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Research Article

Evaluation of Beta-Arrestin Levels in Acromegaly Patients: A Comparison of Patients with and Without Obstructive Sleep Apnea

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Abstract

Background: Acromegaly is a rare endocrine disorder; it has an incidence of 4 per million annually and a prevalence of 40 per million. It is due to a growth hormone-secreting pituitary adenoma. ***Objective***: To evaluate the levels of β-arrestin in patients with acromegaly with and without obstructive sleep apnea (OSA). ***Methods***: One hundred and five registered patients with acromegaly at the National Diabetes Center, Mustansiriyah University, were enrolled in the study. Of the 105 patients with acromegaly, 81 have OSA, while the remaining 24 have no OSA. Obstructive sleep apnea affects 81.8% of males and 72% of females. All recruited patients have given oral consent to participate in the study, which was conducted from January to October 2023. ***Results***: Males with OSA had a mean age of 52 years, while those without OSA had a mean age of 46 years. The Epworth sleepiness scale is higher among those with OSA. β-arrestin is higher in males with OSA (6.309 pg/ml), while in females with OSA, it is 6.278 pg/ml. In no OSA group, the β-arrestin level was 3.067 pg/ml, while in those with OSA, it jumped to 6.29 pg/ml. ***Conclusions***: The results showed that β-arrestin was elevated in patients with acromegaly and obstructive sleep apnea versus those without obstructive sleep apnea. OSA is more common in males, particularly when they get older.

Keywords: Acromegaly, β-arrestin, Obstructive sleep apnea.

تقييم مستويات بيتا أرريستين في مرضى ضخامة النهايات: مقارنة بين المرضى الذين يعانون من انقطاع النفس الانسدادي النومي وبدونه

الخلاصة

الخلفية: ضخامة النهايات هو اضطراب نادر في الغدد الصماء. يبلغ معدل حدوثه 4 لكل مليون سنويا ومعدل انتشاره 40 لكل مليون. ويرجع ذلك إلى ورم في الغدة النخامية يفرز هرمون النمو. **الهدف**: تقييم مستويات β-arrestin في المرضى الذين يعانون من ضخامة النهايات مع وبدون انقطاع النفس الانسدادي النومي (OSA). **الطريقة**: تم أشراك مائة وخمسة مرضى يعانون من ضخامة الأطراف في المركز الوطني للسكري، الجامعة المستنصرية، في الدراسة. من بين 105 مرضى، يعاني 81 منهم من انقطاع النفس الانسدادي النومي، في حين أن ال 24 الباقين ليس لديهم انقطاع النفس الانسدادي النومي. يؤثر انقطاع النفس الانسدادي النومي على 81.8٪ من الذكور و 72٪ من الإناث. أعطى جميع المرضى المعينين موافقة شفهية للمشاركة في الدراسة ، التي أجريت في الفترة من يناير إلى أكتوبر 2023. **النتائج**: كان متوسط عمر الذكور الذين يعانون من انقطاع النفس الانسدادي النومي 52 عاما، بينما كان متوسط عمر الذكور الذين لا يعانون من انقطاع النفس الانسدادي النومي 46 عاما. مقياس إبيوورث للنعاس أعلى بين المصابين بانقطاع النفس الانسدادي النومي. β-arrestin أعلى في الذكور الذين يعانون من انقطاع النفس الانسدادي النومي (6.309 بيكوغرام / مل) ، بينما في الإناث المصابات بانقطاع النفس الانسدادي النومي، يكون 6.278 بيكوغرام / مل. في مجموعة OSA، كان مستوى β-arrestin 3.067 بيكوغرام/مل، بينما في أولئك الذين يعانون من انقطاع النفس الانسدادي النومي ارتفع إلى 6.29 بيكوغرام/مل. **الاستنتاج**: أظهرت النتائج أن β-arrestin كان مرتفعا في المرضى الذين يعانون من ضخامة النهايات وانقطاع النفس الانسدادي النومي مقابل أولئك الذين لا يعانون من انقطاع النفس الانسدادي النومي. انقطاع النفس الانسدادي النومي أكثر شيوعا عند الذكور، خاصة عندما يكبرون في السن.

