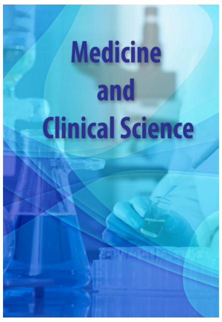
Medicine & Clinical Science

Original Article



Association Between Growth Differentiation Factor 15 (GDF15) and Glucose Metabolism in Patients With Acromegaly

Jie Liu, Ya-yin Shen, Jia-ni Ma, Mo Zhou, Lin-man Li, Wei Ren*

Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Correspondence

Jie Liu
Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
Email: renwei67@Sina.com

- Received Date: 21 Nov 2023
- Accepted Date: 30 Nov 2023
- Publication Date: 05 Dec 2023

Keywordst

Growth differentiation factor-15, Acromegaly, Influencing factor, Glucose metabolism, Homeostasis model assessment for insulin resistance

Abstract

Objective: *To analyze the changes of serum growth differentiation factor-15 (GDF-15) and its influencing factors in patients with acromegaly, and to investigate its correlation with glucose metabolism.*
Methods: *Sixty acromegaly patients were recruited from the Endocrinology Department of the First Affiliated Hospital of Chongqing Medical University from July 2021 to September 2023, and thirty healthy persons matched in gender, age and body mass index as nomal controls were selected in the same period. To collect clinical and laboratory data, conduct statistical processing, and analyze the level changes and influencing factors of GDF-15.*
Results: *Compared with nomal controls, the level of GDF-15 increased significantly in patients with acromegaly ($P<0.05$). After operation, the level of GDF-15 decreased gradually with the decrease of serum growth hormone (GH) and insulin-like growth factor-1 (IGF-1). The level of GDF-15 decreased significantly at 3 and 6 months after operation compared with pre-operation level($P<0.05$); Compared with 3 months after operation, the GDF-15 level decreased significantly at 6 months after operation($P<0.05$). In univariate linear correlation analysis the GDF-15 was positively correlated with GH, IGF-1, FPG, HbA1c, FINS, HOMA-IR (r=0.503, 0.623, 0.427, 0.476, 0.345, 0.419, $P<0.05$) and negatively correlated with HOMA-β, AUCINS(r=-0.342,-0.261,$P<0.05$) in pre-operation patients with acromegaly. Multivariate linear regression analysis showed that IGF-1,HOMR-IR,HOMA-β and AUCINS were all identified as the positive predictors of the serum GDF-15 in patients with acromegaly ($P<0.05$).*
Conclusions: *The level of serum GDF-15 increased in patients with acromegaly, and decreased significantly after operation. The serum GDF-15 was closely related to glucose metabolism in patients with acromegaly.*

Introduction

Growth Differentiation Factor-15 (GDF-15) was first discovered by Bootcov et al. in 1997 and is also known as macrophage inhibitor-1, placental transforming growth factor-β, etc., is a member of the transforming growth factor-β superfamily. Under stress, GDF-15 is released by macrophages, adipocytes, endothelial cells, cardiomyocytes, etc. [1,2], and its levels rise sharply as the disease progresses [3]. People with high GDF-15 have a significantly increased risk of hyperlipidemia and diabetes [4], and increase the aggressiveness of pituitary tumors. GDF-15 has been shown to be a novel biomarker for the diagnosis, progression or prognosis of cardiovascular disease, diabetes, tumor, cachexia, obesity and other diseases [5-8], and is an indicator of important clinical value. More than 95% of patients with acromegaly is caused by growth hormone-secreting pituitary adenomas, which significantly increase the risk of diabetes, hypertension, coronary heart disease and other diseases. However, studies of GDF-15 levels and the correlation between GDF-15 and glucose metabolism in patients with acromegaly have been poorly reported. In this study, we detected the level of serum GDF-15, analyzed its influencing factors, and discussed the correlation between serum GDF-15 and glucose metabolism in patients with acromegaly. And the study was carried out to provide a theoretical basis for clinicians to monitor GDF-15 in patients with acromegaly and abnormal glucose metabolism.

