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Assessment of Obesity, Dyslipidemia, Hyperglycemia, and Pro-Inflammatory Cytokines as Cardiovascular Disease Risk Factors in Acromegaly Patients

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Abstract:

Cardiovascular disease is one of the most common comorbidities associated with enlarged extremities, occurring in 60 % of patients with acromegaly. The aim of this study is to evaluate the relationship of growth hormone and insulin such as growth factor-1 with obesity, dyslipidemia, hyperglycemia, and pro-inflammatory cytokines (IL-2, IL-6, IL-10), as risk factors for cardiovascular disorder in acromegaly patients. Eighty subjects were included and categorized into two groups: 40 acromegaly patients and 40 of the control group. The results indicated weight excess, hyperglycemia, hypertension, lipid disorder, and elevated levels of interleukins (2, 6, and 10). The correlation of both GH and IGF-1 with each of weight, BMI, systolic blood pressure, diastolic blood pressure, FBS, HbA1c, cholesterol, triglyceride, LDL, IL6, IL2, and the atherogenic index was found to be positive and significant. Meanwhile, only IGF-1 was significantly correlated with IL10. We conclude that elevated levels of IL2, IL6, IL 10 and their association with both GH and IGF-1 as well as to lipid disorder, hyperglycemia, and hypertension criteria of acromegaly patients are all risk factors for cardiovascular disease, suggesting the necessary clinical examination for cardiovascular disorder in patients with acromegaly patients.

Keywords: Acromegaly, Cardiovascular, Growth hormone, Insulin-like growth factor-1, Interleukin

Introduction:

Acromegaly is a chronic systemic disease caused by the benign pituitary adenoma secreting growth hormone (GH) in excess, whose peripheral effect is mediated by insulin-like growth factor 1 (IGF-I) produced by the liver¹. The incidence of acromegaly is 3-5 million / year, with a 40-130 million prevalence². Although acromegaly has a broad variety of clinical manifestations, enlarged soft tissue and acral, joint pain, heart and respiratory failure, diabetes, high blood pressure are the salient signs, leading to increased morbidity and mortality¹. For all patients with clinical features of acromegaly (such as mass tumor symptoms, systemic effects of excess GH / IGF-1, Heart and vascular properties, and manifestations of respiratory and bone joint and or the consequences of other endocrine), screening is recommended. However, screening for patients with many medical conditions known to be

associated with acromegaly can also be suggested³. One of the most common comorbidities associated with acromegaly is cardiovascular disease, occurring in 60 percent of acromegaly patients. Cardiovascular conditions in patients with acromegaly serve as a detrimental predictor of life expectancy in acromegaly patients. Biventricular hypertrophy, common cardiomyopathy, is linked to acromegaly, and hypertension is one of the most common cardiovascular syndromes⁴. Valvular defects, arrhythmias, endothelial dysfunction, heart failure, lipid disorder, and coronary artery disease are all important risk factors.⁵ Numerous studies have established that systemic inflammation is closely linked to the development of CVD in recent years^{6,7}. There are numerous reports on the interactions between the immune and endocrine systems, especially the axis of growth hormones.

Growth hormone works primarily indirectly through insulin-like growth factor-1, which activates the processes of growth and development, lipid, protein, and carbohydrate metabolism, and also has a modulating effect on immune system cells⁸ IL6 has both pro-and anti-inflammatory properties. In 1990, the first connection between IL-6 and cardiovascular disease was discovered in clinical practice⁹. Both GH and IGF-1 influence the development of ex vivo cytokines, but only when used as a co-stimulus with more potent inflammatory stimuli. Anti-inflammatory IL-10 has a short-term response to the pro-inflammatory effects of GH and IGF-1.⁷ Thus this study was designed to evaluate the relationship of growth hormone and insulin-like growth factor-1 with obesity, dyslipidemia, hyperglycemia, and pro-inflammatory cytokines (IL-2, IL-6, IL-10), as risk factor for cardiovascular disorder in acromegaly patients.