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INTRODUCTION

Acromegaly is a rare endocrine disorder due to growth hormone (GH) secreting pituitary adenoma [1]. 70% of patients harbor a macroadenoma, while the remaining 30% have a microadenoma [2]. Its prevalence ranges between 34 and 137 per million, with an annual incidence of 4-6 per million; its incidence and prevalence have no gender predilection [3]. Acromegaly is characterized by enlargement of the acral parts (hands, feet, and faces) with marked perspiration and increased secretion of sebum. Arthralgia affects a good number of patients; the effect on other hormones may result in symptoms of hypothyroidism and hypogonadism; at the same time, the mass effect within the cranium can cause headaches and visual symptoms due to pressure on the optic chiasma [4]. Growth hormone augments the hepatic secretion of insulin-like growth factor-1 (IGF-1), which has an impact on gene transcription, thus resulting in cardiomyocyte hypertrophy and impaired diastolic ventricular filling. The main cause of death in patients with acromegaly is cardiovascular complications [5]. There is a functional similarity between β-arrestin and G-protein-coupled receptors (GPCRs), as β-arrestin is regarded as one of these GPCRs family of adapter proteins, which have a fundamental role in controlling signaling and trafficking of these GPCRs [6]. There are two types of β-arrestin: β-arrestin-1, which has a molecular weight of 53 KDA, and β-arrestin-2, which has a molecular weight of 46 KDA. Their synthesis is controlled by genes located on chromosomes 7 and 11, respectively [7]. These two proteins are needed to control cell proliferation, migration, and invasion. They also have another role, which is the prevention of apoptosis. Their role in tumorogenesis, angiogenesis, and drug resistance shouldn't be forgotten [6]. One of the favorable things in the treatment of acromegaly is the overexpression of somatostatin receptor 2 (SSTR2) in the harbored adenoma, which is the main target of somatostatin analogs. A new player appears in the field, which is β-arrestin, as it was found to regulate SSTR2 function [8]. Patients with acromegaly are prone to chest infection due to the effect of IGF-1 on the bronchial tissues, as well as the craniofacial changes and macroglossia that may alter the airways and induce OSA [9]. Obstructive sleep apnea affects 60% of men and 24% of women, particularly after the age of 60 [10]. Obstructive sleep apnea results from cessation of airflow, thus resulting in apneic spells and interrupted sleep. Snoring can be detected by the sleep partner, and those patients with OSA complain of unsatisfactory sleep, headaches, daytime sleepiness, and fatigue [9].

METHODS

Study design and patient selection

In the National Diabetic Center (NDC) at Mustansiriyah University, three hundred and fifteen patients with acromegaly are registered, and each one has a fully written medical record. One hundred and five patients with acromegaly who are very compliant are selected to be enrolled in the study; their ages range between 30 and 50) years. Those patients were selected randomly after informed consent was taken and patients with other causes of OSA (hypothyroidism, polycystic ovary syndrome, use of alcohol, nasal obstruction, and history of stroke) were excluded. Any recruited patient is familiar with a monthly visit that is pre-specified to be examined, investigated, and receive their monthly somatostatin analogous (SST) injection.

