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Growth Differentiation Factor 15 in Patients with Acromegaly: A Case–Control Study

ORIGINAL ARTICLE
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ABSTRACT

Objective: It was previously shown that the levels of several biomarkers increase due to acromegaly disease-related inflammation, and some markers are parallel to the disease's activity. The current study compared the possible relationship of growth differentiation factor-15 (GDF-15) with acromegaly disease activity in healthy subjects.

Methods: This case–control study was conducted in a single center. It included 40 acromegaly patients (25 active/15 controlled) (47.7 ± 9.4 years, 20 female/20 male) and 24 healthy individuals (49.9 ± 10.1 years, 13 female/11 male) with age–sex–body mass index similar to the patient group. Demographic data, metabolic and hormonal parameters, and GDF-15 levels of the study population were studied.

Results: The median GDF-15 levels were significantly higher in patients with acromegaly compared to healthy subjects (HS) (280.4 (Q1-Q3: 197.0-553.2) vs. 213.3 (Q1-Q3: 179.9-297.2) ng/L, P = .01). Serum GDF-15 levels of active and controlled acromegaly patients were comparable (P = .39). Interestingly, compared to HS, GDF-15 levels were significantly higher in controlled disease (P = .013), whereas GDF-15 levels tended to be higher in active disease but did not reach statistical significance (P = .06). Growth differentiation factor-15 levels were positively correlated with fasting plasma glucose (r = 0.304, P = .01) and HbA1c (r = 0.292, P = .02). When evaluated across the entire cohort, GDF-15 levels were found to be higher in diabetic patients compared to non-diabetic individuals (P = .04).

Conclusion: Plasma GDF-15 levels were increased in the patients with acromegaly compared to healthy subjects. This increment may be due to accompanying diseases such as diabetes rather than a disease-specific effect.

Keywords: Inflammation, GDF-15, growth hormone, insulin-like growth factor-1, acromegaly

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Introduction

Acromegaly is a rare disease characterized by excess growth hormone (GH) secretion and increased insulin-like growth factor-1 (IGF-1) levels due to mostly GH-secreting pituitary adenomas.[1] Recent data showed that the time from the first symptom onset to diagnosis in acromegaly is 8-10 years.[2] This late diagnosis period predisposes many patients to significant cardiovascular and metabolic complications at the time of diagnosis. Cardiovascular disease (CVD) is the most common comorbidity in acromegaly and one of the most important causes of morbidity and mortality.[3] In addition, metabolic comorbidities such as diabetes mellitus, insulin resistance, and dyslipidemia, which are more common in acromegaly, also increase endothelial dysfunction, atherosclerosis, and ultimately coronary arteropathy.[3] Many cardiovascular markers and adipokines have been previously investigated in patients with acromegaly.[4] It has been demonstrated that biomarkers such as soluble alpha-klotho, endothelin-1, and matrix metalloproteinase 2 are significantly higher in active acromegaly disease compared to healthy individuals and controlled disease, and their levels decrease with treatment.[5-7]

Growth differentiation factor 15 (GDF-15) is a protein with pleiotropic functions that belongs to the transforming growth factor-β superfamily. However, it is weakly synthesized in many tissues under physiological conditions. When inflammation and tissue damage develop, its levels in the blood increase strongly and act as a metabolic regulator.[8] It has been shown that GDF-15 levels increase significantly in CVD, acute inflammation, rheumatic diseases, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and obesity.[9,10] In addition, some studies have recently suggested that GDF-15 is a cardiac hormone affecting body growth.[8,11] Increased circulating levels of GDF-15 are thought to inhibit IGF-1 production by an unknown mechanism.[8] Plasma GDF-15 has been shown to increase in children with concomitant cardiac disease and developmental delay.[11] In this context, it can be hypothesized that GDF-15

will increase in response to the effects of increased endothelial damage and atherosclerosis due to high IGF-1 levels in acromegaly patients, thus trying to oppress the destructive impact. The current literature shows limited data on the relationship between acromegaly and GDF-15 levels.