Materials and Methods:

A case – control study was carried in this study in which 80 subjects were collected from March 2020 to July 2020, and grouped into two categories: (40) acromegaly patients as cases diagnosed depending on the levels of GH and IGF-I, and tumor size. Forty healthy subjects without any systemic disease were termed as control group. This study was conducted at National Diabetes Center for Research and Treatment/Mustansiriyah University. The ages of the subjects ranged (30 - 59 years) with mean value of 42.3 year, and was matched with the control group. Five milliliters of venous blood was obtained from patients and control group using 5 ml disposable syringe drained into plain tubes and left in room temperature (25C°)

for 15 minutes, then it was centrifuged at 2000 xg for 10 minutes in order to collect sera. To avoid multiple freezing, they were melted and kept frozen. For further experiment sera aliquots were placed in Eppendorf tubes and stored at -40C° until used. Age, systolic blood pressure, diastolic blood pressure, weight, and height were recorded. Based on measurements of height and weight, BMI was also calculated. Serum of growth hormone, insulin-like growth factor-1, IL2, IL 6, IL10 was determined by using enzyme-linked immunosorbent assay (ELISA) for in vitro diagnostic quantitative, manufactured by MyBioSource. Fasting blood sugar and lipid profile was done by Roche/Hitachi Cobas c 311device. Atherogenic index (AI) was estimated by $AI = \log TG \setminus HDL$. Analysis of data was carried out by using the available Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA, version 23.0) was used. The quantitative variables (measured parameters) were expressed as means \pm standard deviation (SD), (Student t-test) was used to compare between means (P-value \leq 0.05 has been deemed to be statistically significant). The relationship between the variables was measured by Pearson linear correlation.

Results:

Table 1 shows that the following variables: weight, BMI, SBP, FBS, HbA1C%, TC, TG, LDL, GH, IGF-1, IL6, IL2, IL10, AI, Apo A and Apo B were significantly higher in acromegaly patients than in healthy subjects (all P values < 0.050) . However, only HDL was significantly lower in acromegaly patients than in healthy subjects (P<001). Nevertheless, the differences of height and DBP between both groups were not found to be significant (P- values 0.86 and 0.1, respectively).

Table 1. statistical analysis of anthropometric and biochemical variable in control and acromegaly groups

Variable	Control Group Mean \pm SD(SE)	Acromegaly Group Mean \pm SD(SE)	P-value
Weight (kg)	72.50 \pm 12.04 (1.9)	93.45 \pm 16.35 (2.26)	0.001
Height (cm)	169.35 \pm 5.35 (0.84)	169.55 \pm 9.23 (1.33)	0.86
BMI (kg/m ²)	25.20 \pm 3.5 (0.55)	32.45 \pm 5.11 (0.69)	0.001
SBP(mmHg)	125.0 \pm 6.4 (0.32)	143.0 \pm 15.01 (2.28)	0.001
DBP(mmHg)	80.72 \pm 2.02(1.01)	83.12 \pm 7.8 (1.16)	0.1
FBS (mg/dl)	91.18 \pm 5.9(0.94)	123.83 \pm 24.9 (3.54)	0.001
HbA1C %	4.7 \pm 0.3 (0.04)	8.06 \pm 1.5 (0.24)	0.001
TC (mg/dl)	157.85 \pm 28.3 (4.47)	239.40 \pm 40.3 (6.65)	0.001
TG (mg/dl)	92.25 \pm 8.0 (1.27)	187.55 \pm 47.1 (7.29)	0.001
HDL (mg/dl)	53.23 \pm 5.48 (0.86)	45.95 \pm 6.3 (1.18)	0.001
LDL (mg/dl)	18.36 \pm 1.5 (0.25)	37.49 \pm 9.4 (1.45)	0.001
GH (ng/ml)	0.77 \pm 0.24 (0.03)	12.45 \pm 9.6 (1.62)	0.001
IGF-1 (ng/ml)	250.77 \pm 40.32 (6.37)	1319.4 \pm 803.36(145.3)	0.001
AI	0.23 \pm 0.06 (0.00)	0.60 \pm 0.12 (0.02)	0.001
Apo A(ng/ml)	59.86 \pm 17.9(2.90)	130.13 \pm 36.66(5.94)	0.001
Apo B (ng/ml)	43.44 \pm 13.43(2.17)	82.05 \pm 15.64(2.53)	0.001

Table 2. Mean levels of interleukins 6, 2, and 10 in control and acromegaly groups

