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Measurement of Arginase Activity in Sera of Iraqi Acromegaly Patients with Diabetes

Fatima Khazaal Malek^{1*}, Salma Abdul-Rudha Abbas¹, Baydaa Ahmed Abed^{1,2}

¹Department of Chemistry, College of Science, Mustansiriyah University, 10052 Baghdad, IRAQ.

²National Diabetes Center, Mustansiriyah University, Baghdad, IRAQ.

*Correspondent contact: fatima_khazaal@uomustansiriyah.edu.iq

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Abstract

The goal of this study was to measure arginase enzyme activity in diabetic acromegaly Iraqi patients and compare it to a control group. This study included 80 participants, whose ages ranged from 25 to 65, and was conducted on forty diabetic acromegaly Iraqi patients attending the national diabetes center of Mustansiriyah University in Baghdad and forty healthy individuals (as a control group). The results showed a highly significant reduction in arginase activity and High-density lipoprotein-cholesterol (HDL-C), Urea levels were reduced not significantly, whereas a highly significant increase in levels of Growth Hormone (GH), Insulin-Like Growth Factor-1 (IGF-1), Fasting Serum glucose (FSG), Total Cholesterol (TC), Triglycerides (TG), Low-density lipoprotein-cholesterol (LDL-C), and Very low-density lipoprotein-cholesterol (VLDL-C)) compared to control. A significant positive correlation was revealed between arginase activity and FSG levels in diabetic acromegaly patients. In conclusion, diabetic acromegaly patients had a significant decreased in serum arginase activity with no significant decrease urea levels, which indicates that their bodies store more nitrogen compounds to be utilized in constructing processes.

Keywords: Acromegaly, Growth Hormone, Insulin-Like Growth Factor-1, Arginase, Diabetes mellitus, Lipid profile.

الخلاصة

كان الهدف من الدراسة قياس نشاط انزيم الارجينيز في مرضى تضخم الاطراف المصابين بالسكري العراقيين ومقارنته بمجموعة ضابطة. وقد تضمنت الدراسة ٨٠ مشاركا تراوحت اعمارهم بين ٢٥ و ٦٥، حيث اجريت الدراسة على اربعين مريضا مصابا بتضخم الاطراف و السكري من الذين حضروا الى المركز الوطني لعلاج و بحوث السكري التابع للجامعة المستنصرية و اربعين من الاشخاص الاصحاء (كمجموعة ضابطة). اظهرت نتائج هذه الدراسة وجود انخفاض معنوي في كلا من فعالية الارجينيز والبروتين الدهني عالي الكثافة (HDL-C)، مستويات اليوريا كانت منخفضة بشكل غير معنوي، بينما كان هناك زيادة معنوية في مستويات هرمون النمو (GH)، عامل النمو شبيه الانسولين (IGF-1)، فحص السكر الصيامي (FSG)، الكوليسترول (TC)، الدهون الثلاثية (TG)، البروتين الدهني منخفض الكثافة (LDL-C)، والبروتين الدهني منخفض الكثافة جدا (VLDL-C) مقارنة بالمجموعة الضابطة. لقد وجدنا ارتباطا ايجابيا معنوي بين نشاط الارجينيز ومستويات FSG في مرضى تضخم الاطراف المصابين بالسكري. نستنتج ان مرضى تضخم الاطراف المصابين بالسكري لديهم انخفاض معنوي في نشاط ارجينيز المصل مع انخفاض غير معنوي في مستويات اليوريا، مما يشير إلى أن أجسامهم تخزن مزيدا من مركبات النيتروجين لاستخدامها في عمليات البناء.

