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Increased Serum Growth Differentiation Factor 15 Levels may be Associated with Diastolic Dysfunction in Acromegaly

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ABSTRACT

Introduction: Growth differentiation factor-15 (GDF-15) is a cytokine that is associated with various metabolic and cardiac changes. Acromegaly is a chronic multisystemic disease that causes cardiac dysfunction due to an increased levels of growth hormone. We evaluated the association of GDF-15 with diastolic dysfunction in acromegaly.

Methods: Fifty-four patients with acromegaly [active (n=24), inactive (n=30)] and 34 healthy controls were included in the study. The acromegaly group (AG) and control group (CG) were compared for their blood pressures, metabolic parameters, GDF-15 levels, and echocardiographic findings. The correlation analysis was performed between the GDF-15 and the parameters that may be associated with it in the AG.

Results: GDF-15 was significantly higher in AG than in the CG ($p<0.001$). GDF-15 was positively correlated with body mass index ($r=0.4$, $p=0.008$) and negatively correlated with fasting blood glucose ($r=-0.4$, $p=0.004$). GDF-15 was also positively correlated with diastolic blood pressure (DBP) ($r=0.4$, $p=0.002$). Among echocardiographic findings, end-diastolic volume (EDV), and stroke volume (SV) were negatively correlated with GDF-15 levels ($r=-0.4$, $p=0.003$, and $r=-0.4$, $p=0.03$, respectively).

Conclusion: GDF-15 was detected to be significantly increased in patients with acromegaly. This increment was associated with subtle changes in DBP, EDV, and SV. Therefore, GDF-15 may play a role in diastolic impairment at the cardiac involvement in acromegaly.

Keywords: Acromegaly, cardiac complications, diastolic dysfunction, growth differentiation factor 15

Introduction

Acromegaly is a multisystemic disease that also causes cardiac dysfunction (1). Both excessive insulin-like growth factor-1 (IGF-1) and growth hormone (GH) cause cardiac changes in acromegaly (2,3). Various underlying mechanisms involving changes in calcium influx, expression of muscle-specific genes, and the composition of myosin isoform are held responsible for the effects of IGF-1 and GH on the cardiovascular system (4-7). However, all the mechanisms have not yet been identified.

Growth differentiation factor-15 (GDF-15) is a novel cytokine that is a member of the transforming growth factor β superfamily released by activated macrophages (8,9). It is present in different tissues and cells, including the vessels and cardiomyocytes (10). Stress, ischemia, anoxia, and inflammatory cytokines are among the triggers of GDF-15 release (11,12). Increased GDF-15 is associated with metabolic and cardiac changes. GDF-15 predict increased cardiovascular risk and all-cause mortality (13,14). It also maintains vascular integrity and increases cardiomyocyte and endothelial cell viability (15). Whether GDF-15 takes a role in cardiac involvement in acromegaly is unknown. The We evaluated the association of GDF-15 with cardiac changes in acromegaly.

Methods

Fifty-four patients with acromegaly [active (n=24), inactive (n=30)] were involved in this prospective study. The healthy control group (CG) was composed of age, gender, and body mass index (BMI)-matched 34 subjects. Patients with acromegaly were monitored at our hospital endocrine clinic during this study. Patients with malignancy, rheumatologic disease, chronic kidney failure, and patients with older stents were excluded from the study based on these criteria. This study was approved by the Ethics Committee of Universtiy of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2011-KAEK-50, date: 06.05.2022). A written informed consent form was obtained from all patients before the study.

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The presence of typical clinical symptoms with failure to suppress the GH levels to less than 1 ng/mL according to the oral glucose tolerance test and elevated IGF-1 levels led to the diagnosis of acromegaly. Acromegaly remission criteria were defined as normal IGF-1 levels according to the age-adjusted range and GH levels less than 1 ng/mL. Active disease was defined as elevated IGF-1 levels according to the age-adjusted range.

Bilateral diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured three times with 5 min intervals in all patients.

