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Research Article

Glycemic Status in Acromegaly Patients Receiving Depot Long-Acting Octreotide

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Abstract

Background: Acromegaly is an uncommon, chronic, debilitating condition characterized by hyperinsulinism, insulin resistance, diabetes and prediabetes. One possibility for managing acromegaly's questionable influence on glucose homeostasis is the somatostatin analogues. ***Aim***: To analyze the frequency and risk factors for impaired glucose homeostasis in acromegaly patients treated with depot long-acting octreotide (octreotide LAR), as well as the relationship between risk and treatment duration. ***Methods***: The study included 52 Iraqi adults with acromegaly receiving octreotide LAR. Demographic, anthropometric, and clinical data were collected, as well as the duration of Octreotide LAR administration. Growth hormone, IGF-1, and adenoma size were reported retrospectively from patient data. The glycemic state was assessed and classified as DM, prediabetes, or normal. ***Results***: The prevalence of DM was 39% and prediabetes was 40%, with the exception of being male, which was substantially related with prediabetes. DM and octreotide LAR use had a non-significant correlation. However, octreotide use altered 13% of patients from normal glycemic to prediabetes, with no correlation to treatment duration. Other than hypertension and a family history of diabetes, no other variables were found to be significant. ***Conclusion***: Acromegaly patients have abnormal glucose metabolism, which is associated with prediabetes owing to octreotide LAR medication. Hypertension and family history of diabetes are risk factors.

Keywords: acromegaly, glycemic status, octreotide LAR, risk factors

حالة نسبة السكر في الدم في مرضى أكروميجالي المعالجين بالأوكتريوتيد طويل المفعول

الخلاصة

الخلفية: أكروميجالي هو حالة غير شائعة ومزمنة ومنهكة تتميز بفرط الأنسولين ومقاومة الأنسولين والسكري ومقدمات السكري. أحد الاحتمالات لإدارة تأثير أكروميجالي المشكوك فيه على توازن الجلوكوز هو استخدام مشتقات السوماتوستاتين. **الهدف**: لتحليل وتيرة وعوامل الخطر لضعف توازن الجلوكوز في مرضى أكروميجالي الذين عولجوا بالأوكتريوتيد طويل المفعول ، فضلا عن العلاقة بين المخاطر ومدة العلاج. **الطرائق**: شملت الدراسة 52 من البالغين العراقيين الذين يعانون من الأكروميجالي الذين يتلقون أوكتريوتيد طويل المفعول. تم جمع البيانات الديموغرافية والبشرية والسريرية، فضلا عن مدة استخدام أوكتريوتيد ومستوى هرمون النمو, IGF-1, وحجم الورم الحميد والتي تم الإبلاغ عنها بأثر رجعي من بيانات المريض. تم تقييم حالة نسبة السكر في الدم وتصنيفها على أنها DM أو مقدمات السكري أو العادية. **النتائج**: كان انتشار السكري 39٪ ومقدمات السكري 40٪، باستثناء كونه ذكرا، والذي كان مرتبطا بشكل كبير بمقدمات السكري. وكان بين DM واستخدام الأكتريوتيد ارتباط غير كبير. ومع ذلك، فإن استخدام الأوكتريد يغير 13٪ من المرضى من نسبة السكر في الدم العادية إلى مقدمات السكري، مع عدم وجود ارتباط بمدة العلاج. بخلاف ارتفاع ضغط الدم والتاريخ العائلي لمرض السكري، لم يتم العثور على متغيرات أخرى لتكون كبيرة. **الأستنتاج**: مرضى أكروميجالي لديهم استقلاب الجلوكوز غير طبيعي، والذي يرتبط مع مقدمات السكري بسبب أستخدام أوكتريوتيد. ارتفاع ضغط الدم والتاريخ العائلي لمرض السكري هي عوامل الخطر.

