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Research Article

Assessment of Filamin-A Levels in Patients with Acromegaly Only and those Associated with Diabetes Mellitus

Hiba Ghassan Rajab[1,2]*, Shatha Mohammed Jawad Al-Khateeb[2], Abbas Mahdi Rahmah[3]
[1]Department of Pharmacology, College of Medicine, University of Baghdad, Baghdad, Iraq; [2]Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, Baghdad, Iraq; [3]National Diabetes Center, Mustansiriyah University, Baghdad, Iraq

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Abstract

Background: Acromegaly is a rare endocrine disorder characterized by elevated levels of insulin-like growth factor-1 and growth hormone, which are typically brought on by a somatotroph adenoma of the pituitary gland. It has an incidence of 4 per million annually and a prevalence of 40 per million. The elevated IGF-1 levels cause somatic growth and metabolic effects, with subsequently increased morbidity and mortality, particularly when GH and IGF-1 levels remain persistently elevated. ***Objective***: To evaluate the levels of filamin-A (FLNA) in patients with acromegaly with and without diabetes mellitus type 2 (T2DM) compared to a control group. ***Methods***: In this case-control study, one hundred patients with acromegaly registered at the National Diabetes Center, Mustansiriyah University, were enrolled in the study. 76 participants as control. All recruited participants have given oral consent to participate in the study, which was conducted from February 2024 to August 2024. ***Results***: The age distribution differences were not statistically significant. The gender distribution showed 47 females and 53 males in the acromegaly group. The FLNA level was higher among patients compared to controls and showed the highest level in acromegaly and DM (687.24 ng/L), followed by acromegaly without DM (359.39 ng/L), controls with DM (205.96 ng/L), and controls without DM (143.29 ng/L). ***Conclusions***: The results showed that serum FLNA was elevated in patients with acromegaly in comparison to the control group and in the T2DM group versus those without T2DM.

Keywords: Acromegaly, Actin-binding protein, Diabetes mellitus, FLNA, Pituitary adenoma.

تقييم مستويات الفيلامين أ في المرضى الذين يعانون من ضخامة النهايات فقط وتلك المرتبطة بداء السكري

الخلاصة

الخلفية: ضخامة النهايات هو اضطراب الغدد الصماء النادر يتميز بمستويات مرتفعة من عامل النمو الشبيه بالأنسولين-1 وهرمون النمو، الذي عادة ما يتم افرازه عن طريق الورم الحميد somatotroph في الغدة النخامية. ويبلغ معدل الإصابة به 4 لكل مليون سنويا ومعدل انتشاره 40 لكل مليون. مستويات IGF-1 مرتفعة تسبب فرط النمو الجسدي والآثار الأيضية، مع زيادة المراضة والوفيات في وقت لاحق، لا سيما عندما تظل مستويات هرمون النمو وعامل شبيه الأنسولين-1 مرتفعة باستمرار. **الهدف**: تقييم مستويات الفيلامين أ (FLNA) في المرضى الذين يعانون من ضخامة النهايات مع وبدون داء السكري من النوع 2 (T2DM) مقارنة بالمجموعة الضابطة. **الطرائق**: في هذه الدراسة الضابطة، تم تسجيل مائة مريض يعانون من ضخامة الأطراف في المركز الوطني للسكري بجامعة المستنصرية في الدراسة. 76 مشاركا كضابط. أعطى جميع المشاركين موافقة تحريرية على المشاركة في الدراسة، التي أجريت في الفترة من فبراير 2024 إلى أغسطس 2024. **النتائج**: لم تكن فروق التوزيع العمري ذات دلالة إحصائية. أظهر التوزيع بين الجنسين 47 أنثى و 53 ذكرا في مجموعة ضخامة النهايات. كان مستوى FLNA أعلى بين المرضى مقارنة بالضوابط وأظهر أعلى مستوى في ضخامة النهايات ومرض السكري (687.24 نانوغرام/لتر) ، يليه ضخامة النهايات بدون DM (359.39 نانوغرام/ لتر) ، والضوابط مع DM (205.96 نانوغرام/ لتر) ، والضوابط بدون DM (143.29 نانوغرام/لتر). **الاستنتاجات**: أظهرت النتائج أن مستوى المصل من FLNA كان مرتفعا في المرضى الذين يعانون من ضخامة النهايات مقارنة بالمجموعة الضابطة وفي مجموعة T2DM مقابل أولئك الذين لا يعانون من T2DM.