Materials and methods

Subjects

A total of 60 patients with acromegaly diagnosed between July 2021 and September 2023 from the Department of Endocrinology of the First Affiliated Hospital of Chongqing Medical University (45 postoperative patients with complete follow-up data) were selected Example), and 30 healthy people who matched their sex, age and body mass index in the physical examination department during the same period as normal controls. Clinical data were collected retrospectively from all patients. Exclusion criteria: type 1 diabetes mellitus (T1DM); the presence of serious diabetic complications, such as diabetic ketoacidosis;

Citation: Liu J, Shen YY, Ma JN, Zhou M, Li LM, Ren W. Association Between Growth Differentiation Factor 15 (GDF15) and Glucose Metabolism in Patients With Acromegaly. Med Clin Sci. 2023;5(8):1-6.

Type 2 diabetes mellitus (T2DM) who has been diagnosed and taking drugs that promote insulin secretion or use insulin and lipid-lowering drugs; Cardiovascular emergencies; Acute and chronic infectious diseases, rheumatic immune diseases, abnormal thyroid function; Chronic cardiac, hepatic and renal insufficiency; Menstruating women; Patients with tumors of other systems.

Specimen collection

All enrolled persons underwent glucose suppression test and 75g oral glucose tolerance test (OGTT) and used to assess the function of the pituitary growth hormone (GH)-insulin-like growth factor-1 (IGF-1) axis and glucose metabolism. All patients and normal control groups were admitted to the hospital to measure height and weight, and calculate body mass index (BMI). In the early morning of the 2nd day, blood pressure was measured awake, quiet, and fasting, 3 times in a row, with an interval of 5 minutes, take the average. The body weight body fat measuring device (V-BOOY, HBF-371) was used to measure body fat proportion, visceral fat index and basal metabolic rate. All patients undergo pituitary magnetic resonance imaging (MRI). The test was carried out on an empty stomach for 8 hours, and 10ml of venous blood was drawn, of which 5ml was immediately sent to the laboratory department of our hospital for IGF-1 measurement, GH, triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), total cholesterol (TC), fasting blood glucose (FPG), fasting insulin (FINS), glycated hemoglobin (HbA1c). The other 5ml was centrifuged at 3000g at room temperature for 2 h for 15min, and 3ml of the supernatant was placed there -80 °C refrigerator low temperature storage, by special personnel for testing.

The diagnosis of acromegaly follows the "Chinese Consensus on the Diagnosis and Treatment of Acromegaly (2021 Edition)". Diagnostic criteria: (1) pituitary GH Clinical manifestations of patients with large limbs due to adenomas; (2) GH trough (OGTT-GH trough) in oral glucose growth hormone suppression test≥ 1 μg/L; (3) blood clearance IGF-1 levels above the normal range for age and sex matching; (4) Sellar imaging examination showed pituitary adenoma.

Treatment and follow-up

Among the 60 patients, 50 patients received surgery alone, 5 patients received long-acting octreotide injection after surgery, 3 patients received radiotherapy after surgery, 2 Patients received medical therapy alone. In all patients, treatment was effective and a complete biochemical response was achieved (OGTT test GH trough <1.0 ug/L) patients 41 patients. A total of 45 patients underwent surgery with complete follow-up data, with an average follow-up time of 6 months. Follow-up includes general information, laboratory tests, and MRI of the pituitary gland.

Table 1. Comparison of serum growth differentiation factor-15 and related clinical indexes between acromegaly patients and control group [$\bar{x}$±s, M (P25, P75)]

Project	Acromegaly group (n=60).	Normal control group (n=30).	P
Age (years)	48.63±12.82	50.26±8.32	0.530
Systolic blood pressure (mmHg).	132.63±16.76	116.77±11.13	0.002
Diastolic blood pressure (mmHg).	80.57±7.78	73.43±8.37	0.001
BMI (kg/m2)	25.29±4.23	23.58±2.22	0.057
Body fat proportion (%)	17.50±1.90	21.71±2.92	<0.001
Visceral fat index	7.87±3.00	8.40±2.40	0.621
Basal metabolic rate (kcal).	1425.60±213.34	1278.10±157.84	<0.001
GH (μg/L)	12.09 (6.37,21.12)	0.12 (0.07,0.32)	<0.001
IGF-1 (μg/L)	596.27±171.87	149.70±25.09	<0.001
TC (mmol/L)	4.20±0.71	4.18±0.65	0.906
TG (mmol/L)	1.65±0.87	1.03±0.35	0.621
HDL (mmol/L)	1.31±0.37	1.63±0.36	0.002
LDL (mmol/L)	2.55±0.86	2.66±0.89	0.294
FPG (mmol/L)	6.41±1.40	5.27±0.43	<0.001
Impaired glucose tolerance, n(%)	24 (40)	0 (0)	-
DM, n(%)	6 (10)	0 (0)	-
HbA1c (%)	6.58±1.26	4.89±0.68	<0.001
GDF-15(ng/L)	993.17 (697.06,1552.61)	512.61 (394.83, 601.36)	<0.001
FINS(mIU/L)	17.19±3.96	10.21±1.91	<0.001
HOMA-IR	5.09±2.13	2.40±0.58	<0.001
HOMA-B	135.02±43.37	118.81±24.63	0.621
AUCINS (mIU/L)	103.86 (85.99,138.65)	79.81 (69.04,91.63)	0.001