The primary aim of the present study was to compare acromegaly patients with active and controlled disease with control subjects to investigate whether there is a difference between the groups regarding GDF-15 levels. The second goal was to examine the relationship between cardiovascular risk factors such as arterial hypertension, dyslipidemia, diabetes, and GDF-15 levels.

Materials and Methods

Study Participants and Design

With a cross-sectional observational design, this case–control study was conducted at Dışkapı Yıldırım Beyazıt Training and Research Hospital (newly Ankara Etlik City Hospital) Endocrinology Outpatient Clinic which is a tertiary referral center between June and December 2022. A total of 40 acromegaly patients over 18 years of age, who were either newly diagnosed in our clinic or had a controlled disease under follow-up, were consecutively included in the patient group of the study. Patients with active infection, liver or kidney failure, a history of cardiovascular events, rheumatological connective tissue diseases, pregnancy, and a history of any malignancy were excluded from the study. The control group consisted of 24 healthy randomly selected individuals with age–sex–body mass index (BMI) similar to the patient group, without any known active disease or medical history, and without medication use.

The diagnosis of acromegaly was established in a patient whose age-, sex-adjusted IGF-1 levels were higher than the upper limit of normal, with the nadir serum GH levels >1 ng/mL after a 75 g oral glucose load, and the detection of a pituitary tumor on magnetic resonance imaging.[12] Patients, using or not using somatostatin receptor analog (SSA), after surgical treatment were considered to have controlled disease if age-, sex-adjusted IGF-1 normalization was achieved during the study. Demographic data, anthropometric measurements, blood pressure measurements, fasting plasma glucose (FPG), glycated hemoglobin-A1c (HbA1c) levels, serum lipid panels, GH, IGF-1, and GDF-15 levels of the patient and control groups were studied. Symptom duration before diagnosis, comorbidities, and acromegaly-related treatments received by patients were also recorded.

The current study was conducted ethically according to the World Medical Association Declaration of Helsinki. Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee granted ethical approval for the study (approval number 141/14, date: July 4, 2022). Written informed consent was provided from all patients and healthy volunteers participating in the study.

Evaluation of Biochemical Parameters

All blood samples were studied after an overnight fast at 8:00 AM. HbA1c was measured using the high-performance liquid chromatography method. Plasma levels of total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein, and FPG were measured using an automated chemistry analyzer (Aeroset, Abbott, Holliston, MN, USA) using commercially available kits (Abbott, USA).

Plasma GH and IGF-1 levels were investigated with the IMMULITE 2000 Immunoassay System (Siemens Healthcare GmbH, Erlangen, Germany). GH measurement was performed with a solid-phase, dual-site chemiluminescent immunometric assay (Siemens Healthcare Diagnostics Products—Glyn Rhonwy Llanberis, Gwynedd LL55 4EL, United Kingdom). Insulin-like growth factor-1 levels were evaluated according to age-, sex-adjusted normal reference ranges obtained from the manufacturer's instructions.

Peripheral venous blood from each participant was separately collected and centrifuged for GDF-15 measurement, with the serum then refrigerated at −80°C for later use. According to the manufacturer's instructions, the GDF-15 serum level for both patients and healthy subjects was detected using a sandwich enzyme-linked immunosorbent assay (catalog number: E0037Hu, BT-Lab, Shanghai, China). The standard detection curve range of the kit is 100-3200 ng/L.

Statistical Analysis

Statistical analyses were done with the Statistical Package for the Social Sciences version 23.0 (IBM Corp., Armonk, NY, USA). Shapiro–Wilks test was used to determine data distribution. Continuous variables were presented as mean ± standard deviation or median (quartile 1–quartile 3 (Q1-Q3)), and compared using the independent samples *t*-test or one-way analysis of variance (ANOVA) test for normally distributed data, or using the Mann–Whitney *U*-test or independent samples Kruskal–Wallis *H* test for non-normally distributed data. Post hoc tests of one-way ANOVA, the Tukey test with Bonferroni correction for multiple comparisons was performed. For post hoc tests of the Kruskal–Wallis *H* test, Dunn's test with a Bonferroni correction was used. Nominal data were demonstrated as numbers and percentages (%) and compared using the chi-square or Fisher's exact test. Pearson's correlation calculated correlations between GDF-15 and metabolic parameters. In addition, a linear regression analysis was performed to examine the relationship between GDF-15 and biological confounders that increase the risk of CVD. A P-value $< .05$ was considered significant.