* ***Corresponding author***: Hiba G. Rajab, Department of Pharmacology, College of Medicine, University of Baghdad, Baghdad, Iraq; Email: heba-ghassan@uomustansiriyah.edu.iq

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INTRODUCTION

Acromegaly is a rare endocrine disorder that typically results from a somatotroph adenoma of the pituitary gland [1]. It is characterized by elevated levels of insulin-like growth factor 1 (IGF-1) and growth hormone (GH). Thirty percent of patients have microadenomas, while seventy percent of patients have macroadenomas [2]. Its incidence and prevalence are gender-neutral, with a range of 34 to 137 per million and an annual incidence of 4-6 per million [3]. The elevated IGF-1 levels cause somatic growth and metabolic effects, with later increased morbidity and mortality, particularly when GH and IGF-1 levels are still persistently elevated [4]. Biochemical tests, such as random IGF-1 and GH levels in the blood after a glucose load [5], confirm the diagnosis in people who are thought to have acromegaly. The standard of care is to first perform a pituitary magnetic resonance imaging (MRI) to check

for signs of an adenoma. About half of patients with macroadenoma do not achieve a cure following resection and require repeat surgery, medications, or radiation [6]. Acromegaly is characterized by slowly progressive somatic disfigurement (mainly involving the face and extremities) and multiorgan/system impairment [7-8]. The liver releases insulin-like growth factor-1 (IGF-1) in response to growth hormone. IGF-1 changes gene transcription and lowers diastolic ventricular filling while also increasing cardiomyocyte hypertrophy [9]. Cardiovascular problems are acromegaly patients' primary cause of mortality [10,11]. In 1975, filamin-A (FLNA) was initially identified as a protein that cross-links non-muscle actin filaments, also referred to as a gelation factor [12]. The filamin family includes three homologous subtypes: filamin-A, -B, and -C. Filamin-A (FLNA) is a universally expressed cytoskeletal protein in the human body, and it possesses numerous roles [13]. In vitro studies showed that FLNA helps with the signaling and stability of a lot of receptors that are found in pituitary tumors. These include SSTR-2, SSTR-5, and the dopamine receptor D2 (DRD2) [14]. The function of FLNA in several pathophysiological processes has been investigated [15]. Its significance in carcinogenesis and metastasis has been emphasized, and research has shown that different malignancies, including those of the breast, lung, and prostate, express FLNA differently. Additionally, recent studies point to a potential connection between FLNA expression and pituitary adenomas, the tumors that cause acromegaly, and their behavior [14]. In this case, FLNA might interact with growth hormone receptors, which could change how the tumor spreads and grows, as well as how it reacts to medical treatments, especially somatostatin analogs [16]. FLNA functions are tightly regulated by several mechanisms, including FLNA phosphorylation, mechanical force, intramolecular inhibition, competition with other molecules, and proteolysis [17]. These regulatory mechanisms are crucial for preserving FLNA's dynamic function in cellular construction, signal transduction, and receptor interactions. Dysregulation of these activities can lead to pathological conditions such as abnormal FLNA activity, which affects cellular integrity, disrupts signaling pathways, and is associated with the development of diseases such as cancer, cardiovascular disorders, and endocrine dysfunctions [18]. This study aims to evaluate the levels of FLNA in patients with acromegaly with T2DM and those without T2DM compared to a control group.

METHODS

Study design

This case-control study was conducted in the Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University, and the National Diabetes Center (NDC). The National Diabetes Center (NDC) is a specialized center that offers diabetes care, treatment, and public health awareness. The study was executed from February 2024 to August 2024.

Sample selection

A total of 176 individuals were included in this case-control study. They are allocated into two main groups: Group 1 includes 100 patients with acromegaly, and Group 2 includes 76 participants as controls. People with acromegaly who registered at the NDC during the study period and showed up for their scheduled visits (aged 30 to 70 years) were recruited. The acromegaly group included in this study was divided into two groups: patients with acromegaly and T2DM and patients with acromegaly without T2DM. The control group includes 76 participants subdivided into two subgroups according to the presence or absence of T2DM.