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INTRODUCTION

Growth hormone (GH) hypersecretion is the primary cause of Acromegaly, which is also related with diabetes, hypertension, cardiomyopathy, poor respiratory function, and neoplasms. Untreated, it raises late morbidity and mortality [1,2]. Growth hormone counteracts several of insulin's activities. Growth hormone promotes lipolysis, resulting in higher quantities of non-esterified fatty acids in the blood. As a result of the Randle cycle, glucose uptake is reduced and insulin resistance increases. Growth hormone also promotes gluconeogenesis and inhibits muscle glycogen synthase [3]. Insulin signaling is directly altered by GH. A decrease in insulin signaling and glucose absorption in muscle and fat is a result of GH depletion. Contrary to non-acromegaly diabetics, acromegaly patients have less visceral fat, and insulin resistance is linked to GH/IGF-1 excess. In fact, visceral fat dysfunction, rather than total fat, determines insulin resistance and glucose metabolism in acromegaly patients. Despite less visceral and subcutaneous adipose tissue, active acromegaly patients have more intramuscular adipose tissue than healthy controls. Muscle adipose content may be linked to GH-induced insulin resistance. Adipose tissue failure can also change adipokine secretion, affecting the metabolic profile. Visfatin is a reliable indicator of metabolic changes like insulin resistance and adipose dysfunction in active acromegaly [4]. Somatostatin analogues (SSAs) of the first generation can modify glucose homeostasis by decreasing pancreatic insulin and glucagon release, albeit the therapeutic importance of these actions is debated. Indeed, the improved insulin sensitivity caused by first-generation SSAs may offset the lower insulin secretion over time. Increasing first-generation SSA doses or frequency does not appear to impair glucose metabolism [5-8]. In the current study, acromegaly patients receiving octreotide LAR were evaluated for DM and prediabetes, as well as risk factors for glucose metabolism abnormalities.

METHODS

Study design and patient selection

The study included adult patients with acromegaly who were on acromegaly-octreotide LAR medical therapy at the Iraqi National Center for Diabetes. From May to October 2018, 52 patients' files were reviewed for age, sex, weight, height, BMI, waist circumference, duration of octreotide LAR medication regardless of dose, GH, IGF1 levels, and pituitary adenoma size at initial presentation. Chronic problems such as DM and prediabetes were also assessed, as was hypertension and its timing in relation to octreotide LAR treatment. The recruited participants were divided into three groups based on their glycemic status: normal, diabetic, and pre-diabetic. A positive family history of diabetes was defined as one or more first-degree relatives with diabetes (parent, sibling, or offspring). Patients with known glycemic disorders were excluded from the research, as were those taking corticosteroids, beta-blockers, or thiazides.

Ethical consideration

The research proposal was fully discussed and approved by the ethical and scientific committee of The Iraqi Board for Medical Specializations. The agreement of the health authorities of the National Center for Diabetes was achieved before starting the collection of data. Verbal consent was taken from each patient after a full explanation of the aim of the study and assurance that the collected data would be used only for research purposes.

Statistical analysis

The acquired data was processed and imported into SPSS v24 for statistical analysis. Tables and graphs depicted descriptive statistics. Chi square and Fisher Exact tests were employed to determine the relationship between variables. Throughout the investigation, McNemar's test was employed to assess the significance of differences in categorical data. A P value of 0.05 or less was considered significant.

RESULTS

The demographic and anthropometric features of the included patients are summarized in Table 1.

Table 1: distribution of studied cases according to studied variables

Parameter		n(%)
Gender	Male	35(67.3)
	Female	17(32.7)
Age (Year)	< 40	24(46.2)
	≥ 40	28(53.8)
IGF1	<twice normal	31(59.6)
	≥2 times normal	21(40.4)
Growth hormone	<3times	26(50.0)
	≥3 times	26(50.0)
Size of adenoma	Macroadenoma	41(78.8)
	Micro adenoma	11(21.2)
Waist circumference (cm)	Normal	3(5.8)
	Abnormal	49(94.2)
Body Weight status	Normal	3(5.8)
	Overweight	15(28.8)
	Obese G1	25(48.1)
	Obese G2	4(7.7)
	Obese G3	5(9.6)
Blood pressure	Normotensive	26(50.0)
	Hypertensive	26(50.0)
Family history of DM	Negative FH	23(44.2)
	Positive FH	29(55.8)