The mean of each SBP and DBP was used for statistical analysis. Serum fasting blood glucose (FBG), hemoglobin A1C, insulin, cholesterol levels were measured in all patients. Homeostatic model assessment for insulin resistance has been used to determine insulin resistance (16).

The quantitative sandwich enzyme-linked immunosorbent assay method was used to measure the GDF-15 (Human GDF-15 ELISA Kit, USA).

For each attendant, transthoracic echocardiography at rest was performed with Philips EPIQ 7 diagnostic ultrasound system equipment and 2.5 MHz transducers. All measurements were taken at the same time of day and by the same competent cardiologist to the recommendations from the American Society of Echocardiography (17). Left ventricular internal end-diastolic diameter, left ventricular posterior wall thickness during diastole, left ventricular mass (LVM), left atrium diameter, interventricular septum thickness (IVST), end-diastolic volume (EDV), end-systolic volume (ESV), and left ventricular ejection fraction (EF) were measured. The Devereux and Reishek Formula was used to determine LVM. The ratio of the LVM to the body surface area was used to calculate the LVM index (18). Stroke volume (SV) was calculated using measurements of ventricular volumes from an echocardiogram, i.e., subtracting ESV from EDV.

Acromegalic group (AG) and healthy CG participants were compared concerning their laboratory, clinical and echocardiographic findings. Correlation analysis was performed between the GDF-15 and the parameters that may be associated with it in the AG.

Statistical Analysis

Statistical analysis was assessed using the SPSS 22.0 package program. The chi-square test was used to evaluate the categorical variables. Kolmogorov-Smirnov test was used to evaluate the normality of the distribution of the quantitative variables. Normally distributed data were evaluated using the student's test, and non-normally distributed data were evaluated using the Mann-Whitney U test. Pearson's correlation analysis was used to evaluate the associations between variables. Statistical significance was set with $p<0.05$.

Results

The mean age in the AG was 46.9±13.4 years, and it was 44.8±12.3 years in the CG (p=0.7). Gender was not different between the two groups (37 female/17 male in the AG and 22 female/12 male in the CG, p=0.7).

The mean time since the initial diagnosis in patients with acromegaly was 40.8±11.8 months. Thirty patients (57%) with acromegaly had controlled disease. The clinical findings of the patients with acromegaly are given in Table 1.

BMI in the AG and CG was 30.7±6 kg/m^2 and 29.3±5.3 kg/m^2, respectively (p=0.3). The mean SBP and DBP in the AG were 123.1±18 and 82.2 ±11.9 mmHg, and in the CG were 118.4± 14.8 and 78.4±10.5 mmHg (for SBP p=0.2, for DBP p=0.1).

GDF-15, IGF-1, and GH were significantly higher in AG than in the patients in the CG ($p<0.001$, $p<0.001$, and p=0.002, respectively). Laboratory findings in the AG and CG are shown in Table 2.

In patients with acromegaly, GDF-15 was positively correlated with BMI (r=0.4, p=0.008) and negatively associated with FBG levels (r=-0.4, p=0.004). GDF-15 was not correlated with the mean SBP (r=0.1, p=0.7), whereas it was positively correlated with DBP (r=0.4, p=0.002). GH, IGF-1 levels, cholesterol levels, and the passed time since the initial diagnosis of acromegaly was not correlated with GDF-15 levels.

LVM, IVST, EDV, and ESV was significantly higher in AG than in the patients in the CG (p=0.009, p=0.002, p=0.03, and p=0.005, respectively). Comparisons of the echocardiographic parameters between the two groups are given in Table 3. Among echocardiographic findings, EDV and SV were negatively associated with GDF-15 levels in AG (r=-0.4, p=0.003, and r=-0.4, p=0.03, respectively) (Figure 1). Additionally, EF was positively correlated with GDF-15 (r=0.3, p=0.01).