A post hoc power analysis was performed using G*Power 3.1.9 to measure the power of the current study population and test the hypotheses. The effect size of the main result in the current study was studied with Cohen's *d* formula, and the large effect (0.78) was calculated. Accordingly, with the current sample sizes, assuming an effect size of 0.8 and a type 1 error of 0.05, the power of non-parametric tests was measured as 84%.

Results

Patients with Acromegaly vs. Healthy Controls

Forty patients with acromegaly (47.7 ± 9.4 years, 20 female/20 male) and 24 healthy individuals (49.9 ± 10.1 years, 13 female/11 male) were included in the final analysis. The comparisons between the

MAIN POINTS

- It is known that growth differentiation factor 15 (GDF-15) is increased in several cardiovascular, inflammatory, and metabolic diseases.
- The present study revealed that plasma GDF-15 levels were increased both in patients with controlled and active acromegaly compared to healthy subjects.
- GDF-15 was high in patients with controlled acromegaly and patients with active acromegaly.
- Increased GDF-15 levels in acromegaly may be attributed to the increased frequency of diabetes in these patients rather than acromegaly itself.

Table 1. Comparisons of Acromegaly Patients and Healthy Subjects

Variables	Acromegaly Group (n = 40)	Healthy Subjects (n = 24)	*P*
Age, mean ± SD, years	47.7 ± 9.4	49.9 ± 10.1	.40
Female gender, n (%)	20 (50.0)	13 (54.2)	.75
Body mass index, mean ± SD, kg/m^2	29.7 ± 6.4	28.9 ± 4.5	.65
Waist circumference, mean ± SD, cm	98.5 ± 12.5	94.6 ± 9.9	.20
Diabetes mellitus, n (%)	11 (27.5)	0 (0.0)	–
Fasting plasma glucose, median (Q1-Q3), mg/dL	95.0 (89.0-106.0)	86.0 (81.0-91.7)	**<.001**
HbA1c, median (Q1-Q3), %	5.9 (5.6-6.3)	5.6 (5.3-5.6)	**<.001**
Hypertension, n (%)	13 (32.5)	0 (0.0)	–
Systolic blood pressure, median (Q1-Q3), mm Hg	125.0 (120.0-133.7)	120.0 (110.0-120.0)	**<.01**
Diastolic blood pressure, median (Q1-Q3), mm Hg	77.5 (70.0-80.0)	70.0 (70.0-70.0)	**<.01**
Total cholesterol, mean ± SD, mg/dL	189.8 ± 36.4	196.2 ± 40.6	.52
Triglyceride, median (Q1-Q3), mg/dL	127.6 (90.0-199.7)	116.0 (81.7-170.7)	.66
LDL cholesterol, mean ± SD, mg/dL	127.1 ± 31.4	140.4 ± 36.6	.13
HDL cholesterol, mean ± SD, mg/dL	47.5 ± 11.6	48.8 ± 11.5	.66
Growth-hormone, median (Q1-Q3), mcg/L	8.54 (2.53-19.25)	1.40 (1.00-2.00)	**<.001**
IGF-1, median (Q1-Q3), ng/mL	467.5 (173.0-574.2)	161.0 (132.0-215.0)	**<.001**
GDF-15, median (Q1-Q3), ng/L	280.4 (197.0-553.2)	213.3 (179.9-297.2)	**.01**

*Statistically significant values are in bold.
GDF-15, growth differentiation factor 15; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein; SD standard deviation.

acromegaly patient group (PG) and healthy subjects (HS) were summarized in Table 1. Median FPG, HbA1c, and systolic and diastolic blood pressure levels were significantly higher in PG compared to the HS ($P < .01$). Both groups' mean blood lipid levels were similar ($P > .05$). The median GDF-15 levels were significantly higher in PG compared to HS (280.4 ng/L (197.0-553.2) vs. 213.3 ng/L (179.9-297.2), $P = .01$).

