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Prevalence of glucose intolerance and hypertension of patients with acromegaly in Iraq

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Abstract

Acromegaly is a chronic endocrine disorder caused by hypersecretion of growth hormone (GH) mostly because of pituitary adenoma.

Aim: This study designed to identify the prevalence of glucoseintolerance and hypertension in Iraqi patients with acromegaly and to identify the impact of treatment modalities for acromegaly on glucose intolerance.

Study design:A case control study

Patients and Methods:from Jan. -Dec. 2017 68 patients with acromegaly enrolled from 2 centers compared with 68 non acromegalic subjects. Mean age 46 +/-11 years .57.4%males. The mean disease duration 7.97+/- 6.86 years).FBS, during GTT and HbA1c conducted, measurement of systolic and diastolic blood pressure with other variables.

Results:

Normoglycemia diagnosed in 41.2%.Glucose intolerance found in 58.8% of these; 44.1% vs.17.6% had diabetes and14.7% vs. 13.2% prediabetes (IFG and/or IGT) compared with control (P; =0.002).There was no statistically significant differences in age, gender, duration or activity of the disease, basal or last GH or IGF-1 between normoglycemic patients and those with glucose intolerance. Hypertension found in 39.7%vs 19.1%of control (P =0.008).

Conclusion

The prevalence of both glucose intolerance and hypertension in patient with acromegaly were 2 times higher than general populations. Diabetic and prediabetic patients had higher BMI ,but there are no statistically significant differencesin age, gender adenoma size ,duration of disease ,activity of disease or level of (both GH, or IGF1)between normoglycemic patients and patients with glucose intolerance.The treatment modalities (medical ,neurosurgical or radiotherapy) have no impact on glucose intolerance.

Key-words: DM, diabetes mellitus, impaired glucose tolerance, impaired fasting glucose, HbA1c, hypertension, acromegaly

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Introduction

Acromegaly is a chronic endocrine syndrome caused by growth hormone (GH) hypersecretion from pituitary adenoma (mostly macroadenoma).GH induces the formation of Insulin like Growth Factor1 (IGF1) from the liver [1]. Acromegaly is frequently associated with glucose intolerance. While the development of frank diabetes mellitus (DM) has been frequently assessed in patients with acromegaly, with estimates of 19 to 56% [2].

The increment of GH levels is responsible for insulin resistance in the liver and peripheral tissues, which leads to glucose intolerance or frank DM[3].type 2 DM and Impaired glucose tolerance (IGT) is aknown risk factor of premature atherosclerosis as well as the propensity to develop type 2 DM[4].

Arterial hypertension is commonly found in patient with acromegaly, occurring in approximately 1/3 of the patients, and has a major role on acceleration of atherosclerosis [5].

However the proper GH &IGF1control of hypersecretion will control on these comorbidities to some degree, but sometimes it may persist even with GH and IGF1 control[6].

Patients and method

This is a case control study in which 68patients with acromegaly were enrolled in this study compared with 68 non-acromegalic subjectsfrom January 2017- December 2017 from 2 endocrinology specialized centers.

The enrolled subjects were already diagnosed as acromegaly clinically ,biochemically andradiologically. The diagnosis of acromegaly was based on unsuppressed GH level after OGTT (>1.2 mUI/L) and increased IGF-1 value for age and sex; fortified by detection of pituitary adenoma by MRI either macroadenoma(>10mm) or microadenoma(<10mm).

The activity of acromegaly was assessed as described in the 2009 international consensus statement [7].The collection of data in regard of age per years, sex, height, weight, systolic and diastolic blood pressure (a mean of 3 measurementsin 3different times) ,duration of acromegaly, size of tumor (micro-or macroadenoma),history of hypophysectomy, radiotherapy,medical therapy (total dose for each patient) GH level in 1stand last visits(by chemiluminescent immunoassay), IGF1 in 1st and last visits (according to sex and age matched limits measured by immunochemiluminomertic assay).

Blood glucose inFasting and2 hours post Glucose Tolerance Test in mg/dl , (GTT) and hemoglobin A1c (HbA1c) conducted to all subjects in the study (patients and control).

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Prediabetes (IFG and IGT) and Type 2 DM were diagnosed according to the American Diabetes Association (ADA) recommendations 2017[8].