Outcomes measurements

All the patients fasted for 8–12 hours. At the time of the appointment, the blood samples were taken in the morning before 9 a.m., 10 ml of venous blood was withdrawn and centrifuged at 3000 rpm for 10 minutes and the sera were taken to measure GH, IGF-1, and B-arrestin. The other hormonal profiles, such as thyroid function tests and sex hormones, are checked every few months according to the request of the consultant endocrinologist. A physical examination was conducted to measure their vital signs, plus a regional examination was followed by a detailed history to stratify the severity of OSA. Two scores were utilized to achieve this goal: the Epworth sleepiness scale and the STOP-BANG score. The Epworth sleepiness scale (Ep.s) checks the readiness to sleep on variable occasions; its details are listed below [11]. The EP has 4 scores ranging from zero to 3, thus zero is regarded as normal and such people never doze in abnormal situations, while score 3 is the worst, thus they doze in normal situations like sitting in a public place. The scores are gathered in order to find out the final number, and if the gathered number exceeds 10, this patient is complaining from OSA. The STOP-BANG questionnaire is a series of 8 questions to be answered by yes or no, and its details are listed below. When the STOP-BANG is 0–2, it is regarded as normal; 2–5 is a gray zone; and a score exceeding 5 is consistent with OSA [12]. Growth hormone, IGF-1 and other hormones are measured using a fully automated device with the Electrochemiluminescence Immunoassay (ECLIA) principle (Cobas E411). 1 ml of the remaining serum from every patient was stored at -20 ºC until the time analysis using the sandwich ELISA assay in order to measure β-arrestin levels.

Statistical analysis

The statistical package for the social science program (SPSS) version 20 was used to analyze the data. The differences between groups were evaluated using a chi-square test and an independent *t*-test. Significance differences were considered at $p<0.05$.

RESULTS

The results in Table 1 indicated that, out of 105 patients with acromegaly who have been enrolled in this study, 55 were males. Forty-five out of the 55 males (81.8%) have OSA, while OSA affects 36 females out of 50 females with acromegaly; thus, their

percentage is only 72%. The obstructive sleep apnea (OSA) percentage difference between males and females is 9.2% in favor of males; however, the difference didn't reach statistical significance. The count of patients with OSA who harbor macroadenoma was 56, and 25 harbor microadenoma, and the difference is close to statistical significance (p=0.059).

Table 1: Sex and pituitary adenoma size in patients with acromegaly with and without OSA

Parameters		No OSA	OSA	*p*-value
Sex	Female	14	36	0.168
	Male	10	45	
Adenoma size	Microadenoma (≤ 10 mm)	3	25	0.059
	Macroadenoma (>10 mm)	21	56	

The results in Table 2 indicated that the mean age of patients with OSA is 52 years, whereas those without OSA have a mean age of 46 years. The difference reaches statistical significance (p=0.016). Patients with a mean body mass index (BMI) of 32.78 kg/m^2 have OSA, while their counterparts without OSA were found to have a mean BMI of 30.58 kg/m^2, but the difference didn't reach statistical significance (p=0.089). The mean duration of acromegaly since the time of diagnosis is 10 years in those with OSA and 7 years in those without OSA; the difference is significant (p=0.049). The cumulative dose of octreotide was 1490±995 mg in patients with OSA, and in patients without OSA, it was 1274±926 mg. The differences are statistically not significant. The growth hormone (GH) level in patients without OSA was 5.67±6.47 ng/ml and 5.08±6.3 ng/ml in patients with OSA, and the differences were not significant.

Table 2: Age, BMI, disease duration, cumulative somatostatin analogue dose, GH, IGF-1, EP.S, STOP-BANG, and β-arrestin in patients with acromegaly with and without OSA

Parameters	No OSA	OSA	*p*-value
Age (years)	46±13	52±11	0.016
BMI (Kg/m^2)	30.58±4.48	32.78±5.74	0.089
Duration (years)	7.0±3.0	10±7.0	0.049
Cumulative somatostatin analogue dose (mg)	1274±926	1490±995	0.343
GH (ng/ml)	5.67±6.47	5.08±6.30	0.689
IGF-1 (ng/ml)	487±210	549±231	0.243
Ep.s	5.0±5.1	15.6±8.5	0.001
STOPBANG	2.0±1.0	5.0±1.0	0.001
β-arrestin (pg/ml)	3.07±0.69	6.295±1.15	0.001

Values were presented as mean±SD.

The insulin-like growth factor-1 (IGF-1) level in patients without OSA was 487±210 ng/ml and 549±231 ng/ml in patients with OSA, and the difference didn't reach statistical significance. Epworth scale (Ep.s) was 15.6 in those with OSA and 5 in those without OSA, and the difference is highly significant (p=0.001) (Figure 1).