GDF-15 and Disease Control Status

Patients with acromegaly were separated into two groups according to disease control status: active patient group (aPG) ($n = 25$) and controlled patient group (cPG) ($n = 15$). These groups and healthy subjects were compared in Table 2. All patients in cPG underwent transnasal transsphenoidal adenomectomy. At the time of the study, 8 of those in cPG (53.3%) had been receiving SSA for a median of 64 (43-105) months, and the median follow-up time of these patients was 82 (54-132) months. The duration of symptoms before diagnosis and the frequency of obesity, diabetes, and hypertension were similar in both active and controlled acromegaly patients ($P > .05$). The HDL cholesterol levels were higher in the cPG than in the aPG ($P < .01$). Serum GDF-15 levels of active and controlled acromegaly patients were comparable ($P = .39$). Interestingly, compared to HS, GDF-15 levels were significantly higher in controlled disease ($P = .013$), whereas GDF-15 levels tended to be higher in active disease but did not reach statistical significance ($P = .06$) (Figure 1).

GDF-15 and Associated Factors

Growth differentiation factor-15 levels were positively correlated with FPG ($r = 0.304$, $P = .01$) and HbA1c ($r = 0.292$, $P = .02$) levels in the study population. However, in the linear regression analysis, no independent relationship was observed between GDF-15 levels and age, gender, BMI, HbA1c, systolic and diastolic blood pressures, GH, IGF-1, and serum lipid levels ($P > .05$). The analysis included only acromegaly patients; no difference was observed in GDF-15 levels between those with and without diabetes ($P = .17$). When evaluated across the entire cohort, GDF-15 levels were found to be higher in diabetic patients compared to non-diabetic individuals ($P = .04$) (Table 2).

Discussion

The current study revealed that plasma GDF-15 levels were elevated in patients with acromegaly compared to the healthy population. The subgroup analyses showed that those with controlled acromegaly disease had the highest GDF-15 levels. In addition, compared to non-diabetic individuals, patients with diabetes had higher levels of GDF-15. Therefore, the elevated plasma GDF-15 levels in patients with acromegaly might be secondary to comorbidities such as DM rather than the effect of the disease itself. However, since this inference is low in the reliability of the current study results, the relationship between GDF-15 and DM status should be examined by studies with larger sample groups.

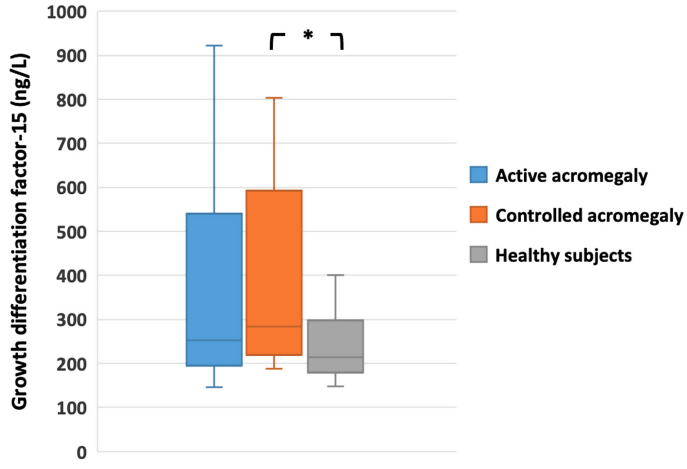

Figure 1. The graph depicts the distribution of growth differentiation factor-15 levels in acromegaly patient subgroups and healthy individuals. *Statistically significant ($P = .01$).