Table 1. Clinical findings of the patients with acromegaly

	Acromegaly (n=54)
Time elapsed since diagnosis (months)	40.8±11.8
Operation (n, %)	47 (87)
GKN/CKN (n, %)	11 (20)
Somatostatin analog (n, %)	30 (56)
Cabergoline treatment (n, %)	10 (19)
Controlled (n, %)	30 (57%)

GKN: Gamma knife, CKN: Cyber knife

Table 2. Laboratory findings of the patients with acromegaly and control groups

	Acromegaly (n=54)	Control group (n=34)	p-value
Fasting blood glucose (mg/dL)	108.9±34.1	104.2±32.1	0.5
HOMA-IR	3.8 ± 3.5	3.6 ± 2.7	0.8
Total cholesterol (mg/dL)	194.3±41.1	213.249.9	0.06
LDL cholesterol (mg/dL)	109 ±36	125.2±44	0.08
Triglyceride (mg/dL)	141.7±77.4	154.4±68.9	0.4
HDL cholesterol (mg/dL)	55.9±14.7	59.2±14.6	0.3
GDF-15 (pg/mL)	1179.7±344.6	510.6±319.8	**<0.001**[a]
GH[b] (ng/mL)	1.7 (0.7-3.2)	0.7 (0.1-1.8)	**0.002**[a]
IGF-1 (ng/mL)	287.5±169	135±46.3	**<0.001**[a]

HOMA-IR: Homeostasis model of assessment-insulin resistance, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, GDF-15: Growth differentiation factor, GH: Growth hormone, IGF-1: Insulin like growth factor-1, [a]Statistically significant p values, [b]Data were expressed as median and interquartile range

Table 3. Comparison of the echocardiographic parameters between the groups

	Acromegaly (n=54)	Control group (n=34)	p-value
EF (%)	59.8±3.3	63.5±3.9	**<0.001**[a]
LAd (mm)	35.9±4.5	34.4±5.6	0.2
LVID (mm)	4.7±0.4	4.5±0.8	0.2
LVPWd[b] (mm)	0.9 (0.9-1)	0.9 (0.9-1)	0.1
LVM (g)	170.8±42.1	145.9±40.4	**0.009**[a]
LVMI (g/m^2)	46.5±11.2	42.8±14.4	0.2
IVST (mm)	0.99±0.13	0.88±0.18	**0.002**[a]
EDV (mL)	17.9±4.6	15.1±2.5	**0.03**[a]
ESV[b] (mL)	4.8 (4.2-5.4)	4.3 (3.7-4.6)	**0.005**[a]
SV (mL)	12.1±7.6	10.9±2.4	0.6

EF: Ejection fraction, LAd: Left atrium diameter, LVID: Left ventricular internal end-diastolic diameter, LVPWd: Left ventricular posterior wall thickness during diastole, LVM: Left ventricular mass, LVMI: Left ventricular mass index, IVST: Interventricular septum thickness, EDV: End-diastolic volume, ESV: End-systolic volume, SV: Stroke volume, [a]Statistically significant p-values, bData were expressed as median and interquartile ranges

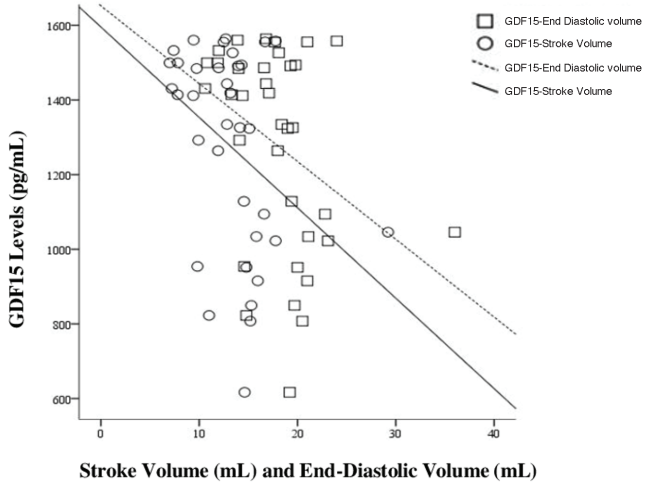

Figure 1. Correlation of GDF-15 with stroke volume and end-diastolic volume
GDF-15: Growth differentiation factor 15

Discussion

GDF-15 was found significantly higher in patients with acromegaly compared to healthy subjects in our study. Additionally, EF value was lower in patients with acromegaly, and EF value was positively associated with GDF-15 values. GDF-15 was also found to be negatively correlated with EDV and SV in acromegaly. Patients with acromegaly also had a higher LVM and a thicker interventricular septum.