Continuous variables were expressed by mean +/- SD while categorical variables as percentage ,all these collected data and variables analyzed by using crosstab chi square test for categorical variables or Student's paired t-test for continuous variable and ANOVA test between categorical and continuous variables .The value of <0.05 considered as statistically significant.

Results:

Sixty eight patients with acromegaly enrolled in this study;their mean age 46 +/-11years.Thirty nine (57.4%) males and 29(42.6%)females.Disease duration range from 1year -30years (mean 7.97+/- 6.86 years).AGH producing macroadenoma was the cause of acromegaly in 60 patients (88.2%) and in the remaining 8(11.7%) had microadenoma. Thirty-four(50%) underwent neurosurgical treatment (hypophysectomy). Seven patients (10.2%) exposed to radiotherapy.

Hypophysectomy, radiotherapy and/or medical therapy for acromegaly induced a significant reduction of mean GH and IGF-1 levels (28.34 +/- 25.84 vs. 4.68 +/- 6.72 ng/ml, p< 0.001 and 792+/- 516.35 vs. 414.6 +/- 275.7 ng/ml, p < 0.001 respectively)(figure 1), but both GH and IGF-1 values normalized only in 11 (16.1%);while the remainder 57(83.9%) had active disease.

The control group was composed of 68 non-acromegalic subjects36 (52.9% females)and 32 (47.1%) male with a mean age of 45+/-11 years.

Normoglycemia diagnosed in 28(41.2%).Glucose intolerance found in 40(58.8%) of these; diabetes diagnosed in 30(44.1%) and 10(14.7%) had prediabetes (either IFG,IGT or both) in comparison with control group which had diabetes in 12(17.6%) and prediabetes in 9(13.2%) which was statistically significant (P value; =0.002).So, the prevalence of glucose intolerance in acromegaly isabout 2time higher than in the general populations.

As well as hypertension found in 27(39.7%) patients that was statistically significant in comparison with control group that had hypertension in 13 (19.1%),P value , =0.008) (table 1).So, the prevalence of hypertension in acromegaly is about 2 time higher than in the general populations

Table (2) shows the comparative characteristics of patients with acromegaly and matched participants control group.

Fasting blood sugar, blood sugar 2 hour post glucose tolerance test and HbA1cwere significantly different between acromegaly group versus control group (p<0.0001 for all).The height ,systolic and diastolic blood pressure were significantly different between patient of acromegaly versus control group (p=

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0.011,P=0.011, and P=0.005 respectively) which explain the significant prevalence of hypertension (both systolic and diastolic)in patients with acromegaly versus general populations.

In table (3), the patients subdivided according to glucose intolerance. FBS, 2 hour post GTT and HbA1c was significantly different among all 3 group (p value <0.0001 for each one). Body weight and BMI were significantlyhigh in diabetes and prediabetes groups (P value <0.0001 for both).

We could not found statistically significant differences in age ,gender ,basal or last GH,basal or last IGF1,disease duration ,adenoma size ,and activity of disease between patient with normoglycemia and patients with glucose intolerance.

Interestingly, we couldn't found any relationship between glucose intolerance and medical treatment (table 3), surgical treatment or radiotherapy (table 4); that may exhibit the safety of these treatment modalities on glucose metabolism despite significant reduction of both GH &IGF1 (figure 1).

In (table 5); the comparison conducted between hypertensive and non-hypertensive patients. Hypertensive patients were older, female predominant and shorter stature than non-hypertensive patients(p value ;0.008, 0.006 and 0.007 respectively).While there were no statistically significant differences indisease duration or disease activity, GH (basal or last)or IGF1(basal or last) between hypertensive and non-hypertensive patient with acromegaly.

Discussion

This study conducted on Iraqi patients with acromegaly in comparison with non-acromegalic subjects to assess the prevalence of both glucose intolerance and hypertension in patients with acromegaly; as these are the most important risk factors for development of atherosclerosis.Most of our patients had glucose intolerance (58.8%);of these 44.1% had frank diabetes and 14.7% had prediabetes (both IFG and IGT),while the remainder 41.2% had normoglycemia.

However our results can be accepted if we compared it with previous studies results like Dreval et al.[9]which found 52.5% of patients had DM and26% of subjects had either IFG or IGT. In Biering H. et al study [10] 40.5% of the patients hadDM and in 28.2% had prediabetes.