Note: BMI: Body mass index; GH: Growth hormone; IGF-1: Insulin-like growth factor 1; TC: Total cholesterol; TG: Triglycerid; HDL: high-density lipoprotein-cholesterol; LDL: Low density lipoprotein-cholesterol; FPG: fasting plasma glucose; DM: Diabetes mellitus; GDF-15: Growth differentiation factor-15; FINS: fasting insulin; HOMA-IR: Homeostasis model assessment for insulin resistance; HOMA-β: Homeostasis model assessment for β cell function. AUC_{INS}: the area under the insulin curve of 0~120min glucose tolerance test.

Laboratory index testing

GH The assay was determined by chemiluminescent enzyme immunoassay, IGF-1, UNTIL The determination of the method is direct chemiluminescence, FPG The determination of glucose oxidase method,HbA1cwas determined by high-pressure liquid chromatography.TC The determination of cholesterol oxidase method, TG The determination was performed by the free glycerol method, LDL-C, HDL-C Selective protection was used for determination(Direct assay). Steady-state model review Estimated insulin resistance index(HOMA-IR)Assess the degree of insulin resistance, HOMA-IR=Fasting insulin(mIU/L) ×Fasting blood sugar(mmol/L) / 22.5, Islets assessed by steady-state models β Cell function index(HOMA-B) and glucose tolerance test 0~120minThe area under the insulin curve(AUCINS) Islets are assessed β Cell function, HOMA-B=20×Fasting insulin(mIU/L)/ [Fasting blood sugar(mmol/L)-3.5], AUCINS=(INS0min+INS30min)×0.5/2+(INS30min+INS60min)×0.5/2+(INS60min+INS120min)×1/2, INS is the insulin value at each time point.Serum was measured by enzyme-linked immunosorbent assay GDF-15 level Kits were purchased from the United States R&D SystemsLtd, Intra-batch coefficient of variation<2.8%, Batch-to-batch coefficient of variation<5.6%.

Statistics

Statistical analysis was performed using SPSS 25.0 software, and the measurement data of normal distribution are expressed as mean ± standard deviation ($\bar{x}$ ±s). The t-test was used for comparison of the means of the two groups. Non-normally distributed metrics are measured by the median (interquartile range) [M(P 25, P 75)]. Indicates that the rank sum test was used for the median comparison between the two groups. The comparison between the three groups of data before and after surgery was analyzed by repeated measurement ANOVA, and the rank sum test was used for non-compliance with the normal distribution. The correlation analysis of the indicators selected preoperative data, by linear correlation analysis and multivariate linear regression analysis, and P values <0.05 were considered significant.

Results

Changes in serum growth differentiation factor-15 levels and related clinical indicators in patients with acromegaly.

Among the 60 patients with acromegaly, 43 were female and 17 were male, with mean age 48 63±12.82 years. The levels of GH and IGF-1 in patients with acromegaly were significantly higher than those in the control group, and the difference was statistically significant (P <0.05. 50% of patients with acromegaly have impaired glucose tolerance or diabetes. Compared with the normal control group, the levels of SBP, DBP, basal metabolic rate, GDF-15, FPG, HbA1c, FINS, HOMA-IR, AUCNS are elevated, as the levels of body fat proportion, HDL were descended in patients with acromegaly (P <0.05; The TC, TG, HOMA-β levels were slightly elevated, and the visceral fat index, LDL levels were slightly descended, and there was no significant difference between the two groups (P >0.05) (Table 1).

Changes of serum growth differentiation factor-15 level and related indexes before and after surgical treatment.