Variable	Control Group Mean ± SD(SE)	Acromegaly Group Mean ± SD(SE)	P-value
IL6(ng/ml)	49.37 ± 7.4 (1.18)	55.72 ± 22.7 (3.39)	0.001
IL2 (ng/ml)	28.81 ± 7.8 (1.24)	44.4 ± 1.9 (0.31)	0.001
IL10(ng/ml)	33.73 ± 11.6 (1.83)	54.54 ± 30.1 (4.47)	0.001

The results also demonstrated a significant positive correlation of both GH and IGF-1 with each of weight, BMI, systolic blood pressure, diastolic blood pressure, FBS, HbA1c, cholesterol, triglyceride, LDL, IL6, IL2, atherogenic index, Apo A and Apo B. Meanwhile, only IGF-1 was significantly correlated with IL10. While significant negative correlation was observed between HDL with both GH and IGF-1 as shown in Table 3.

Table 3. Correlation coefficients of growth hormone and insulin-like growth factor-1 with clinical and biochemical parameters in acromegaly patients

Variable	r for GH	r for IGF-1
Age (year)	0.141	0.173
Weight (kg)	0.291**	0.262*
Height (cm)	-0.045	-0.141
BMI (kg/m ²)	0.342**	0.358**
SBP(mmHg)	0.361**	0.357**
DBP(mmHg)	0.202*	0.152
FBS (mg/dl)	0.532**	0.549**
HbA1C %	0.559**	0.572**
TC (mg/dl)	0.619**	0.589**
TG (mg/dl)	0.524**	0.547**
HDL (mg/dl)	-0.296**	-0.35**
LDL (mg/dl)	0.522**	0.561**
GH (ng/ml)	-	0.949**
IGF-1 (ng/ml)	0.949**	-
IL6(ng/ml)	0.308**	0.252**
IL2 (ng/ml)	0.569**	0.581**
IL10(ng/ml)	0.16	0.184*
AI	0.568**	0.605**
Apo A(ng/ml)	0.452**	0.485**
Apo B (ng/ml)	0.520**	0.551**

* At the 0.05 level correlation is significant

** At the 0.01 level correlation is significant

Discussion:

Acromegaly-related cardiac disorders are collectively referred to as acromegaly cardiomyopathy and include almost all facets of the cardiovascular system: myocyte and intercellular myocardial composition, ventricular systolic and diastolic activity, valvar heart disease, and cardiac electrical disturbances¹⁰. Although recent data suggest a decreased role of traditional cardiovascular complications reflecting mortality of acromegaly patients, it still remains an important factor¹¹, especially those with uncontrolled disease due to delayed diagnosis or lesser availability of modern efficacious therapies⁵. Obesity is one of the

most important factors in the initiation and development of cardiovascular comorbidities in acromegaly.¹² Regarding BMI, the present results revealed that patients with acromegaly were obese as compared with those who were healthy an initial cardiovascular diagnostic strategy may involve a baseline blood pressure examination. Despite the fact that the global prevalence of hypertension in adults is estimated to be about 40%¹³, the incidence of acromegaly in patients is higher and the prevalence is between 18% and 60%¹⁴. Our results indicated elevated systolic and diastolic blood pressure in acromegaly patients, and this is in agreement with the fact that elevated diastolic blood pressure is a feature of acromegaly-related hypertension. Expansion of plasma volume and retention of sodium and water, stimulation of smooth muscle cell formation, increased vascular responsiveness to angiotensin II, increased cardiac rate, and peripheral resistance are some of the possible mechanisms involved in the development of hypertension associated with acromegaly.^{12,15} Interestingly, the concomitant involvement of additional classical cardiovascular risk factors in acromegaly, such as hyperglycemia, dyslipidemia, and over body weight, appears to have a greater influence on the development of coronary artery disease and atherosclerosis than chronic and long-term GH / IGF-I excess exposure¹⁶. Increased levels of FBS, HbA1c, cholesterol, triglyceride, LDL, and decreased HDL indicated that patients are at risk of cardiovascular disorder. This confirms the atherogenic index that revealed an increased level in acromegaly patients. Hunter C. A reported that in patients with cancer, infection, or autoimmune diseases, IL-6 was used to “monitor” inflammation levels¹⁷. In other research, IL-6 has been shown to have undeniable prognostic importance in the early stages of inflammation. In acromegaly patients, reports on circulating inflammatory markers are conflicting. Circulating IL-6 concentrations have been reported to be similar in healthy controls and patients with either active or controlled acromegaly¹⁸. However, IL-6 concentrations were lower in patients with active disease compared to those with controlled disease¹⁹ and were inversely correlated with IGF-1 and GH levels⁷. Patients with active acromegaly are characterized by the increased pro-inflammatory activity of both the adipocytes and adipose tissue macrophages. Since adipose tissue