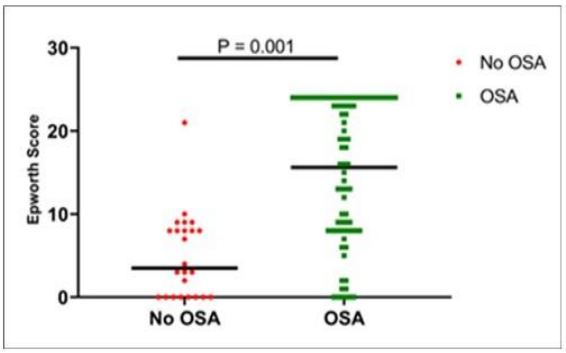

Figure 1: Epworth sleepiness scale distribution of patients with acromegaly with and without OSA.

STOP-BANG score is almost more than double in those with OSA (5 vs. 2), and the difference is highly significant from the statistical point of view (p=0.001) (Figure 2). β-arrestin in patients with OSA has a mean of 6.295 pg/ml, while the mean decreased to 3.067 pg/ml in those without OSA. The difference is highly significant (p=0.001) (Figure 3). The results in Table 3 indicated that females with and without OSA have higher mean body mass indices compared to males (32.55 *vs.* 34.08 kg/m^2, respectively), while males without OSA have a BMI of 27.83 kg/m^2 and those with OSA have a BMI of 31.71 kg/m^2 and the difference in BMI is found to be statistically significant.

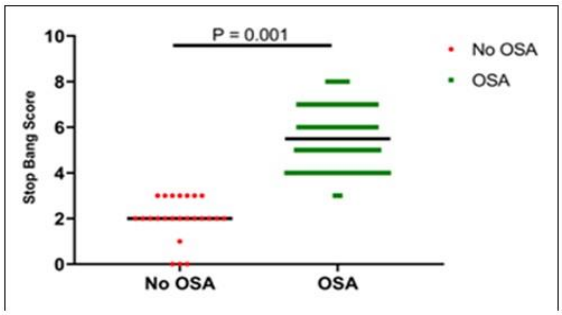

Figure 2: STOP-BANG score distribution of patients with acromegaly with and without OSA.

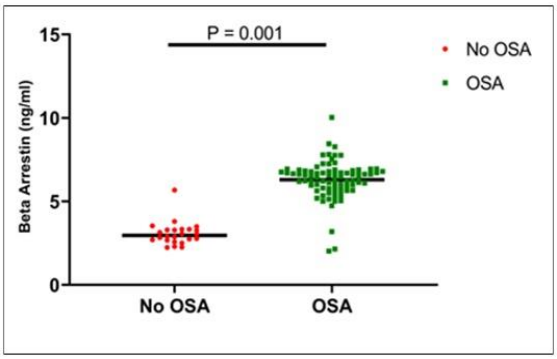

Figure 3: β-arrestin distribution of patients with acromegaly with and without OSA.

When females and males without OSA are compared with each other, the difference in BMI is highly significant in favor of males (p=0.008); however, in the presence of OSA, the difference in BMI between males and females did not reach statistical significance (p=0.065). The disease duration and cumulative somatostatin analogue dose show no significant difference if males and females were compared with each other, irrespective of having or not having OSA. Gender has no impact on the value of both GH and IGF-1, and the difference didn't reach statistical significance between males and females in both groups (with and without OSA). The Epworth sleepiness scale and STOP-BANG are higher in males than females in patients with OSA, and the difference is highly significant (p= 0.001 and 0.03 respectively).