Inclusion criteria

The acromegaly patients who are registered in the NDC during the study period during their prespecified scheduled visits (aged 30-70 years).

Exclusion criteria

The patients who are maintained on cancer treatment drugs that target the actin cytoskeleton, which potentially affects FLNA, patients with neuro-inflammatory or immune disorders, and pregnant or breastfeeding patients were excluded due to potential hormonal fluctuations that can affect FLNA levels, as well as ethical considerations.

Outcome measurements

Blood samples were collected in the morning prior to 9 a.m. from all the participants in a fasting state. About 10 ml of venous blood was withdrawn and centrifuged at 3000 rpm for 10 minutes. The sera were subsequently analyzed for GH, IGF-1, fasting blood glucose, HbA1C, and FLNA levels. A fully automated device based on the electrochemiluminescence immunoassay (ECLIA) principle (Cobas E411) is used to measure growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Serum human FLNA levels were determined by using a FLNA ELISA kit; the principle was an enzyme-linked immunosorbent assay (ELISA). About 1 ml of the serum from every patient was stored at -20ºC until the time of analysis using the sandwich ELISA assay in order to measure FLNA.

Ethical consideration

The Research Ethics Committee of the College of Medicine at Mustansiriyah University approved the study protocol. All participants were informed about the aims of the study, and written consent was obtained from each participant.

Statistical analysis

The statistical package for the social science program (SPSS) version 20 was used to analyze the data. Chi-square test for gender distribution, one-way ANOVA for age comparisons across groups, Post-hoc Tukey test for multiple comparisons, Kolmogorov-Smirnov test for normality of age distribution, Bonferroni correction applied for multiple comparisons, and 95% confidence intervals calculated for mean ages. Significant differences were considered at $p<0.05$.

RESULTS

Table 1 shows that out of 100 patients with acromegaly who have been enrolled in this study, 53 are males and 47 are females, and out of 76 participants without acromegaly, 42 are males and 34 are females.

Table 1: Gender distribution analysis by disease status

Gender distribution	Acromegaly (n=100)	Control (n=76)	*p*-value
Female	47(47)	34(44.7)	0.765
Male	53(53)	42(55.3)	
Female/Male	0.89:1	0.81:1	

Values were expressed as frequency and percentage.

As shown in Table 2, the acromegaly group had an equal distribution of people with and without T2DM (50:50), and the control group had a nearly equal distribution (48.7% DM vs. 51.3% non-DM). There was no significant difference in the distribution of diabetes between the acromegaly and control groups. Macroadenoma (>1 cm) was found in 74% of the total patient group.

Table 2: Diabetes Status Analysis by disease group

Diabetes status	Acromegaly (n=100)	Control (n=76)	*p*-value
T2DM	50(50)	37(48.7)	0.861
Non-T2DM	50(50.)	39(51.3)	

Values were expressed as frequency and percentage.

Table 3 shows that there was a significant difference in the number of females and males in acromegaly patients with and without T2DM (60% *vs.* 34%). There was also a significant difference in the number of females and males in acromegaly patients with and without T2DM ($p = 0.023$), but the control group had a more balanced number of women and men. The mean age was higher in the T2DM-associated groups for both acromegaly and control subjects, and there were more elderly patients in the acromegaly with T2DM group. However, this doesn't really change the overall research and results. There were more women in the T2DM-associated group than men in both the acromegaly and control groups.

Table 3: Demographics of study population by group and diabetes status

Characteristic	Acromegaly with T2DM (n=50)	Acromegaly without T2DM (n=50)	Control with T2DM (n=37)	Control without T2DM (n=39)	*p*-value
Gender n(%)					
Female	30(60)	17(34)	19(51.4)	15(38.5)	0.023
Male	20(40)	33(66)	18(48.6)	24(61.5)	
Age groups n(%)					
30-40 years	8(16)	15(30)	9(24.3)	12(30.8)	
41-50 years	28(56)	27(54)	20(54.1)	19(48.7)	0.156
>50 years	14(28)	8(16)	8(21.6)	8(20.5)	

As shown in Figure 1, people with acromegaly and T2DM were significantly older than people without T2DM.