GDF-15 is a novel anti-inflammatory cytokine released from activated macrophages (8,9). Although cytokines are mostly controlled via Nuclear Factor-κb transcription factors, GDF-15 is upregulated by p53, which is a tumor suppressor protein (12,19). Under physiological conditions, it is present at low levels, and it is increases because of an injury such as inflammation (20). Additionally, GDF-15 increases with cardiovascular events, including atherosclerosis, myocardial infarction, and heart failure (21-23). It is controversial whether GDF-15 is responsible for cardiac damage or whether it is secreted to protect against cardiac damage (11,21). GDF-15 is also depicted as a heart-derived hormone that blocks GH signaling (24). Changes in GDF-15 levels have not been previously investigated in acromegalic patients.

GDF-15 levels in patients with acromegaly were significantly higher than those in healthy subjects in this study. In a study that evaluated the between GDF-15 and obesity, GDF-15 was associated with BMI (25). This study determined that GDF-15 in obese individuals was an independent marker of impaired glucose control in obese individuals (25). Consistent with this study, we found that BMI was positively correlated with GDF-15 acromegaly. These results suggest that there is a link between GDF-15 and obesity. Interestingly, FBG was negatively associated with GDF-15 levels in our patients with acromegaly. These findings are in contrast to previous studies that showed glucose tolerance impairing effects of GDF-15 (25-27).

EF values were statistically lower in the acromegaly group. Additionally, EF was positively correlated with GDF-15 in acromegaly. However, lower EF values did not indicate systolic heart failure. As also previously known, EF may be normal due to remodeling and reduced ventricular cavity volume in hypertrophic cardiomyopathy and diastolic dysfunction (28,29). The chronic effect of an increased level of GH and IGF-I secretion in acromegaly causes biventricular concentric hypertrophy (3). Consistent with this, LVM and IVST was also significantly higher in the acromegaly group in our study. Also, patients with diastolic dysfunction are unable to increase SV by increasing their left ventricular EDV (30). Since GDF-15 was negatively related to EDV and SV, it may also have a role in diastolic impairment at the early stages of cardiac involvement in acromegaly. Moreover, GDF-15 was positively correlated with DBP. Therefore, GDF-15 may also have a role in hypertension observed in the patient with acromegaly.

It is well established that complications of acromegaly are linked to the increased levels of IGF-1 and GH levels (1-4). Neither GH nor IGF-1 levels were associated with GDF-15 levels in acromegaly. The time passed since the initial diagnosis of acromegaly was also uncorrelated with GDF-15. Therefore, the increment of GDF-15 in acromegaly may be an irreversible change, and it may be independent of the disease activity and IGF-1 levels.

Study Limitations

The main limitation of this study was that it is a single-center study with few cases, so further studies with a more significant number of patients are needed to confirm the associations between GDF-15 and cardiac changes in acromegaly.

Conclusion

GDF-15 was significantly increased in acromegaly. This increment was associated with subtle changes in cardiac functions, namely, diastolic dysfunction. An effective prediction model of GDF-15 needs to be explored in patients with acromegaly. Further prospective studies with a larger number of cases are needed to confirm our results.

Ethics Committee Approval: This study was approved by the Ethics Committee of Universtiy of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2011-KAEK-50, date: 06.05.2022).

Informed Consent: A written informed consent form was obtained from all patients before the study.

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Authorship Contributions

Concept: Y.H., M.E.P., E.H.; Design: Y.H., M.E.P., B.H.; Data Collection or Processing: Y.H., P.K.; Analysis or Interpretation: B.H., E.H., M.N.; Writing: M.E.P., P.K., E.H.

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