INTRODUCTION

Acromegaly (ACRO) is an uncommon, complex hormonal illness that is defined as a chronic condition associated with increased GH and thus IGF-1, which is usually generated by a GH-secreting pituitary tumor. It has a multisystem influence, mainly on the musculoskeletal system, the brain, the heart, the respiration and

circulatory system, the kidneys, the liver and pancreas, the thyroid, adipose tissue, and the metabolism system. The ACRO can also lead to sexual impairment [1-6]. This unusual illness primarily affects adults. Untreated, it can lead to serious illnesses and shorten the probable average lifespan [7][8]. Gigantism is brought on by an excess of GH in early life [9]. On average,

40 to 70 people per million people have this disorder [10]. Growth hormone regulates a variety of physiological functions, such as those that impact bones, muscles, and fats, and ultimately contribute to growth. In most tissues, GH promotes anabolic action through metabolism, with the exception of adipose, where it promotes catabolic action by breaking down accumulated TG into free fatty acids (FFA) [11]. It works either directly through its receptors or indirectly by stimulating the synthesis of IGF-I. Their combined effects may encourage growth or they may have the opposite effect, as with the influence on glucose metabolism [12].

The IGF-1, a vital growth factor, controls the anabolic and catabolic processes in skeletal muscle. It also stimulates protein synthesis in skeletal muscle [13]. Its metabolic effects include reduced hepatic gluconeogenesis and glycogenesis at carbohydrate metabolism while driving enhanced glucose uptake, insulin sensitivity, and hypoglycemia. The IGF-I indirectly regulates glucose homeostasis by inhibiting GH and boosting insulin action [14-18]. A common ACRO consequence, diabetes mellitus (DM) has an incidence that ranges from 20 to 53%. [19][20]. It is one of the most prevalent endocrinopathies seen in clinical practice [21]. The DM is a clear medical problem in relation to ACRO. Insulin resistance, which is primarily caused by extended exposure to high levels of GH and its mediators, but it could also happen as an unwanted effect of ACRO therapy, impairs glucose metabolism in ACRO [22][23]. Insulin resistance plays a crucial role in the development of ACRO complications since ACRO is a rare condition characterized by high insulin resistance and low body fat [24].

Arginase (ARG) is a urea cycle hydrolase that converts L-arginine to urea and L-ornithine. Arginase1 (ARG1) and Arginase 2 (ARG2) are the two isoforms of mammalian arginase [25]. The ARG is crucial for controlling beta-cell function and insulin resistance [26]. Expression of ARG rises in a variety of pathological cases [27]. A recent study found that people with type 2 diabetes have significantly increased ARG activity [28]. The current study aims to measure

arginase activity in diabetic ACRO Iraqi patients and compare it to a control group.

MATERIALS AND METHODS

Patients and Control

This study included 80 participants, whose ages ranged from 25 to 65. The study was conducted on forty Iraqi diabetic acromegaly patients who attended the national diabetes center of Mustansiriyah University in Baghdad. Also, forty samples have been drawn from healthy volunteers as a control group. The participants were matched for age and gender.

Samples

From each subject, 10 ml of blood was drawn from a vein using disposable syringes, after an 8 to 10 hours fast, and were placed in a gel tube. After taking the blood sample, a 3000 rpm centrifuge was utilized to spin it for 10 minutes. The obtained serum was maintained at -20 °C in four Eppendorf containers until it was time for analysis. Acromegaly patients who did not have diabetes were excluded from the study.

Sample Analysis

Arginase activity was manually measured, based on the idea that just ornithine forms a red product with ninhydrin with the highest absorbance of about 515 nm under the influence of concentrated acetic acid, the amount of ornithine produced is used to estimate enzyme activity using Porembaska's approach. Even at quantities several times greater than those found in serum, urea does not effect on the development of color [29]. Human GH and IGF-1 serum concentrations were measured using a solid-phase ELIZA kit given by DRG Company /Germany. Kenza240 TX Biolabo kit was utilized to assay FSG, urea, TC, TG, and HDL-C.

Statistical Analysis

Version (26) of the Statistical Package of Social Science (SPSS) was used to analyze the data. The relationship between the data was evaluated using the correlation and independent-samples student's t-test. A p-value of equal to or less than 0.05 was considered significant, whilst one greater than 0.05 was considered non-significant.