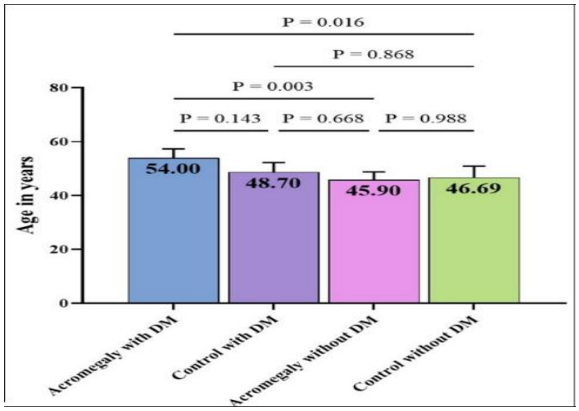

Figure 1: Age distribution across the groups studied.

The results in Table 4 show that FLNA levels showed significant differences between all groups and a consistent pattern of elevation in acromegaly. Acromegaly with T2DM showed the highest levels (687.24±256.46 ng/L), which was significantly higher than acromegaly without T2DM (359.39±131.84 ng/L). Both subgroups of the controls showed markedly lower levels (T2DM: 205.96 ± 93.05 ng/L; without T2DM: 143.29±22.85 ng/L). The difference between acromegaly in people with and without T2DM was highly significant ($p < 0.001$). This suggests that acromegaly and diabetes may affect FLNA levels in a way that is not purely one-way, as shown in Figure 2.

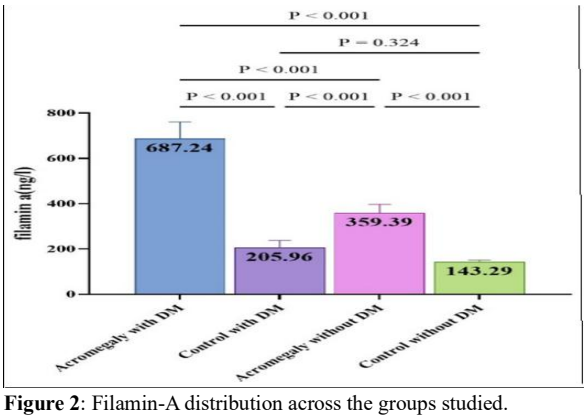

Figure 2: Filamin-A distribution across the groups studied.

HbA1C levels were significantly higher in both diabetic groups (acromegaly with T2DM: 8.47±1.64%; control with T2DM: 7.30±0.9%) compared to non-diabetic groups (acromegaly without T2DM: 5.33±1.43%; control without T2DM: 5.36±0.95%). Notably, acromegaly patients with T2DM showed significantly higher HbA1C levels compared to controls with T2DM (p<0.001), suggesting poorer glycemic control in this group, as shown in Figure 3. Table 4 shows that IGF-1 levels were significantly higher in both acromegaly groups (with T2DM: 403.24±168.18 ng/mL; without T2DM: 409.44±184.63 ng/mL) compared to control groups (with T2DM: 242.89±53.04 ng/mL; without T2DM: 247.50±47.40 ng/mL; p<0.001 for both comparisons).

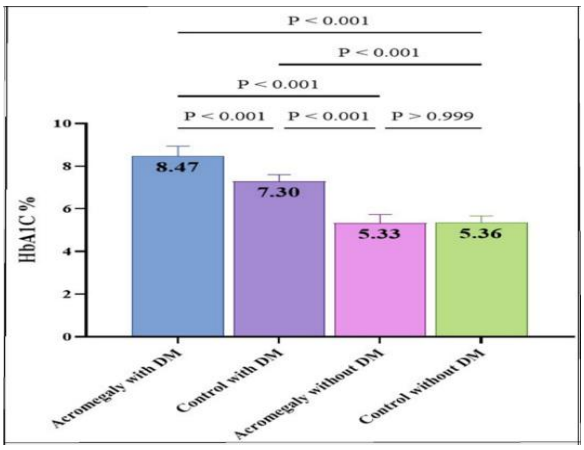

Figure 3: HbA1C distribution across the groups studied.