The GH and IGF-1 levels of patients with postoperative acromegaly were significantly lower than those before surgery. Compared with preoperative, the levels of GDF-15, GH, IGF-1, FPG, HbA1c, FINS, HOMA-IR, HOMA-β and AUC INS at 3 months and 6 months after surgery decreased significantly, and the difference was statistically significant (P <0. 05). Compared with 3 months after surgery, GDF-15 levels and IGF-1 levels at 6 months after surgery decreased significantly(P <0.05). The GH, FPG, HbA1c, FINS, HOMA-IR, AUCINS levels decreased mildly, and HOMA-β level was mildly increased, but the differences were not statistically significant (P >0.05). In the follow-up of patients before surgery, 3 months and 6 months after surgery, the indicators of BMI, basal metabolic rate, body fat proportion and visceral fat index showed no significant differences(P >0.05) (Table 2).

Linear correlation analysis of serum GDF-15 and related indexes in patients with acromegaly

Since GDF-15 follows a skewed distribution, Spearman rank correlation analysis was performed on the data, and the results

Table 2. The changes of serum growth differentiation factor-15 and related indexes after surgery in patients with acromegaly [$\bar{x}$ ±s, M (P25, P75)]

	Preoperative (n=45)	3 months postoperatively (n=45)	6 months postoperatively (n=45)
BMI (kg/m^2)	25.24±4.47	25.90±3.76	25.66±3.66
Body fat proportion (%)	17.01±1.23	19.69±1.50	19.81±2.39
Visceral fat index	7.27±3.13	9.07±3.15	9.00±2.85
Basal metabolic rate (kcal)	1557.73±341.70	1515.47±291.11	1538.87±315.77
GH (μg/L)	13.87 (6.66,15.98)(1)(2)	2.0 (0.74,5.06)	0.99(0.34,4.03)
IGF-1 (μg/L)	594.73±136.51(1)(2)	333.00±165.65(3)	205.46±77.77
FPG (mmol/L)	6.89±1.51(1)(2)	5.70±0.82	5.58±0.79
GDF-15(ng/L)	1043.31 (779.83,1229.28)(1)(2)	708.17 (621.50, 777.06)(3)	518.72 (448.17, 549.28)
HbA1c (%)	6.44±0.72(1)	5.85±0.34	5.77±0.51
FINS(mIU/L)	16.95±4.77(1)(2)	8.17±1.71	7.90±1.45
HOMA-IR	5.62±2.40(1)(2)	2.12±0.68	1.98±0.57
HOMA-B	115.23±41.74(1)(2)	80.75±19.29	82.62±17.75
AUCINS (mIU/L)	118.72(61.83,143.40) (1)(2)	88.38(61.83,112.18)	81.09(48.96,97.58)

Note: preoperative compared with 3 months after surgery, (1) P <0.05; preoperative compared with 6 months after surgery, (2) P <0.05; 3 months after surgery compared with 6 months after surgery, (3) P <0.05.

Table 3. Correlation analysis of serum GDF-15 and different indexes in patients with acromegaly

factor	GDF-15	
	r	P
age	-0.085	0.519
gender	-0.012	0.949
Course	-0.002	0.998
BMI (kg/m^2)	-0.233	0.073
Body fat proportion (%)	0.080	0.546
Visceral fat index	-0.145	0.268
Basal metabolic rate (kcal).	0.022	0.866
GH (μg/L)	0.503	<0.001
IGF-1 (μg/L)	0.623	<0.001
TC (mmol/L)	0.021	0.911
TG (mmol/L)	-0.018	0.926
HDL (mmol/L)	-0.073	0.701
LDL (mmol/L)	-0.005	0.981
FPG (mmol/L)	0.427	0.001
HbA1c (%)	0.476	<0.001
FINS(mIU/L)	0.345	0.007
HOMA-IR	0.419	0.001
HOMA-B	-0.342	0.008
AUCINS (mIU/L)	-0.261	0.044

showed that GDF-15 was positively related to GH ($r = 0.503$, $P < 0.001$) , IGF- 1 ($r = 0.623$, $P < 0.001$) , FPG ($r = 0.427$, $P = 0.001$) , HbA1c ($r = 0.476$, $P < 0.001$) , FINS ($r = 0.345$, $P = 0.007$) , and HOMA-IR ($r = 0.419$, $P = 0.001$) ; It was negatively related to HOMA-β ($r = -0.342$, $P = 0.008$) and AUCINS ($r = -0.261$, $P = 0.044$) (Table 3).