While the comparison with old studies may be difficult because of the revised criteria for the diagnosis of diabetes, like Emmer study [11]. Our patients with glucose intolerance (both DM and prediabetes had higher weight and BMI than patients with normoglycemia; these result also observed in other studies [12].

We could not found statistically significant differences in age, gender, basal or last GH, basal or last IGF1, disease duration, adenoma size, and activity of disease between patient with normoglycemia and patients with glucose intolerance like Stelmachowska-Banaś M, et al study [13] and Fieffe et al. [14]

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Interestingly,we could not found statistically significant differencesbetween glucose intolerancefrom one side and medical treatment,surgical treatment or radiotherapy on the other side despite significant reduction of both GH and IGFlike other reports[15].

Arterial hypertension (both systolic and diastolic) hypertension diagnosed in (39.3%) of patient with a significant prevalence in comparison with general population. While the majority of our patients were normotensive (60.7%). These results like other reports that noted the prevalence hypertension were 35.4% [15].

Hypertension presented in our patients with middle age group (40-60), female predominance and shorter staturebut there were no significant relationship between hypertension and GH (first or last) or IGF1 (first or last);in accordance to other studies[16].

We fail to found a significant correlation between hypertension (whether systolic or diastolic) and glucose intolerance.

Conclusion:

The prevalence of glucose intolerance in patient with acromegaly is 2 times higher than general populations.Patients with glucose intolerance (both prediabetes and DM) were more obese and had higher BMI ,but we could not found statistically significant differences in age ,gender ,basal or last GH, basal or last IGF1,disease duration ,adenoma size ,and activity of disease between patient with normoglycemia and patients with glucose intolerance. The treatment modalities (medical ,neurosurgical or radiotherapy) have no impact on glucose intolerance. The prevalence of hypertension in acromegaly were 2 times higher than general population. Hypertensive patient were mainly female gender ,in middle age group and shorter stature. There were no statistically significant differences in duration or activity of the disease or level of hormones (both GH, or IGF1)between hypertensive and non-hypertensive acromegalic patients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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Table 1: significance of difference in the prevalence of diabetes and hypertension between acromegaly and control group:

			Presence of acromegaly		P value*
			Acromegaly group	Control group	
Diabetes	Non diabetics	No	28	47	0.002*
		%	41.2%	69.1%	
	Dm	No	30	12	
		%	44.1%	17.6%	
	Prediabetes	No	10	9	
		%	14.7%	13.2%	
	Total	No	68	68	
		%	100.0%	100.0%	
Hypertension	hypertensive	No	27	13	0.008*
		%	39.7%	19.1%	
	not hypertensive	No	41	55	
		%	60.3%	80.9%	
	Total	No	68	68	
		%	100.0%	100.0%	

* Pearson's Chi square.

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Table 2: Comparative characteristics of patients with acromegaly and matched participants in control group

Characteristics	Group	Mean	Std. Deviation	P value*
age	acromegaly group	46.04	11.038	0.778
	control group	45.49	11.203	
Body mass index	acromegaly group	29.1482	4.92939	0.358
	control group	28.19	5.721892	
HbA1c	acromegaly group	6.9369	1.93585	0.0001*
	control group	5.6294	1.67377	
FBS	acromegaly group	123.99	34.109	0.0001*
	control group	100.71	23.769	
2hr post GTT	acromegaly group	187.46	70.976	0.0001*
	control group	137.29	59.222	
Height	acromegaly group	169	6.079	0.011
	control group	171.81	5.66	
Weight	acromegaly group	83.1176	13.83865	0.955
	control group	83.29	17.611	
Systolic BP	acromegaly group	132.34	23.482	0.011
	control group	122.35	21.914	
Diastolic BP	acromegaly group	86.79	17.005	0.005
	control group	77.84	15.912	

*Paired T-test

Table (3)General characteristics of the different groups of patients with acromegaly subdivided according to Glucose intolerance:

