronounced in individuals with an elevated initial CV risk [5]. However, the relationship between arterial stiffness in patients with premature myocardial infarction is not clear [21]. In our study, PWV was not different in our patient group compared to the control group.

Myocardial infarction represents the final stage within the progression of atherosclerotic pathophysiology. When endothelial function is compromised, factors that promote vasoconstriction, inflammation, proliferation, and thrombosis take precedence, leading to a significantly proatherogenic condition [24]. A universal definition or standardized set of diagnostic criteria for early-stage MI is currently lacking. The majority of studies have chosen an age range of 40–45 years to categorize patients as "young" in the context of coronary artery disease (CAD) or acute MI[3], [25]. Traditional risk factors for acute myocardial infarction at a young age include physical inactivity, smoking, alcohol consumption, dyslipidemia, diabetes mellitus, hypertension, and obesity [26]. The most dominant of these is smoking[27].

Although plaque-based mechanisms dominate as the etiology for myocardial infarction (MI) in young individuals [28], non-traditional risk factors, drugs and toxins, allergic reactions and hypersensitivity, infections, immune-mediated inflammatory diseases, and thrombophilia constitute another important part of the etiology of premature myocardial infarction[3]. However, PWV usually increases in patients with traditional cardiovascular risk factors including diabetes, hypertension, hyperlipidemia, smoking, and aging [21]. Therefore, PWV may not fit to predict premature atherosclerosis as a surrogate marker in the young population. The GDF-15 molecule may be useful in the evaluation and follow-up of this special group with premature myocardial infarction.

In our study, we found that HDL levels were lower in patients with premature myocardial infarction than in the control group. Similar to our study, one study showed that HDL levels were a lipid parameter strongly associated with premature AMI, and HDL levels at the onset of AMI could predict cardiovascular events in young males [29]. We also found a statistically significant negative correlation between HDL and GDF-15 levels in all study groups.

In our study, uric acid levels were found to be higher in the patient group compared to the control group and also there was a positive correlation between uric acid levels and GDF-15 levels. In parallel with our result, the URRAH study (Uric Acid Right for Health) with 23,467 participants found that elevated serum uric acid level is an independent risk factor for fatal AMI, even after accounting for potential confounding factors [30]. Also, in one study GDF-15 levels were positively correlated with CAD in male patients with hyperuricemia[31]. It may be due to the fact that uric acid is associated with processes such as higher oxidative stress, inflammation, and endothelial dysfunction [32]. Also, we found that GDF-15 was positively correlated with triglyceride levels in our patient group. In previous studies, it was indicated that GDF-15 may be one of the clinical biomarkers of cardiometabolic risk in the community [33].

Despite significant advancements in CVD prognosis achieved through the management of risk factors like hypertension, diabetes, and dyslipidemia, the burden of CVD remains considerable [34]. It has been widely suggested that these traditional risk factors do not entirely explain the increasing

prevalence of CVD, with more than 50% of CVD patients exhibiting none of these risk factors [21]. Furthermore, a substantial number of individuals afflicted by fatal CVD events, including sudden cardiac death, myocardial infarction, or stroke, do not exhibit preceding symptoms or warning indicators[35]. Hence, early detection of subclinical atherosclerosis and the identification of individuals with a heightened risk for future CVD, such as angina and myocardial infarction is crucial.

Hence, it holds promise as a potentially valuable new biomarker with the ability to offer distinct prognostic insights and guide effective treatment approaches. Ongoing clinical trials are essential for a more comprehensive understanding of the advantages of GDF-15 in foreseeing the outcomes of individuals diagnosed with acute coronary syndrome.

Conclusion

This study provides, to the best of our knowledge, the first evidence in patients with premature myocardial infarction for an association between plasma GDP-15 levels and arterial stiffness parameters. Our study indicates that patients with premature myocardial infarction have high plasma GDP-15 levels when compared to controls. This pilot study may trigger further studies to elucidate the central role of GDP-15 in pathophysiology of early atherosclerosis in young population.

Author Contributions: Conceptualization, Zekeriya Dogan and Cigdem Ileri; Methodology, Yusuf Emre Gurel, Beste Sadic and Tulin Ergun; Software, Nurten Sayar; Formal analysis, Zekeriya Dogan and Yusuf Emre Gurel; Investigation, Mustafa Kursat Tigen; Resources, Zekeriya Dogan and Tulin Ergun; Data curation, Zekeriya Dogan and Ayse Esin Kaya; Writing – original draft, Zekeriya Dogan and Cigdem Ileri; Writing – review & editing, Murat Sunbul, Beste Sadic and Mustafa Kursat Tigen; Visualization, Nurten Sayar; Supervision, Murat Sunbul and Tulin Ergun; Project administration, Murat Sunbul; Funding acquisition, Tulin Ergun.

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Institutional Review Board Statement: The study was approved by the ethics committee of the Marmara University School of Medicine and was carried out in accordance with the Declaration of Helsinki, and all patients gave written informed consent for their participation.

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: Certain confidentiality constraints prevent us from disclosing the underlying database used in this study.

Conflicts of Interest: None declared

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