Analysis of influencing factors of serum GDF-15 in patients with acromegaly

GH, IGF-1, FPG, HbA1c, HOMA-IR HOMA-β and AUCINS were used as the independent variables, and GDF-15 as the dependent variable, and multiple linear regression analysis was carried out, and the results showed that IGF-1, HOMR-IR, HOMA-β, and AUCINS were independent influencing factors of GDF-15 in patients with acromegaly ($P <0.05$) (Table 4). .

Discussion

Acromegaly is an insidious onset, slowly progressing endocrine disease that is often diagnosed with complications such as acromegaly cardiomyopathy, hypertension, glucose tolerance, diabetes, sleep apnea-hypopnea syndrome, new tumors, and abnormal distribution of body composition [9]. Patients with acromegaly are at higher risk of glucose metabolism disturbances than the general population [10]. GDF-15 is a stress-responsive protein that is involved in the pathological process of a variety of diseases and has become a biomarker or potential therapeutic target for a variety of diseases. This article discusses the serum GDF-15 level in patients with acromegaly and its correlation with glucose metabolism. The results show: 1.The serum level of GDF-15 in patients with acromegaly was significantly increased, positively correlated with GH and IGF-1, and gradually decreased with the control of the disease, IGF-1 is GDF-15 independent influencing factors; 2. Patients with acromegaly have serum GDF-15 and FPG, HbA1c, FINS, and HOMA-IR positively correlated, negatively correlated with HOMA-β, AUCINS, and HOMR-IR, HOMA-β and AUCINS are independent influencers of GDF-15. Growth hormone-secreting pituitary adenomas are the leading cause of acromegaly. The pathogenesis and development mechanism of pituitary tumors are still unclear, mainly involving signaling pathway regulation, abnormal gene expression, cytokine regulation, angiogenesis, etc. [11]. Nuclear factor-KB (NF-KB) is an important nuclear transcription factor by promoting matrix metalloproteinase-9 as well as major histocompatibility complex-class 1 chain molecularly associated antigen A , promote the occurrence and development of pituitary tumors. GDF-15 inhibits the NF-KB pathway by inhibiting the activation of transforming growth factor kinase 1, resulting in tumor cell escape [12]. Macrophage infiltration favors the growth of pituitary tumors. GDF-15 can significantly induce macrophage polarization, improve cell tumorigenesis activity, and lead to tumor cell proliferation and metastasis. Vascular endothlial growth factor (VEGF) plays a role in stimulating pituitary tumor cell division and proliferation, neoangiogenesis, and VEGF expression is significantly increased in patients with pituitary tumors. GDF-15 can promote the expression of VEGF and participate in the generation of new blood vessels in pituitary tumors. GDF-15 is highly expressed in pituitary tumors and is positively correlated with the aggressiveness of pituitary tumors. This study found that GDF-15 was significantly elevated in patients with acromegaly before surgery, suggesting that GDF-15 plays an important role in the occurrence and development of acromegaly. Excessive secretion of growth hormone (GH) and elevated levels of insulin-like growth factor 1 (IGF-I) are characteristic of acromegaly[13]. IGF1 has been found to have both acute and long-term pro-inflammatory effects [14]. The long-term pro-inflammatory effect of IGF1 on human monocytes is called "training immunity" [15]. As homologous cells of monocytes, macrophages express the synthesis of GDF-15. Growth hormone promotes the secretion of IL-1-α, IL-6 and TNF-α in whole blood through lipopolysaccharide-activated monocytes, inducing the expression of GDF-15 by macrophages , resulting in a significant increase in serum GDF-15 levels [16-18]. Pro-inflammatory activity of macrophages in adipocyte tissue in patients with active acromegaly is enhanced and oxidative stress is increased [19,20]. When exposed to oxidative stress,

Table 4. Analysis of influencing factors of serum GDF-15 in patients with acromegaly

variable	Partial regression coefficient	standard error	Standard regression coefficients	t	P
IGF-1	1.554	0.250	0.632	6.171	<0.001
HOMA-IR	57.461	19.992	0.291	2.874	0.006
HOMA-B	-4.073	1.286	-0.354	-3.167	0.003
AUCINS	-3.615	1.193	-0.314	-3.030	0.004

fat cells synthesize and secrete GDF-15. In addition, excess GH/IGF-1 leads to endothelial dysfunction through several different mechanisms, including increased endothelial cell proliferation, endothelial progenitor cell dysfunction, increased oxidative stress, and impaired oxidative defenses [21]. GDF-15 is strongly associated with endothelial cell activation as well as inflammation of the vascular wall. This study showed that GH and IGF1 were positively correlated with GDF-15, and IGF-1 was an independent influencing factor of serum GDF-15. We speculate that the inflammatory response plays an important role in this, but the specific mechanism needs to be further studied.