RESULTS AND DISCUSSION

Table 1 illustrates that alterations in age between the control group 44.69 ± 10.30 years and ACRO patients 49.63 ± 8.96 years were not significant ($p > 0.05$). The value of BMI was elevated significantly $p < 0.0001$ in ACRO patients 33.32 ± 3.54 kg/m^2 compared to the control 24.30 ± 2.05 kg/m^2 .

This increase was explained by the favorable correlation between body weight and bone mineral density rather than obesity. Abdullah *et al.* [30] observed that BMI was considerably greater in ACRO patients when compared to the control group, which is consistent with our findings.

Table 2 illustrates that ARG activity was significantly $p < 0.0001$ decreased in the ACRO patients 3.45 ± 1.30 compared to control 5.98 ± 2.39 . While the levels of GH in ACRO patients 4.44 ± 1.49 were significantly $p < 0.0001$ raised compared to the control 1.02 ± 0.37 , Levels of IGF-1 in ACRO patients 595.45 ± 274.04 were significantly $p < 0.0001$ raised compared to control 259.25 ± 53.94 , Levels of FSG in ACRO patients 215.96 ± 81.87 were higher significantly $p < 0.0001$ than in control 87.80 ± 5.17 , and no statistically significant $P > 0.05$ differences were noticed in the levels of serum urea between control 28.70 ± 6.32 and ACRO patients 28.51 ± 9.21 .

To our current knowledge, it is the first research about arginase activity in patients with acromegaly. Our findings found that arginase activity was decreased (GH suppresses arginase enzyme activity) to prevent the body's nitrogen molecules from being depleted through the urea cycle and to enable the body to employ nitrogen-containing proteins for construction. The GH which is overproduced encourages nitrogen retention in combination with IGF-1 and insulin [15]. Insulin resistance, hyperinsulinemia, and the possibility of developing diabetes are all caused by prolonged GH signaling, which blunts the effects of insulin on glucose metabolism [31][32]. According to Hussain, there is a significant positive correlation between arginase activity and hyperglycemia [33]. This increase of GH in patients compared to control induced by the interior loop of active pituitary tumor. Hameed *et al.* [34] reported that GH in ACRO patients was higher compared to the control. It is wealth to mention that the study of Hameed *et al.* [34] was in agreement with our findings. In the same manner, Hameed *et al.* [35] and Abdullah *et al.* [30] found that IGF-I levels in ACRO patients were higher compared to the control, these studies concur with our results. The present investigation found that FSG levels in the patients group were significantly higher than control. Also, Hameed's study [36] reported that FSG levels in patients were considerably greater compared to the control.

Table 1. Characteristics of the participants in the study.

Groups		Control (N = 40)		ACRO (N = 40)		p-value
		Means ± SD		Means ± SD		
Parameters						
Age year		44.69±10.30		49.63±8.96		NS
BMI kg/m²		24.30±2.05		33.32±3.54		0.0001*
		NO.	%	NO.	%	
Gender	Male	20	50%	19	47.5%	
	Female	20	50%	21	52.5%	

*ACRO, Acromegaly; BMI, Body Mass Index.

Table 2. Arginase activity, GH, IGF-1, FSG, and Serum Urea levels.

Table 2: Arginase activity, GH, IGF-1, IGF, and serum GH levels.			
Groups Parameters	Control (N = 40)	ACRO (N = 40)	p-value
	Means ± SD	Means ± SD	
Arginase U/L	5.98±2.39	3.45±1.30	0.0001*
GH ng/mL	1.02±0.37	4.44±1.49	0.0001*

IGF ng/mL	259.25±53.94	595.45±274.04	0.0001*
FSG mg/dL	87.80±5.17	215.96±81.87	0.0001*
Serum Urea mg/dL	28.70±6.32	28.51±9.21	NS

*ACRO, Acromegaly; GH, Growth Hormone; IGF-1, Insulin-Like Growth Factor-1; FSG, Fasting Serum Glucose; NS, not significant.