Table 2. Comparisons According to the Status of Acromegaly Disease with Healthy Subjects

Variables[a]	Active Patients (A)	Controlled Patients (C)	Healthy Subjects (H)	*P*[b]	Post Hoc Analyses[c]
Number of patients	25	15	24		
Age (years)	47.2 ± 9.7	48.7 ± 9.1	49.9 ± 10.1	.62	–
Female gender (%, n)	14 (56.0)	6 (40.0)	13 (54.2)	.58	–
Symptom duration (years)	3 (2-5)	4 (3-6)	N/A	.27	–
SSA use (%, n)	N/A	8 (53.3)	N/A	–	–
Obesity (%, n)	11 (44.0)	4 (26.7)	9 (42.8)	.55	–
Body mass index (kg/m^2)	30.6 ± 7.3	28.1 ± 4.5	28.9 ± 4.5	.38	–
Waist circumference (cm)	99.0 ± 14.2	97.8 ± 10.2	94.6 ± 9.9	.43	–
Diabetes mellitus (%, n)	7 (28.0)	4 (26.7)	0 (0.0)	**.02**	A~C (.93)
FPG (mg/dL)	97.0 (92.5-107.0)	89.0 (77.0-98.0)	86.0 (81.0-91.7)	**<.001**	**A > H (<.001)**
HbA1c (%)	5.9 (5.6-6.9)	5.9 (5.7-6.0)	5.6 (5.3-5.6)	**.001**	**A and C > H (<.01)**
Hypertension (%, n)	7 (28.0)	6 (40.0)	0 (0.0)	**.005**	A~C (.43)
SBP (mm Hg)	125.0 (120.0-130.0)	125.0 (110.0-140.0)	120.0 (110.0-120.0)	**.016**	**A > H (.01)**
DBP (mm Hg)	80.0 (70.0-80.0)	70.0 (70.0-80.0)	70.0 (70.0-70.0)	**.01**	**A > H (.004)**
Total cholesterol (mg/dL)	179.8 ± 31.2	205.9 ± 39.2	196.2 ± 40.6	.09	–
Triglyceride (mg/dL)	137.0 (92.5-236.0)	121.9 (70.8-148.0)	116.0 (81.7-170.7)	.32	–
LDL cholesterol (mg/dL)	119.8 ± 27.9	139.4 ± 34.0	140.4 ± 36.6	.06	–
HDL cholesterol (mg/dL)	43.0 ± 9.6	54.6 ± 11.4	48.8 ± 11.5	**.007**	**C > A (.005)**
Fasting GH (µg/L)	12.8 (4.4-21.5)	0.9 (0.8-2.4)	1.4 (1.0-2.0)	**<.001**	**A > C and H (<.001)**
IGF-1 (ng/mL)	549.0 (478.0-633.0)	161.0 (130.0-223.0)	161.0 (132.0-215.0)	**<.001**	**A > C and H (<.001)**
GDF-15 (ng/L)	253.3 (194.5-539.7)	283.9 (218.8-592.0)	213.3 (179.9-297.2)	**.031**	**C > H (.013)**

Statistically significant values are in bold.
DBP, diastolic blood pressure; FPG, fasting plasma glucose, GDF-15, growth differentiation factor 15; GH, growth hormone; HDL, high-density lipoprotein; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein; N/A, not applicable; SBP, systolic blood pressure; SSA, somatostatin analogue; SD, standard deviation.
[a]Normally distributed data were presented using mean ± SD, while non-normally distributed data were presented using median (Q1-Q3).
[b]In the comparison of continuous variables, *P*-values were studied with the one-way ANOVA test (for normally distributed data) and the independent samples Kruskal–Wallis test (for non-normally distributed data). In the comparison of categorical variables, *P*-values were calculated with the χ^2 test. The significance level was set at $P < .05$.
[c]In post hoc analyses, the significance level was set at $P < .016$.