With the decline of GH and IGF-1 after surgery, the level of GDF-15 decreased significantly, the specific mechanism is not clear, combined with the above mechanism research, it may be related to the mechanism of formation of pituitary tumor after resection, the patient's systemic inflammatory response is reduced, oxidative stress is weakened, and endothelial cell function is normalized. Although studies have found that patients with controlled acromegaly still have a persistent inflammatory response, which may lead to persistently elevated GDF-15, the combined effect is the main aspect. The prevalence of glucose metabolism abnormalities in patients with acromegaly is high, and the incidence of diabetes mellitus and impaired glucose tolerance varies between 15%~31.6% and 16%~56%, respectively[22].

In this study, 50% of patients with acromegaly had diabetes or impaired glucose tolerance, which is similar to what is reported in the literature. GH plays an important role in the regulation of glucose metabolism in acromegaly. GH inhibits a key signaling pathway for glucose uptake, further leading to insulin resistance [23]. Insulin resistance secondary to growth hormone excess is usually compensated by increased insulin secretion by β cells, while patients with acromegaly with insulin resistance have impaired pancreatic β cell function, and decreased insulin secretion is insufficient to compensate, resulting in glucose metabolism disorders. The hyperglycemic state activates inflammatory factors and promotes increased expression of GDF-15 in macrophages, resulting in elevated serum GDF-15 levels. Adipose tissue is one of the targets of GH excess and adipose tissue dysfunction can cause more fat inflammation, leading to insulin resistance or diabetes. When adipocytes are under oxidative stress, GDF-15 is synthesized and secreted. This study found that serum GDF-15 in patients with acromegaly was positively correlated with FPG, FINS and HOMA-IR. HOMR-IR is an independent influencing factor of serum GDF-15 and is largely consistent with literature reports. At the same time, GDF-15 was negatively correlated with HOMA-β and AUCINS, HOMA- β and AUCINS are independent influencing factors of GDF-15, suggesting that GDF-15 can promote the protection of pancreatic islet β cells, consistent with the literature [24]. It is worth noting that the correlation analysis of this study showed that there was a positive correlation between GDF-15 levels and HbA1c in patients with acromegaly, and HbA1c in patients with acromegaly was significantly higher than that in the control group, with higher GDF-15 Levels suggest poorly controlled diabetes.

Limitations of this study: First, due to the limitations of sample size and follow-up time, the results of this study are still not comprehensive. Secondly, this study is a cross-sectional study, and the results only suggest a correlation, and further prospective studies and basic studies are needed to clarify the complex role of GDF-15 in acromegaly.

Conclusion

The serum GDF-15 level in patients with acromegaly is elevated, gradually decreases with the control of the disease, and is closely related to glucose metabolism. Monitoring of this indicator can help clinicians understand the disease status of patients with acromegaly.

Acknowledgments

The authors thank all the patients who participated in this study, the financial funding from Changchun Genescience Pharmaceutical Co., Ltd., the technical support from the Chongqing Key Laboratory of Translational Medicine in Major Metabolic Diseases, and the Department of Endocrinology, the First Affiliated Hospital of Chongqing Medical University.

Funding sources

This study was supported by Changchun Genescience Pharmaceutical Co., Ltd (Grant no. cqmuhx2022001) and the Special Funded Project for Scientific and Technological Innovation in Social Undertakings and Livelihood Security of Chongqing Science and Technology Committee (Grant no. cstc2015shmszx1067). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethics statement

This study passed the review of the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (2022-K341) and written informed consent was provided to all of the participants.