The results of this study showed that out of 52 acromegaly patients on octreotide LAR, males represented 67.3% of the studied cases, and 53.8% of all

cases were ≥40 years old. The elevation of IGF1 in 59.6% of cases was less than twice of the normal value, while the level increased twice or more in 40.4% of studied cases. Serum growth hormone increased more than 3 times the normal value in 50% of cases. Moreover, macroadenoma was found in 78.8% of cases, waist circumference was abnormally increased in 94.2%, and a normal BMI value was reported in 5.8% of the cases, while 28.8% of patients were overweight and all others were obese (class 1 obesity 48.1%, class 2 obesity 7.7%, and class 3 obesity 9.6%. Half of the patients were hypertensive, and 55.8% had a family history of DM. The reported glycemic status in relation to octreotide LAR use was summarized in Figure 1.

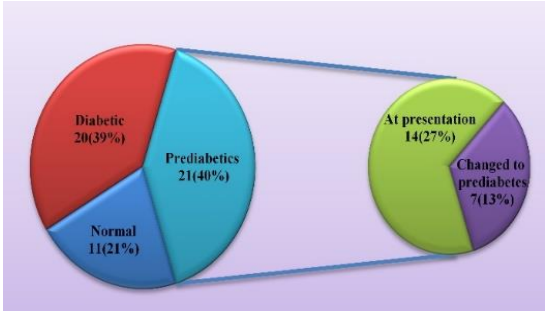

Figure 1: Distribution of patients according to the glycemic status.

It shows that at the time of the last checkup, 11 (21%) patients had a normal glycemic status, 20 (39%) patients had confirmed DM, and 21 (40%) of patients had prediabetes. From the last category (the prediabetes subgroup), 14 (27%) patients presented with prediabetes from the time of registration, while 7 (13%) patients converted from normal glycemic status, while 11 (14) patients converted from normal glycemic control. The difference in the rate of DM before and after treatment with octreotide LAR was summarized in Figure 2. It demonstrates that treatment with octreotide LAR did not change the rate of normal glycemic status into confirmed DM according to the McNemar's test, with a *P*-value= 1.

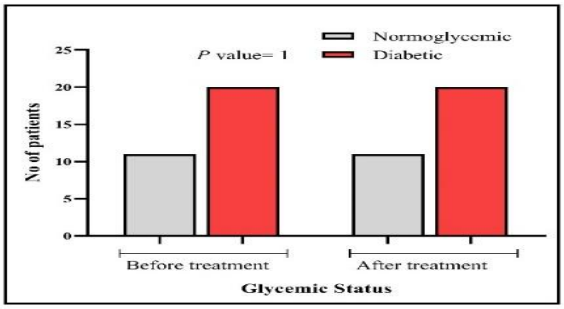

Figure 2: Difference in the rate of DM before and after treatment according to McNemar's test.

Figure 3 summarizes the difference in the rate of pre-diabetes before and after treatment with octreotide LAR; it shows that 7 out of 18 patients (with normal glycemic status before treatment) were changed to prediabetes status (after treatment) at the end of the assessment period, and McNemar's test proved that this change was statistically significant (*P*= 0.016).

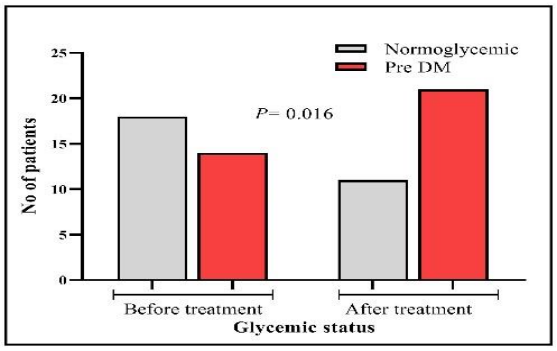

Figure 3: difference in the rate of pre DM before and after treatment according to McNemar's test.

