SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 9.
Issue: 1
Page N. 112-117
Year: 2025

Original Article www.wjahr.com

TESTOSTERONE SCREENING IN POSTOPERATIVE IRAQI ACROMEGALY MALE PATIENTS WITH AND WITHOUT DIABETES

Lujain A. Ghannawi[1*], Omar Yasir Shakir[1], Jihad Anad Khalaf[2], Karam Gharab[1], Haidar Fadhil Al-Rubay'e[1], Mohamed A. Thamer[1]

[1*]National Diabetes Center, Mustansiriyah University, Baghdad, Iraq.
[2]College of Medicine, Al-Iraqia University, Baghdad, Iraq.

Article Received date: 14 November 2024 **Article Revised date:** 04 December 2024 **Article Accepted date:** 24 December 2024

***Corresponding Author: Lujain A. Ghannawi**

National Diabetes Center, Mustansiriyah University, Baghdad, Iraq.

ABSTRACT

Acromegaly is a syndrome, that results from excessive pituitary growth hormone (GH) secretion, leading to increased insulin-like growth factor-1 (IGF-1) production, usually due to a pituitary adenoma. Acromegaly often leads to disruptions in hormone levels, including testosterone. Blood testosterone levels are crucial in assessing hypogonadism in these patients moreover; the diabetes may further complicate this imbalance. 120 samples were enrolled in this study (Acromegalic male and healthy control) aged from 30 to 60 years old, collected and grouped into three groups, the first 40 patients were with diabetes, and the other 40 patients were without diabetes. At the same time, the healthy controls were 40 participants. GH, IGF-1, FBS, and testosterone levels were measured for all study groups. Results showed significant differences between acromegaly patients and control in the study parameters, p-value (< 0.05). While, between diabetic and non-diabetic acromegaly only testosterone levels show significant differences (p-value=0.000). As a conclusion, high GH and IGF-1 levels disrupt the HPG axis, leading to hypogonadism and lower testosterone levels, which are linked to erectile dysfunction. Additionally, testosterone levels were significantly lower in acromegaly patients with diabetes compared to non-diabetic acromegaly patients, highlighting the negative impact of diabetes on testosterone production. These hormonal disruptions contribute to common symptoms like reduced libido and fatigue in affected men.

KEYWORDS: Acromegaly; Diabetes; Testosterone; GH; IGF-1.

1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by high blood glucose levels due to insufficient insulin (total or relative lack) along with insulin resistance, cell dysfunction, or both.[1] One of the diseases with the fastest rate of growth in the world is diabetes. Diabetic patients face severe macrovascular consequences such as heart disease as well as microvascular issues such as diabetic kidney disease, diabetic retinopathy, and neuropathy, which can result in increased mortality, kidney failure, blindness, and a lower overall quality of life.[2] In acromegaly, elevated GH levels lead to increased secretion of IGF-1, both of which contribute to insulin resistance and the development of diabetes. GH directly interferes with insulin signaling in muscles and adipose tissue, reducing insulin sensitivity. Although IGF-1 exhibits some insulin-like effects, it can also reduce insulin effectiveness in peripheral tissues and promote increased glucose production in the liver. Together, these factors result in elevated blood glucose levels, which, over time, overwhelm the pancreas's ability to secrete sufficient insulin, leading to the development of insulin resistance and, in many cases, diabetes in acromegaly patients.[3-6]

Acromegaly is a rare systemic disorder, with an incidence of 5.3 per million person-years and a prevalence of 83 cases per million individuals, typically caused by GH-secreting pituitary adenoma.[7] Chronic GH hypersecretion leads to elevated levels of insulin-like growth factor 1 (IGF-1), which in turn contributes to widespread physiological dysfunction, including abnormal somatic growth, physical disfigurement, and multiple comorbidities. This condition is also associated with increased mortality[8,9], primarily due to cardiovascular issues (such as hypertension and heart failure), cerebrovascular events (including stroke), and respiratory complications (such as obstructive sleep apnea). Furthermore, research has indicated a higher prevalence of malignancies, osteoarthritic changes, and

various endocrinological and metabolic disorders in individuals with acromegaly.[10]

Hypogonadism is a common dysfunction present in patients with acromegaly, and it affects 30% to 50% of individuals with acromegaly.[11] It is "the insufficiency of the gonads to produce sex hormones". The possible mechanisms underlying the hypogonadism in acromegaly include the mass effect from the pituitary gland or stalk compression, as well as elevated levels of prolactin (hyperprolactinemia).[12]

In acromegaly male patients that diagnosed with hypogonadism, it is common to observe impaired testicular function, abnormal sperm production, and low testosterone levels in blood. These hormonal imbalances contribute to male infertility, an elevated body mass index (BMI), decreased physical strength, reduced libido, and the absence of morning erections. Blood testosterone levels are crucial in assessing hypogonadism in these patients[13,14,15], as low testosterone is considered a great indicator, also a contributing factor to this condition.