Mahmood *et al.* [37] FSG levels were markedly higher in ACRO patients than in the controls. The previous investigations are in agreement with the findings of the present study.

The present investigation showed that levels of serum urea in patients were not considerably lower than in the control. Moller *et al.* [38] found that GH has an impact on protein metabolism via increasing protein production, reducing breakdown in muscles and throughout the body, as well as reducing hepatic urea generation and amino acid degradation/oxidation. Hamwi *et al.* [39] found that ACRO patients had decreased blood urea nitrogen levels. Table 3. summarizes the lipid profile levels in ACRO patients and control.

The results revealed a significant increase in TC, TG, LDL-C and VLDL-C with a significant decrease in HDL-C in ACRO patients group compared to control group.

This study found that TC, TG, LDL-C, and VLDL-C levels in the ACRO patients were significantly greater than the control, while levels of HDL-C were reduced in patients compared to the control. A recent study conducted by Hameed [36] reported raised levels of TC, TG, LDL-C, VLDL-C, and reduced HDL-C levels in patients compared to control, which agrees with our results.

Table 4 presented the correlation study of arginase activity with the other parameters in the study. Figure 1 illustrates the strong correlation between arginase and FSG levels in patients ($r=0.346$, $p\text{-value}=0.029$).

Table 3. Lipid profile levels.

Parameters	Control (N = 40)	ACRO (N = 40)	p-value
	Means ± SD	Means ± SD	
TC mg/dL	146.20±12.94	216.88± 19.73	0.0001*
TG mg/dL	104.23±22.09	179.20± 43.02	0.0001*
HDL-C mg/dL	48.06± 5.64	35.65± 5.61	0.0001*
LDL-C mg/dL	77.37± 11.75	145.40±18.68	0.0001*
VLDL-C mg/dL	20.85± 4.40	35.83± 8.61	0.0001*

*ACRO, Acromegaly; TC, Total Cholesterol; TG, Triglycerides; HDL-C, High-density lipoprotein-cholesterol; LDL-C, Low-density lipoprotein-cholesterol; VLDL-C, very low-density lipoprotein-cholesterol.

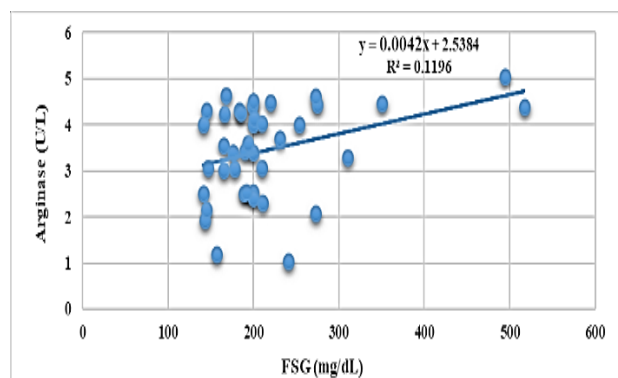


Figure 1. The correlation between arginase activity and FSG in serum of acromegaly patients.

Table 4. Correlation of Arginase with other study's

Parameters	Arginase	
	r	p
Age	-0.106	0.517
BMI	-0.117	0.473
GH	-0.075	0.646
IGF-1	-0.086	0.597
FSG	0.346*	0.029
TC	-0.241	0.134
TG	0.077	0.635
HDL-C	0.064	0.697
LDL-C	-0.310	0.051
VLDL-C	0.080	0.624
Serum Urea	0.134	0.410

CONCLUSIONS

The current study concluded that diabetic ACRO patients had significantly decreased serum arginase activity with not significantly decreased serum urea, which indicates that their bodies store more nitrogen compounds to be utilized in constructing processes. A positive correlation was found between arginase and FSG in the ACRO+DM group.

Disclosure and Conflict of Interest: The authors declare that they have no conflicts of interest.

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