References

1. Bermúdez B, López S, Pacheco YM, et al. Influence of postprandial triglyceride-rich lipoproteins on lipid-mediated gene expression in smooth muscle cells of the human coronary artery. Cardiovasc Res. 2008;79(2):294-303.
2. 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.
3. Brown DA, Breit SN, Buring J, et al. Concentration in plasma of macrophage inhibitory cytokine-1 and risk of cardiovascular events in women: a nested case-control study. Lancet. 2002;359(9324):2159-2163.
4. Lind L, Wallentin L, Kempf T, et al. Growth-differentiation factor-15 is an independent marker of cardiovascular dysfunction and disease in the elderly: results from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) Study. Eur Heart J. 2009;30(19):2346-2353.
5. Adela R, Banerjee SK. GDF-15 as a Target and Biomarker for Diabetes and Cardiovascular Diseases: A Translational Prospective. J Diabetes Res. 2015;2015:490842.
6. Cai L, Li C, Wang Y, Mo Y, Yin J, Ma X. Increased Serum GDF15 Related to Improvement in Metabolism by Lifestyle Intervention Among Young Overweight and Obese Adults. Diabetes Metab Syndr Obes. 2021;14:1195-1202.
7. Spanopoulou A, Gkretsi V. Growth differentiation factor 15 (GDF15) in cancer cell metastasis: from the cells to the patients. Clin Exp Metastasis. 2020;37(4):451-464.
8. Johnen H, Lin S, Kuffner T, et al. Tumor-induced anorexia and weight loss are mediated by the TGF-beta superfamily cytokine MIC-1. Nat Med. 2007;13(11):1333-1340.
9. Melmed S, Bronstein MD, Chanson P, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552-561.
10. Alexopoulou O, Bex M, Kamenicky P, Mvoula AB, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a

study in 148 patients. Pituitary. 2014;17(1):81-89.

11. Xekouki P, Azevedo M, Stratakis CA. Anterior pituitary adenomas: inherited syndromes, novel genes and molecular pathways. Expert Rev Endocrinol Metab. 2010;5(5):697-709. .
12. Ratnam NM, Peterson JM, Talbert EE, et al. NF-κB regulates GDF-15 to suppress macrophage surveillance during early tumor development. J Clin Invest. 2017;127(10):3796-3809.
13. Wang X, Wu L, Liu Q, Wu Y. Dietary Environment in Early Care and Education Settings and Young Children's Eating Behavior: A Systematic Review of Literature. Am J Health Behav. 2022;46(5):541-557.
14. Wolters TLC, van der Heijden CDCC, van Leeuwen N, et al. Persistent inflammation and endothelial dysfunction in patients with treated acromegaly. Endocr Connect. 2019;8(12):1553-1567.
15. Netea MG, Joosten LA, Latz E, et al. Trained immunity: A program of innate immune memory in health and disease. Science. 2016;352(6284):aaf1098.
16. Maffei P, Dassie F, Wennberg A, Parolin M, Vettor R. The Endothelium in Acromegaly. Front Endocrinol (Lausanne). 2019;10:437.
17. Eggers KM, Kempf T, Lagerqvist B, et al. Growth-differentiation factor-15 for long-term risk prediction in patients stabilized after an episode of non-ST-segment-elevation acute coronary syndrome. Circ Cardiovasc Genet. 2010;3(1):88-96.
18. Hong JH, Chung HK, Park HY, et al. GDF15 Is a Novel Biomarker for Impaired Fasting Glucose. Diabetes Metab J. 2014;38(6):472-479.
19. Olarescu NC, Bollerslev J. The Impact of Adipose Tissue on Insulin Resistance in Acromegaly. Trends Endocrinol Metab. 2016;27(4):226-237.
20. Zeyda M, Farmer D, Todoric J, et al. Human adipose tissue macrophages are of an anti-inflammatory phenotype but capable of excessive pro-inflammatory mediator production. Int J Obes (Lond). 2007;31(9):1420-1428.
21. Uronen-Hansson H, Allen ML, Lichtarowicz-Krynska E, et al. Growth hormone enhances proinflammatory cytokine production by monocytes in whole blood. Growth Horm IGF Res. 2003;13(5):282-286.
22. Prusiński T. The Role of Doctor's Authority in Patients' Treatment Decisions. Am J Health Behav. 2022;46(5):503-514.
23. del Rincon JP, Iida K, Gaylinn BD, et al. Growth hormone regulation of p85alpha expression and phosphoinositide 3-kinase activity in adipose tissue: mechanism for growth hormone-mediated insulin resistance. Diabetes. 2007;56(6):1638-1646.
24. Nakayasu ES, Syed F, Tersey SA, et al. Comprehensive Proteomics Analysis of Stressed Human Islets Identifies GDF15 as a Target for Type 1 Diabetes Intervention. Cell Metab. 2020;31(2):363-374.e6.