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	Normoglycemic	Diabetes	Prediabetes	Total	P value
Number	28	30	10	68	
Gender (Male/Female)	19/9	15/15	5/5	39/29	0.342*
Age /years	45.75 +/- 10.47	48.30 +/- 11.87	40.10 +/- 8.24	46.04 +/- 11.04	0.124†
FBS Mean +/- SD in mg/dl	91.18 +/- 5.257	158.6 +/- 18.205	112 +/- 2.867	123.99 +/- 34.109	0.0001†
2hrs post GTT Mean +/- SD in mg/dl	113.39+/- 10.001	260.87 +/- 24.358	174.6 +/- 8.784	187.46 +/- 70.976	0.0001†
HbA1c Mean +/- SD	4.97 +/- 0.23	8.96+/-0.72	6.36+/- 0.06	6.93+/-1.93	0.0001†
Age /years Mean +/- SD	45.75+/- 10.466	48.3+/- 11.87	40.1+/- 8.239	46.04+/- 11.038	0.124†
Height/cm Mean +/- SD	169.5+/- 6.506	168.33+/- 6.036	169.6+/- 5.296	169+/- 6.079	0.729†
Weight/Kg Mean +/- SD	74.39+/- 9.87	89.03+/- 11.36	89.8+/- 17.71	83.11+/- 13.83	0.0001†
BMIMean +/- SD	25.98+/- 3.95	31.46+/- 4.20	31.05+/- 4.90	29.14+/- 4.92	0.0001†
SBP mmHg Mean +/- SD	137.25+/- 24.942	127.37+/- 22.177	133.5+/- 22.242	132.34+/- 23.482	0.277†
DBP mmHg Mean +/- SD	87.14+/- 17.29	84+/- 14.994	95+/- 21.36	86.79+/- 17.005	0.235†

* Pearson's Chi square.

† ANOVA test

Table (4) Specific characteristicsofthe different groups of patients with acromegaly subdivided according to glucose intolerance:

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	Normoglycemic	Diabetes	Prediabetes	Total	P value*
Number	28	30	10	68	
Duration of disease /years (mean +/- SD)	8.86 +/- 7.08	7.3 +/- 6.587	7.5 +/- 7.487	7.97 +/- 6.861	0.676
Total dose of Sandostatin (mean +/- (SD	748.57 +/- 546.15	658.33 +/- 414.447	723 +/- 485.113	705+/- 477.47	0.771
First GH (mean +/- SD)	25.6089+/- 25.86	29.0+/- 25.22	33.98+/- 29.21	28.34 +/- 25.84	0.673
(Last GH (mean +/- SD	4.946 +/- 7.93	4.024 +/- 4.52	5.90+/- 8.87	4.68 +/- 6.72	0.725
First IGF1(mean +/- (SD	812.53 +/- 624.94	801.04 +/- 444.46	707.4+/- 408.80	792.0+/- 516.35	0.855
(Last IGF1(mean +/- SD	405.03 +/- 256.53	423.25 +/- 249.17	416.04 +/- 409.71	414.69 +/- 275.71	0.97

* ANOVA test.

Table (5) characteristics of variables of patients with acromegaly subdivided according to blood pressure status:

Variables		hypertension		Total	P value
		hypertensive	not hypertensive		
Glycemic status	Normoglycemic No.(%)	13(46.4%)	15(53.6%)	28(100.0%)	0.59*
	DM.No.(%)	10(33.3%)	20(66.7%)	30(100.0%)	
	Prediabetes No.(%)	4(40.0%)	6(60.0%)	10(100.0%)	
Age in years	Mean +/- SD	50.04 +/- 8.12	43.41 +/- 11.97	46.04 +/- 11.03	0.014†

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Age (in grouping) in years	20-40yNo.(%)	4(16.0%)	21(84.0%)	25(100.0%)	0.008*
	41-60y No.(%)	19(55.9%)	15(44.1%)	34(100.0%0	
	>60y No.(%)	4(44.4%)	5(55.6%)	9(100.0%)	
Gender	male No.(%)	10(25.6%)	29(74.4%)	39(100.0%)	0.006*
	Female no.(%)	17(58.6%)	12(41.4%)	29(100.0%)	
Height in cm	Mean +/- SD	166.59+/-5.36	170.59+/-6.058	169.0+/- 6.07	0.007†
Disease duration/years	1-10 y No.(%)	18(35.3%)	33(64.7%)	51(100.0%)	0.256*
	11-20 y No.(%)	6(46.2%)	7(53.8%)	13(100.0%)	
	21-30 y No.(%)	3(75.0%)	1(25.0%)	4(100.0%)	
Activity of disease	Active No.(%)	22(38.6%)	35(61.4%)	57(100.0%)	0.458*
	Inactive No.(%)	5(45.5%)	6(54.5%)	11(100.0%)	
First GH	Mean +/-SD	27.29 +/- 28.08	29.02 +/-24.59	28.43 +/-25.84	0.789†
Last GH	Mean +/-SD	6.58 +/-4.88	6.89 +/- 4.54	4.68 +/- 6.72	0.842†
First IGF1	Mean +/-SD	730.33 +/- 389.38	832.61 +/- 586.32	792.+/- 516.35	0.428†
Last IGF1	Mean +/-SD	470.43+/- 332.42	377.98 +/-228.07	414.69 +/- 275.71	0.178†

* Pearson's Chi square.