Figures 4 and 5 showed that the longer the duration of treatment with octreotide LAR, the more significant the changes in the rate of conversion from normal glycemic status to pre-diabetic status, where the *P* value in the short duration of treatment (less than 1 year) was equal to 0.50 while it was 0.063 if the duration of treatment was more than 1 year. Although this change in both conditions was insignificant from a statistical point of view, the overall change was statistically significant (*P*=0.016) as shown in Figure 3.

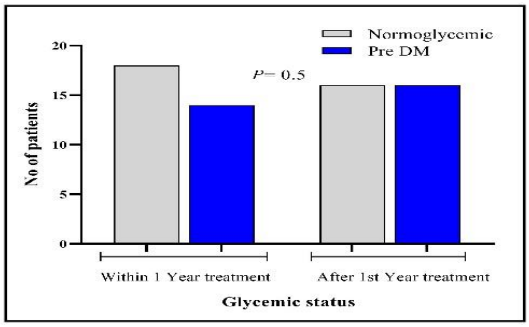

Figure 4: McNemar's test showed differences in the rate of pre DM within 1 year of treatment.

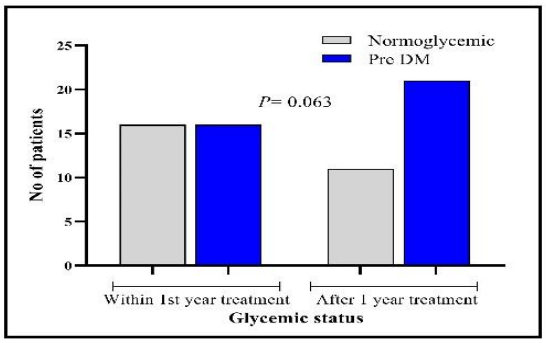

Table 5: McNemar's test showed the differences in the rate of pre DM within and after 1 years of treatment.

Table 2 summarizes the importance of the variables to glycemic status. It indicates that gender is insignificant

regarding the comparison between diabetes and prediabetes with patients having normal glycemic status. Meanwhile, a significant association was noticed between being male and getting prediabetes compared with diabetes status (*P*=0.039). The incidence of hypertension was significantly associated with getting DM in comparison with normal glycemic patients (*P*=0.007) and with pre-diabetic status (*P*=0.038). Patients with a positive family history were significantly more likely to develop prediabetes and diabetes than those with normal glycemic status, with *P* values of 0.008 and 0.001, respectively. No other significant associations were noticed between other studied variables and glycemic status (*P*>0.05). As shown in Table 3, a significant change was found in the rate of conversion from normal glycemic status to pre-diabetic status among male patients (*P*=0.031), and among patients with increased waist circumference (*P*=0.032). No significant changes were noticed in relation to other studied variables.

Table 2: Association between studied variables and glycemic status according to Fisher Exact test

Variables		Normal	Pre DM	DM	*P*-value
		n(%)	n(%)	n(%)	
Gender	Male	8(72)	17(81)	10(50)	0.039
	Female	3(27.3)	4(19)	10(50)	
P-value		Reference	0.467	0.275	
Age	<40yr	7(63.7)	9(42.9)	8(40)	1
	≥40	4(36.4)	12(57.1)	12(60)	
P-value		Reference	0.458	0.273	
IGF1	<twice normal	7(63.6)	12(57.1)	12(60)	1
	≥2 times normal	4(36.4)	9(42.9)	8(40)	
P-value		Reference	1	1	
Growth hormone	<3times	9(81.8)	8(38.1)	9(45)	0.755
	≥3 times	2(18.2)	13(61.9)	11(55)	
P-value		Reference	9	81.8	
Size of adenoma	Macroadenoma	9(81.8)	17(81)	15(75)	0.719
	Microadenoma	2(18.2)	4(19)	5(25)	
P-value		Reference	1	1	
Weight status	Non obese	5(45.5)	8(38.1)	5(25)	0.505
	Obese	6(54.5)	13(61.9)	15(75)	
P-value		Reference	0.721	0.423	
Waist circumference (cm)	normal	1(9.1)	2(9.5)	0(0)	0.488
	abnormal	10(90.9)	19(90.5)	20(100)	
P-value		Reference	1	0.355	
Hypertension	Normotensive	9(81.8)	12(57.1)	5(25)	0.038
	Hypertensive	2(18.2)	9(42.9)	15(75)	
P-value		Reference	0.248	0.007	
FH of DM	Negative FH	10(90.9)	8(38.1)	5(25)	0.505
	Positive FH	1(9.1)	13(61.9)	15(75)	
P-value		Reference	0.008	0.001	