Transsphenoidal surgery (TSR) is the main treatment for most cases of acromegaly, with remission rates of 80-90 % for microadenomas and 40–50 % for macroadenomas.[16] A recent study indicate that hypopituitarism is a frequent complication following pituitary adenomas surgery, affecting up to one-third of patients within months after the operation.[17]

Yet few studies have evaluated the testosterone levels in acromegaly males after the restriction surgery of the pituitary adenoma. This research aimed to screen the testosterone levels in postoperative acromegaly patients, both those with and without diabetes, to evaluate the potential effects of surgical treatment on hormonal balance. As acromegaly often leads to disruptions in hormone levels, including testosterone, moreover, diabetes may further complicate this imbalance. By assessing testosterone levels after surgery, clinicians can determine if testosterone deficiency or abnormalities persist, which may influence recovery, sexual health, and overall well-being.

2. MATERIALS AND METHODS

2.1. Patients

120 samples enrolled in this study (Acromegalic male patients and healthy control) were collected (from August to November 2024) at the National Diabetes Center, Mustansiriyah University. All of the acromegaly patients have been already diagnosed by the physicians, first by magnetic resonance imaging (MRI) to detect (Pituitary Adenoma) and other biochemical tests, including elevated serum IGF-1 and absence of GH suppression after glucose administration. They were grouped into three groups, 40 diabetic acromegaly patients, and 40 non-diabetic acromegaly patients. While the healthy controls were 40 participants. The age range was from 30 to 60 years old. All of the diabetic patients have been diagnosed by the physicians (HbA1c $\geq$ 6.8). All of the Acromegaly patients after surgical operation (by endoscopic transsphenoidal approach), were given Lanreotide injection (90 or 120 mg) intramuscular treatment according to their clinical status. So patients were selected randomly according to their prespecified appointment.

2.2. METHODS

Eight milliliters of complete blood were collected utilizing a disposable plastic needle and recognized in a disposable gel tube. The sample selections were centrifuged for 7 minutes at 3000 rpm to reach blood serum for laboratory examinations. Body mass index was calculated operating the formula BMI = weight (kg)/height^2 (m^2). GH and IGF-1 were tested by a DiaSorin analyzer device (Elecsys hGH kit-Germany) (Elecsys IGF-1 kit-Germany), respectively. Fasting Blood Sugar (FBS) was experimented with by Cobas C1-11 Devise (Gluc2 kit). Testosterone levels were tested by using (Cobas e411) Device (Cobas Testosterone kit (Total) Switzerland).

3. Ethical Approval

Before the commencement of this trial, all patients provided their written and dated consent for their participation. Furthermore, this study received ethical approval from the ethics committee of the National Diabetes Center at Mustansiriyah University in (September 2024), Ensuring adherence to the guidelines set forth in the 1964 Declaration of Helsinki, along with any subsequent revisions or similar ethical standards.

4. Statistical Analysis

Statistical data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc, Chicago, IL, USA) software program. For evaluating the significance levels between the three groups in this study Kruskal-Wallis H test was used, while the Mann-Whitney U test was used to evaluate the level of significance between the two group's patients and control. Results are presented as median, minimum, and maximum. Spearman test was used for correlation. When the p-value less than 0.05 the result was considered statistically significant.

5. RESULTS

In this study, Anthropometric measurements showed significant differences among the acromegaly and healthy control groups (p-value < 0.05) as shown in Table 1.

Table 1: Parameters levels between patients and Control.

Parameters	Control Median (Min-Max)	Patients Median (Min-Max)	p-Value
Testosterone (ng/ml)	430 (288-602)	277 (18-516)	0.000
FBS (mg/dL)	98 (84-105)	116 (80-384)	0.000
GH (ng/ml)	0.66 (0.2-1.6)	3.1 (0.5-50)	0.000
IGF-1 (ng/ml)	268 (190-380)	477 (150-1600)	0.000
BMI	29.9 (22.7-35.9)	30.1 (21.7-44.3)	0.550

In more detail and as shown in (Table 2, and Table 3), there is a reduction in testosterone levels between all of the study groups and it is a significant difference (p-value = 0.000).