† ANOVA test

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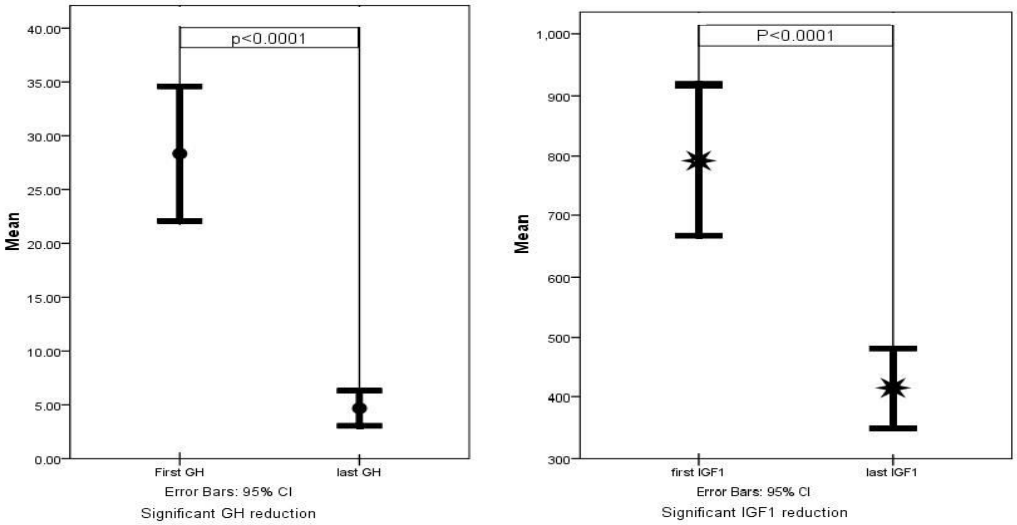

Figure (1) the significance of both GH and IGF1 reduction from first readings and last readings.

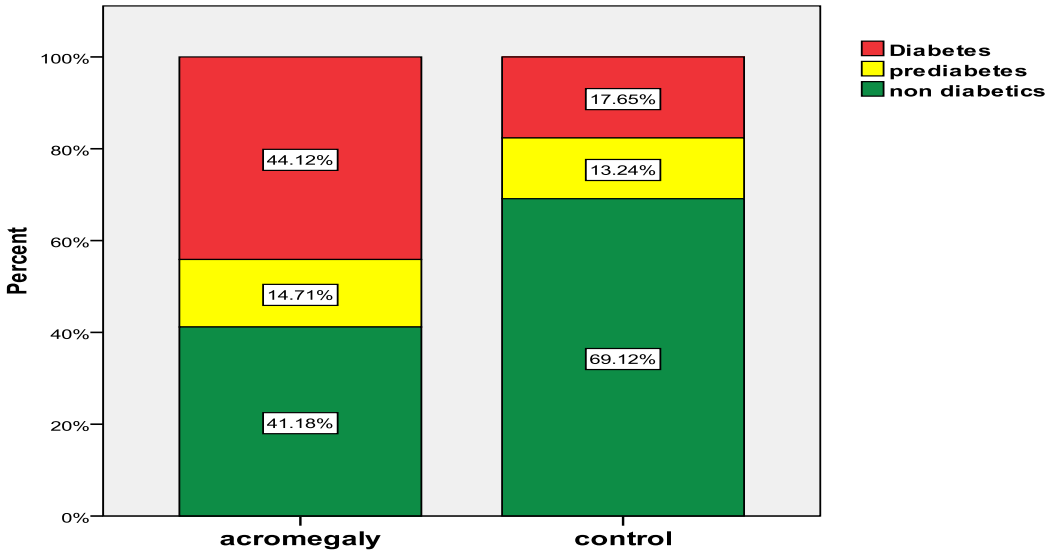

Figure (2): the comparison between the prevalence of glucose intolerance between acromegaly and control groups.