Table 3: Age, BMI, disease duration, cumulative somatostatin analogue dose, GH, IGF-1, EP.S, STOPBANG, and β-arrestin in patients with acromegaly according to their gender with and without OSA

Parameters	No OSA		*p*-value	OSA		*p*-value
	Female	Male		Female	Male	
Age (year)	46±13	46±14	0.968	53±13	52±10	0.717
BMI (kg/m^2)	32.55±4.25	27.83±3.28	0.008	34.08±6.74	31.71±4.57	0.065
Disease duration (year)	7.0±3.0	7.0±4.0	0.923	11±6.0	10±8.0	0.489
Cumulative somatostatin analogue dose (mg)	1191±687	1388±1218	0.618	1447±914	1525±1065	0.726
GH (ng/ml)	7.02±7.24	3.78±4.94	0.234	5.82±6.92	4.48±5.77	0.346
IGF-1 (ng/ml)	520±194	441±234	0.380	505±210	584±243	0.130
Ep.s	4.1±3.6	6.3±6.7	0.302	12.6±6.4	19.3±9.0	0.001
STOPBANG	2.0±1.0	2.0±0.0	0.386	5.0±1.0	6.0±1.0	0.03
β-arrestin (pg/ml)	3.169±0.83	2.924±0.44	0.462	6.278±1.41	6.31±0.9	0.904

Values were presented as mean±SD.

Gender was found to have an impact on β-arrestin level thus females have lower levels compared to males (6.278 *vs.* 6.309 pg/ml) but this gender difference of β-arrestin in patients with acromegaly didn't reach statistical significance irrespective of having or not having OSA (p=0.904 and 0.444, respectively).

DISCUSSION

This study found that obstructive sleep apnea (OSA) was less common in women with acromegaly than in men. This is in line with other studies that found the same thing. This is likely because of the way their airways work and the protective effect of estradiol and progesterone. In addition, the increased prevalence of OSA in males is probably related to insulin resistance that may culminate in beta cell dysfunction; the story may be worsened by the marked increase in visceral fat, while in females the bulk of stored fat was in the subcutaneous tissue [13,14]. According to this study, the prevalence of OSA increases with age and is explicable by fat deposition, changes in the pharyngeal muscles, and a decrease in lean mass. As a result, according to a population-based study by Silva and his team [15], the likelihood of having OSA may reach 25–40% in the elderly. The results of our study showed that having macroadenoma increases the chance of having OSA as well as a prolonged duration of acromegaly. Obesity has an impact on having OSA due to its anatomical and mechanical effects and its effect on metabolic dysfunction, which is in agreement with a study by Bonsignore *et al.* [16]. Our study revealed that GH and IGF-1 levels have no impact on having OSA; the physiological basis of the action of GH and IGF-1 on OSA is still not clear. From a different point of view, GH and IGF-1 may both make central sleep apnea worse by affecting the breathing centers. They may also have a direct effect on the airways, which could lead to bronchoconstriction or make pregnathism and macroglossia worse. Other researchers [17] backed up this explanation. The study results showed that β-arrestin was found to be higher in patients with acromegaly and OSA versus those without OSA, the explanation for that is β-arrestin has had unfavorable effects as a promoter of cell proliferation and migration plus their anti-apoptosis effect which augments tumor cell survival, spread and angiogenesis which in line with findings conducted by Song *et al*. [18], while another study by Mukherjee *et al*. demonstrated that: sensitivity to hypoxia in the carotid body is affected by hypoxia-inducible factor one alpha (HIF-1α), the expression of HIF-1α is affected β-arrestin (ARRB1) gene thus β-arrestin may have an indirect effect on the carotid body response to hypoxia [19]. Another study said that SSTR2 extracellular signals enter cells through β-arrestin recruitment pathways. The β-arrestin recruitment causes receptor internalization, which changes the desensitization of SSTR2. This may lower the clinically beneficial effect through drug resistance; in other words, the expression level of SSTR2 controlling when SST analog octreotide is given to patients with acromegaly and lower of β-arrestin.

Conclusions

The STOP-BANG score is twice as high in people with acromegaly and obstructive sleep apnea as it is in those without. The Epworth drowsiness scale is higher in patients with obstructive sleep apnea than in those without; nevertheless, this was anticipated for enrollment. Males were discovered to be more susceptible to obstructive sleep apnea. The risk of having obstructive sleep apnea increases with age, acromegaly duration, and body mass index. The presence of macroadenomas has been linked to an increased risk of obstructive sleep apnea. β-arrestin

levels were found to be elevated in patients with acromegaly who also had obstructive sleep apnea.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

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

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