DISCUSSION

According to the American Diabetes Association's diagnosis criteria, 79% of patients with acromegaly treated with octreotide LAR had DM, and 40% had prediabetes. According to other studies, the prevalence of DM and prediabetes in acromegaly patients is 15.5-50% and 25.8-44%, respectively. The current study's dysglycemia rate is within the upper range for both conditions, most likely due to ethnic differences in dietary habits and environmental factors. Diabetes mellitus was detected in all instances before starting octreotide LAR treatment, and no case progressed from normal glycemic or prediabetes condition to DM following treatment. Unlike diabetes, octreotide LAR treatment altered 13% of prediabetes from normal to prediabetes, a statistically significant rate. Among patients with normal glycemic control before SSA, 61% stayed stable and did not have aberrant glucose metabolism, while 39% developed prediabetes. The length of octreotide LAR treatment was found to be statistically negligible (*P*=0.063). After SSA treatment, all instances of prediabetes remained in the same group. The effects of somatostatin analogs on glucose metabolism are mixed. Several investigations found no effect of SSA on glucose levels. A meta-analysis found that SSA may have a small impact on glucose homeostasis in acromegaly patients. Another study found that SSA therapy improves glucose metabolism in patients with acromegaly and glucose dysregulation. Other research has shown that SSA treatment worsens glucose tolerance in acromegaly patients, necessitating glucose monitoring [12-16]. Because SSA suppresses insulin secretion, it also inhibits glucagon secretion (which reduces gluconeogenesis and glycogenolysis) and

growth hormone concentration, enhancing insulin sensitivity. Positive and negative impacts may contribute to the net glycometabolic consequence. In addition to acromegaly and its treatment modalities, various risk factors for impaired glucose homeostasis other than acromegaly and its treatment modalities may have influenced the results.

Table 7: McNemar's test showed differences in rate of pre DM before and after treatment according to studied variables

Characteristics	Variables	Before treatment	Total	After treatment		P-value
				Normal	Pre DM	
				n(%)	n(%)	
Gender	Male	Normal	14	8(100)	6(35.3)	0.031
		Pre DM	11	0(0.0)	11(64.7)	
	Female	Normal	4	3(100)	1(25)	1
		Pre DM	3	0(0.0)	3(75)	
Age	<40yr	Normal	11	7(100)	4(44.4)	0.125
		Pre DM	5	0(0.0)	5(55.6)	
	≥40	Normal	7	4(100)	3(25)	0.25
		Pre DM	9	0(0.0)	9(75)	
IGF 1	<twice normal	Normal	11	7(100)	4(33.3)	0.125
		Pre DM	8	0(0.0)	8(66.7)	
	≥2 times normal	Normal	7	4(100)	3(33.3)	0.25
		Pre DM	6	0(0.0)	6(66.7)	
GH	<3 times normal	Normal	11	9(100)	2(25)	0.25
		Pre DM	6	0(0.0)	6(75)	
	≥3 times normal	Normal	7	2(100)	5(38.5)	0.063
		Pre DM	8	0(0.0)	8(61.5)	
Size of adenoma	Macroadenoma	Normal	14	9(100)	5(29.4)	0.063
		Pre DM	12	0(0.0)	12(70.6)	
	Microadenoma	Normal	4	2(100)	2(50)	0.500
		Pre DM	2	0(0.0)	2(50)	
Waist circumference	normal	Normal	2	1(100)	1(50)	1
		Pre DM	1	0(0.0)	1(50)	
	abnormal	Normal	16	10(100)	6(31.6)	0.032
		Pre DM	13	0(0.0)	13(68.4)	
Weight status	Non obese	Normal	8	5(100)	3(37.5)	0.250
		Pre DM	5	0(0.0)	5(62.5)	
	Obese	Normal	10	6(100)	4(30.8)	0.125
		Pre DM	9	0(0.0)	9(69.2)	
Blood pressure	Normotensive	Normal	12	9(100)	3(25)	0.250
		Pre DM	9	0(0.0)	9(75)	
	Hypertensive	Normal	6	2(100)	4(44.4)	0.125
		Pre DM	5	0(0.0)	5(55.6)	
FH of DM	negative FH	Normal	12	10(100)	2(25)	0.500
		Pre DM	6	0(0.0)	6(75)	
	positive FH	Normal	6	1(100)	5(38.5)	0.063
		Pre DM	8	0(0.0)	8(61.5)	