Increased oxidative stress and endothelial dysfunction, secondary to the supraphysiological elevated GH and IGF-1 effect in acromegaly, lead to an increase in the release of various cytokines and adipokines.[4] The current study showed that GDF-15 protein, also defined as a cardiokine, was at increased levels in acromegaly patients. Recently, Hacıoğlu et al[13] similarly detected increased GDF-15 levels in acromegaly patients.[14] This study claimed that GDF-15 may have a role in diastolic impairment in patients with acromegaly.[13] Interestingly, recent evidence suggests that GDF-15 may be a protein that antagonizes the activity of GH in the liver.[8] Indeed, elevated IGF-1 levels and increased endothelial injury in patients with acromegaly may trigger GDF-15 release. However, it is also noteworthy that no correlation was detected between IGF-1 and GDF-15 levels in the current and previous study.[13]

Growth differentiation factor-15 levels were significantly elevated in controlled disease compared to healthy controls. Contrary to expectations, although GDF-15 levels were high in active disease, they did not reach a significant difference from the healthy control subjects. This result is important because it may show that even though acromegaly is under control, irreversible endothelial changes that occur due to late diagnosis continue to have an effect. In addition, Sardella et al[15] found a 1.4-fold increased risk of diabetes in patients whose disease was controlled with SSA therapy compared to patients who were cured after surgery. The authors thought SSAs suppressing insulin secretion and providing less effective control than surgery might be effective in this issue.[16,17] In the current study, 53.3% of patients with controlled disease were followed under SSA therapy. Considering previous studies, the elevated GDF-15 levels in controlled disease may be attributed to the confounding effects of SSA therapy.

Moreover, it may again indicate no correlation between IGF-1 and GDF-15 levels, suggesting that the chain of events secondary to acromegaly increases GDF-15 levels. This demonstrates that GDF-15 is not a disease-specific biomarker for acromegaly. Nevertheless, future studies with larger sample sizes and prospective designs may present more reliable results.

Recent studies also show that GDF-15 is an adipokine that provides metabolic regulation.[18] Increased GDF-15 levels have been associated with metabolic disorders such as diabetes, insulin resistance, and obesity.[8] Growth differentiation factor 15 has been found to reduce food intake and adiposity and improve glucose tolerance.[19] In the current study, GDF-15 levels were positively correlated with FPG and HbA1c levels in the entire cohort. Previously, Hacıoğlu et al[13] showed a positive relationship between BMI, diastolic blood pressure, and GDF-15 levels. In addition, the present study detected higher GDF-15 levels than expected in the diabetic population. In light of these results, it may be speculated that the increased frequency of diabetes can explain the increased GDF-15 levels in patients with acromegaly. However, the failure to establish an independent relationship in linear regression analyses

necessitates the accuracy of this inference to be checked with further studies.

The current study has several limitations. The first and most important is the small number of samples. Second, the fact that the aPGs and cPGs were not in a prospective design may affect the generalizability of the conclusions. Third, further findings were limited by the need to evaluate another biomarker or risk indicator predicting CVD. On the other hand, in this study, patients with active and controlled acromegaly were compared with healthy controls regarding GDF-15 levels for the first time.

In conclusion, higher GDF-15 levels were detected in acromegaly patients compared to controls, but GDF-15 was not considered a disease-specific biomarker. High GDF-15 levels despite controlled disease may be valuable as it shows that these patients are worth close follow-up for CVD events, just like patients with active acromegaly, and that the risk is not eliminated. Nevertheless, further studies with a prospective design and including other cardiovascular biomarkers or risk assessments would be useful to observe the value of GDF-15 in patients with acromegaly.

Ethics Committee Approval: This study was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, University of Health Sciences. (approval number: 141-14; date: July 4, 2022).

Informed Consent: Written informed consent was obtained from all patients and healthy volunteers who agreed to take part in the study.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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References

1. Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S. Acromegaly: pathogenesis, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2022;10(11):804-826. [CrossRef]
2. Petrossians P, Daly AF, Natchev E, et al. Acromegaly at diagnosis in 3173 patients from the Liège Acromegaly Survey (LAS) Database. *Endocr Relat Cancer*. 2017;24(10):505-518. [CrossRef]
3. Pivonello R, Auriemma RS, Grasso LFS, et al. Complications of acromegaly: cardiovascular, respiratory, and metabolic comorbidities. *Pituitary*. 2017;20(1):46-62. [CrossRef]
4. Wolters TLC, Netea MG, Riksen NP, Hermus ARMM, Netea-Maier RT. Acromegaly, inflammation, and cardiovascular disease: a review. *Rev Endocr Metab Disord*. 2020;21(4):547-568. [CrossRef]
5. Schweizer JROL, Schilbach K, Haenelt M, et al. Soluble alpha klotho in acromegaly: comparison with traditional markers of disease activity. *J Clin Endocrinol Metab*. 2021;106(8):e2887-e2899. [CrossRef]
6. Kirilov G, Zacharieva S, Alexandrov AS, Lozanov V, Mitev V. Increased plasma endothelin level as an endothelial marker of cardiovascular risk in patients with active acromegaly: a comparison with plasma homocysteine. *Methods Find Exp Clin Pharmacol*. 2009;31(7):457-461. [CrossRef]
7. Paisley AN, O'Callaghan CJ, Lewandowski KC, et al. Reductions of circulating matrix metalloproteinase two and vascular endothelial growth factor levels after treatment with pegvisomant in subjects with acromegaly. *J Clin Endocrinol Metab*. 2006;91(11):4635-4640. [CrossRef]
8. Rochette L, Zeller M, Cottin Y, Vergely C. Insights into mechanisms of GDF15 and receptor GFRAL: therapeutic targets. *Trends Endocrinol Metab*. 2020;31(12):939-951. [CrossRef]
9. Wang D, Day EA, Townsend LK, Djordjevic D, Jørgensen SB, Steinberg GR. GDF15: emerging biology and therapeutic applications for obesity and cardiometabolic disease. *Nat Rev Endocrinol*. 2021;17(10):592-607. [CrossRef]
10. Adela R, Banerjee SK. GDF-15 as a target and biomarker for diabetes and cardiovascular diseases: a translational perspective. *J Diabetes Res*. 2015;2015:490842. [CrossRef]
11. Wang T, Liu J, McDonald C, et al. GDF15 is a heart-derived hormone that regulates body growth. *EMBO Mol Med*. 2017;9(8):1150-1164. [CrossRef]
12. Kizilgul M, Duger H, Nasiroglu NI, et al. Efficacy of cabergoline add-on therapy in patients with acromegaly resistance to somatostatin analogs treatment and the review of literature. *Arch Endocrinol Metab*. 2022;66(3):278-285. [CrossRef]
13. Hacıoğlu Y, Pişkinpaşa ME, Kılıçkaya P, Niyazoğlu M, Hacıoğlu B, Hatipoğlu E. Increased serum growth differentiation factor 15 levels may be associated with diastolic dysfunction in acromegaly. *Istanbul Med J*. 2022;23(3):179-182. [CrossRef]
14. Iglesias P, Silvestre RA, Díez JJ. Growth differentiation factor 15 (GDF-15) in endocrinology. *Endocrine*. 2023;81(3):419-431. [CrossRef]
15. Sardella C, Cappellani D, Urbani C, et al. Disease activity and lifestyle influence comorbidities and cardiovascular events in patients with acromegaly. *Eur J Endocrinol*. 2016;175(5):443-453. [CrossRef]
16. Urbani C, Sardella C, Calevro A, et al. Effects of medical therapies for acromegaly on glucose metabolism. *Eur J Endocrinol*. 2013;169(1):99-108. [CrossRef]
17. Bogazzi F, Colao A, Rossi G, et al. Comparison of the effects of primary somatostatin analog therapy and pituitary adenomectomy on survival in patients with acromegaly: a retrospective cohort study. *Eur J Endocrinol*. 2013;169(3):367-376. [CrossRef]
18. Ding Q, Mracek T, Gonzalez-Muniesa P, et al. Identification of macrophage inhibitory cytokine-1 in adipose tissue and its secretion as an adipokine by human adipocytes. *Endocrinology*. 2009;150(4):1688-1696. [CrossRef]
19. Macia L, Tsai VWW, Nguyen AD, et al. Macrophage inhibitory cytokine 1 (MIC-1/GDF15) decreases food intake and body weight and improves glucose tolerance in mice on normal & obesogenic diets. *PLoS One*. 2012;7(4):e34868. [CrossRef]