Table 4: Biochemical parameters among the groups studied

Parameter	Acromegaly with T2DM	Acromegaly without T2DM	Control with T2DM	Control without T2DM	*p*-value
Filamin A (ng/L)	687.24±256.46	359.39±131.84	205.96±93.05	143.29±22.85	<0.001
HbA1c (%)	8.47±1.64	5.33±1.43	7.3±0.9	5.36±0.95	<0.001
IGF-1 (ng/mL)	403.24±168.18	409.44±184.63	242.89±53.04	247.5±47.4	<0.001
GH (ng/mL)	6.23±3.42	6.19±2.31	1.46±0.79	1.26±0.61	<0.001
FBG (mg/dL)	201.05±79.96	150.32±63.29	157.43±22.98	104.79±38.41	<0.001

Values were expressed as mean±SD.

There was no significant difference between the two acromegaly groups (p> 0.05), suggesting that diabetes status does not significantly impact IGF-1 levels in acromegaly, as shown in Figure 4.

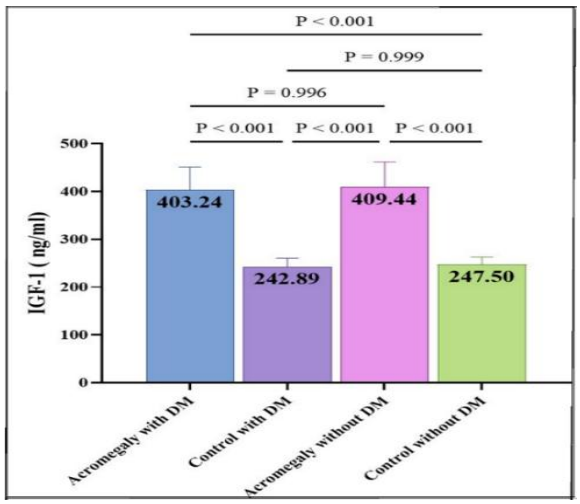

Figure 4: IGF-1 levels in the groups studied.

GH levels were significantly elevated in both acromegaly groups (with DM: 6.23±3.42 ng/mL; without DM: 6.19±2.31 ng/mL) compared to the control group (with T2DM: 1.46±0.79 ng/mL; without T2DM: 1.26±0.61 ng/mL; p<0.001 for both comparisons), as shown in Figure 5.

DISCUSSION

This study found that gender may influence the relationship between diabetes and acromegaly, a condition that impacts metabolic processes. The notable gender disparity in the diabetes group among acromegaly patients suggests a potential gender-related risk for developing diabetes in acromegaly. This finding suggests that females with acromegaly may have a higher risk of metabolic disorders, such as diabetes, due to factors like hormonal effects, changes in body composition, or other gender-specific elements that increase insulin resistance in this population.

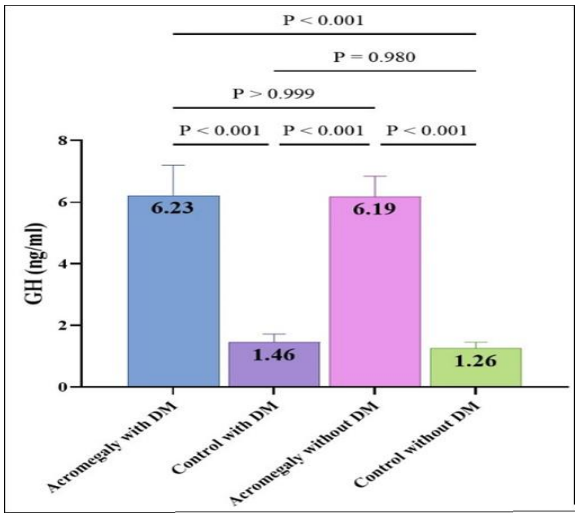

Figure 5: GH levels in the groups studied.

This difference may also be due to differences in lifestyle factors, genetic susceptibility, or the pathophysiology of acromegaly between men and women, which is in line with Fieffe *et al*. [17]. However, the data pertaining to the control group indicates a more equitable gender distribution in both DM and non-DM categories. This finding suggests that, in the absence of acromegaly, gender may exert a diminished influence on the onset of diabetes. The disparity between acromegaly and control groups may indicate that acromegaly modifies the conventional gender-specific risk factors for diabetes. Middle-aged adults (41-50 years) constituted the predominant subgroup across all categories, exhibiting analogous