macrophages in healthy adipose tissue are an important source of anti-inflammatory IL-1Ra and also pro-inflammatory cytokines, changed adipose tissue composition and/or activity may result in the lower IL-1Ra levels and higher circulating pro-inflammatory cytokine levels that characterize patients with active acromegaly²⁰. In the present study elevated level of IL2, IL6, and IL10 were observed in acromegaly patients so this findings may be regarded in early inflammation. This is the first study that provides an association of elevated interleukins and risk of cardiovascular disorder in acromegaly patients.

Conclusion:

The study concludes that elevated levels of IL2, IL6, IL 10 and their association with both GH and IGF-1 in addition to lipid disorder, hyperglycemia and hypertension criteria of acromegaly patients suggest necessary clinical scanning of cardiovascular disorder for acromegaly patients

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine. Besides, the Figures and images, which are not mine ours, have been given permission for re-publication attached with the manuscript.
- Authors sign-on ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee at Mustansiriyah University.

Authors' contributions statement:

Noor Thair Tahir, Sura A. Abdulsattar, and Fatin F. Al-Kazzaz contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript

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تقييم السمنة، اضطراب الدهون، ارتفاع السكر في الدم والسيتوكينات المؤيدة للالتهابات كعوامل خطر لأمراض القلب والأوعية الدموية لدى مرضى ضخامة النهايات

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الخلاصة:

تعد أمراض القلب والأوعية الدموية واحدة من أكثر الأمراض المصاحبة المرتبطة بتضخم الأطراف انتشاراً ، وتحدث في 60 بالمائة من مرضى ضخامة الأطراف. يهدف البحث الى تقييم العلاقة بين هرمون النمو والأنسولين شبيه عامل النمو -1 مع السمنة، اضطراب الدهون، ارتفاع السكر في الدم والسيتوكينات المؤيدة للالتهابات (IL-2, IL-6, IL-10) كعامل خطر لاضطراب القلب والأوعية الدموية لدى مرضى ضخامة النهايات . اشتملت الدراسة على 80 شخصاً تم تقسيمهم إلى قسمين: 40 مريضاً من ضخامة النهايات و 40 شخصاً سليماً كمجموعة تحكم. أشارت النتائج إلى زيادة الوزن ، وارتفاع السكر في الدم ، وارتفاع ضغط الدم ، واضطراب الدهون ، وارتفاع مستويات الإنترلوكينات (2، 6، 10) ، وأظهرت نتائج الارتباط ارتباطاً إيجابياً معنوياً لكل من GH و IGF-1 مع كل من الوزن ، مؤشر كتلة الجسم ، ضغط الدم الانقباضي ، ضغط الدم الانبساطي ، FBS ، HbA1c ، الكوليسترول ، الدهون الثلاثية ، LDL ، IL6 ، IL2 ، ومؤشر تصلب الشرايين ، بينما يظهر فقط IGF-1 ارتباطاً معنوياً بـ IL10. نستنتج أن المستويات المرتفعة من IL2 و IL6 و IL10 وارتباطها مع كل من GH و IGF-1 بالإضافة إلى اضطراب الدهون وارتفاع السكر في الدم ومعايير ارتفاع ضغط الدم لمرضى ضخامة النهايات تقترح ضرورة المسح السريري لاضطراب القلب والأوعية الدموية لمرضى ضخامة الاطراف..

الكلمات المفتاحية : ضخامة النهايات ، القلب والأوعية الدموية ، هرمون النمو ، الأنسولين شبيه عامل النمو -1 ، إنترلوكين