The failure to detect DM after octreotide LAR treatment may be explained by another study's result that SSA treatment does not permanently alter glycemic status in managed acromegaly [17]. Except for being male, being male is statistically significant for getting prediabetes compared to diabetes and for the rate of conversion from normal glycemic to prediabetic status in the current study. As in our study, the male to female ratio in diabetic patients was not statistically different from non-diabetic patients, nor was being older in the diabetes and prediabetes categories [18,19]. Another study found that patients with diabetes were older than those in the other groups, and that the proportion of women in the DM and prediabetes groups was higher than in the normal glucose tolerance group [20,21]. The small sample size and predominance of male patients evaluated possibly explain the discrepancies between our study and others (67.3% of males vs. 32.7% of females). Contrasting DM with prediabetes and normal glycemic status subgroups, the current study found that hypertension was correlated with DM, while family history was associated with both DM and prediabetes. These findings matched those of earlier investigations [22,23]. The present study identified no changes in IGF1 and GH levels or pituitary tumor size between patients with glucose problems and those who were not [24-26]. Conversely, other researches indicated that IGF1 levels but not GH levels predicted impaired glucose metabolism, while other studies found that greater GH levels predicted an increased prevalence of DM [27-29]. In uncontrolled DM, these disparities may be related

to disease severity, the onset of glucose tolerance problems, the projected duration of acromegaly, and the existence of hormone-altering variables. Moreover, heterogeneity in commercially available GH and IGF1 kits may have muddled the function of hormone concentrations in DM [30,31]. Our investigation identified a non-significant link between obesity and glucose metabolism abnormalities, which is consistent with another study that reported no changes in BMI between individuals with impaired fasting glucose/DM and those without carbohydrate metabolism abnormalities [32]. In contrast, Ronchi *et al*. found an elevated BMI to be a major risk factor for DM in acromegaly patients [33]. Obesity prevalence even in normoglycemic patients with acromegaly reached 54.6% of patients with normal glycemia in our study, the possible predominance of other risk factors for DM in the studied population, and considering the increased BMI as 30, while overweight patients (BMI=25.0-29.9) were considered within the non-obese group during. A significant change in the rate of conversion from normal to pre-diabetic status among individuals with increasing waist circumference makes it statistically non-significant as a risk factor for glucose metabolism imbalance. No other studies have studied this parameter; hence the value was not compared.

Conclusions

Acromegaly individuals frequently have glucose metabolism issues. Prediabetes is substantially related with octreotide LAR use (independent of treatment duration) and maleness. A higher incidence of shift from normal to prediabetes after octreotide LAR treatment is associated with male sex and waist circumference. Family history is connected with both prediabetes and DM, while hypertension is associated with DM. A favorable glycometabolic net result is evidenced by the stability of prediabetes and most normoglycemics before and after treatment.

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Conflicting interests

Nothing declared by the authors.

Data sharing statement

Supplementary data can be requested from the corresponding author.

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