age distribution patterns between the acromegaly and control groups. Also, there wasn't a significant difference in age between the T2DM and non-DM groups. This suggests that people in this age group are more likely to have acromegaly, diabetes mellitus, and disorders related to these conditions. The age distribution pattern is consistent in both the acromegaly and control groups, indicating that acromegaly in our sample affects people of all ages and is therefore comparable to the general population. The study results showed that the FLNA level showed significant differences between all groups; it was found to be significantly higher in patients with acromegaly and T2DM than in those with acromegaly without T2DM. The reason for this was that the higher levels of FLNA in the acromegaly and T2DM group may show the combined effects of high blood sugar and poor insulin signaling, which are both known to mess up the movement of cytoskeletal proteins and make cells more sensitive to stress. This may result in an increase of FLNA as a compensatory mechanism for maintaining cellular integrity and function during metabolic stress. These results highlight the relationship between endocrine dysfunction and metabolic stress, indicating that FLNA may function as a biomarker for the severity of systemic metabolic disorders in these paired clinical conditions of acromegaly and T2DM. As far as we know, this is the first study to look at serum FLNA levels in relation to acromegaly. It gives us a new way to think about how this important cytoskeletal protein works throughout the body in a specific group of patients. While no previous studies have specifically examined serum FLNA levels in acromegaly, its role in cytoskeletal dynamics and inflammation suggests that it may be involved in the pathophysiology of acromegaly and acromegaly-related complications and response to treatment, which is in line with Treppiedi *et al*. [19]. New research suggests that there may be a link between FLNA expression and pituitary adenomas, the tumors that cause acromegaly, as well as how they behave [16]. This could be explained by the fact that FLNA is a multifunctional intracellular protein that plays a central role in maintaining cellular structure, facilitating receptor functions, and coordinating intracellular signaling, and its cytoplasmic localization enables it to interact with the cytoskeleton and transmembrane proteins, making it essential for cellular processes like receptor internalization and signal transduction. Internalization helps to regulate the activity of receptors on the cell surface. Many drugs, like octreotide, rely on receptor internalization to exert their effects. By binding of the ligand (e.g., octreotide), this leads to stopping excessive signaling by removing the receptor from the cell surface, so in the case of SST2, internalization is necessary for proper therapeutic responses, such as reducing excessive hormone secretion acromegaly. In acromegaly and diabetes mellitus, cell damage causes intracellular FLNA to be released into the bloodstream. This is caused by oxidative stress, chronic inflammation, and metabolic dysfunction, among other things. High blood sugar (hyperglycemia) damages cell and makes endothelial cells not work properly in diabetes. In acromegaly, on the other hand, elevated levels of growth hormone (GH) and IGF-1 cause mechanical stress, cytoskeletal disruption, and tissue overgrowth. Additionally, hypoxia from impaired blood flow, apoptosis or necrosis due to prolonged stress, and tumor cell damage in GH-secreting adenomas contribute to cell membrane instability and FLNA leakage. These processes suggest that serum FLNA levels could act as a biomarker for disease severity or progression in both conditions. Although there are no directly similar studies, the results findings provide a distinct perspective on the probable role of FLNA in the development and therapeutic response of acromegaly, while no previous research has directly investigated serum FLNA levels in acromegaly; however, its function in cytoskeletal dynamics and inflammation implies potential involvement in the pathogenesis of acromegaly-related problems, which agrees with Treppiedi *et al*. [20]. The results found that HbA1C levels were significantly higher in both diabetic groups compared to non-diabetic groups, suggesting poorer glycemic control in these groups. The increase in HbA1C levels in patients with acromegaly and diabetes may indicate inadequate glycemic management, potentially due to specific physiological alterations associated with acromegaly, including insulin resistance and altered glucose metabolism. In acromegaly, excess growth hormone enhances gluconeogenesis and lipolysis that may lead to complicated hyperglycemia, while the increase in the level of IGF-1 may lead to additional impairment of glucose regulation, which is in line with [21].

Study limitations

The limited number of participants diminishes the reliability of the findings. Future studies should incorporate larger and more diverse populations to enhance statistical power and improve sample size, thereby increasing statistical significance.

Conclusion

T2DM shows higher incidence among females with acromegaly. Higher levels of filamin-A were reported in the serum of patients with acromegaly who also had T2DM compared to those with acromegaly who did not have T2DM and patients in the control group. The patients with acromegaly associated with T2DM have elevated HbA1C levels compared to the diabetic control group.

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Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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