Table 2: Significance difference between control, Non-DM acromegaly, and DM acromegaly patients.

Metabolite	Control median (Min-Max)	Non-DM Acromegaly median (Min-Max)	DM Acromegaly median (Min-Max)	p-Value
Testosterone (ng/ml)	430 (288-602)	353 (150-516)	192 (18-386)	0.000
FBS (mg/dL)	98 (84-105)	102.5 (80-115)	161.5 (117-384)	0.000
GH (ng/ml)	0.66 (0.2-1.6)	2.45 (0.5-11.4)	3.45 (1-50)	0.000
IGF-1 (ng/ml)	268 (190-380)	441.5 (150-1600)	520.5 (145-1590)	0.000
BMI	29.9 (22.7-35.9)	29.3 (23.6-43.6)	30.1 (21.7-44.3)	0.221

Table 3: Parameters levels between Acromegaly sub-group.

Parameters	Non-DM Acromegaly median (Min-Max)	DM Acromegaly median (Min-Max)	p-Value
Testosterone (ng/ml)	353 (150-516)	192 (18-386)	0.000
FBS (mg/dL)	102.5 (80-115)	161.5 (117-384)	0.000
GH (ng/ml)	2.45 (0.5-11.4)	3.45 (1-50)	0.190
IGF-1 (ng/ml)	441.5 (150-1600)	520.5 (145-1590)	0.028
BMI	29.3 (23.6-43.6)	30.1 (21.7-44.3)	0.105

Table 4: Correlation results between study parameters.

		Testosterone	FBS	GH	IGF-1	BMI	Weight	Height
Testosterone	Correlation Coefficient	1.000	-.650**	-.545**	-.305**	-0.141	-.235**	-0.070
	Sig. (2-tailed)		0.000	0.000	0.001	0.126	0.010	0.445
	N	120	120	120	120	120	120	120
FBS	Correlation Coefficient	-.650**	1.000	.541**	.518**	0.159	.313**	.180*
	Sig. (2-tailed)	0.000		0.000	0.000	0.083	0.000	0.049
	N	120	120	120	120	120	120	120
GH	Correlation Coefficient	-.545**	.541**	1.000	.757**	0.157	.315**	.249**
	Sig. (2-tailed)	0.000	0.000		0.000	0.087	0.000	0.006
	N	120	120	120	120	120	120	120
IGF-1	Correlation Coefficient	-.305**	.518**	.757**	1.000	0.150	.313**	.210*
	Sig. (2-tailed)	0.001	0.000	0.000		0.101	0.000	0.021
	N	120	120	120	120	120	120	120
BMI	Correlation Coefficient	-0.141	0.159	0.157	0.150	1.000	.756**	-.212*
	Sig. (2-tailed)	0.126	0.083	0.087	0.101		0.000	0.020

	N	120	120	120	120	120	120	120
Weight	Correlation Coefficient	-.235**	.313**	.315**	.313**	.756**	1.000	.407**
	Sig. (2-tailed)	0.010	0.000	0.000	0.000	0.000		0.000
	N	120	120	120	120	120	120	120
Height	Correlation Coefficient	-0.070	.180*	.249**	.210*	-.212*	.407**	1.000
	Sig. (2-tailed)	0.445	0.049	0.006	0.021	0.020	0.000	
	N	120	120	120	120	120	120	120

6. DISCUSSION

The median of BMI in acromegaly patients was (Median= 30.1), placing them in overweight category.[18] This could be attributed to the lipolytic effects of GH and IGF-1, which promote the release of free fatty acids, as well as the insulin resistance that is commonly observed in these patients, leading to elevated blood glucose levels[19], Table 1. Also, the random GH levels (Median= 3.1) and IGF-1 levels (Median=477) in male patients with acromegaly were higher than in the normal population Table 1.

Hypogonadism is another factor that connects acromegaly to erectile dysfunction, but the metabolic complications associated with acromegaly, along with the potential direct effects of GH, likely play a role in development of this disorder.[9] Increased levels of GH and IGF-1 caused by growth hormone-secreting pituitary adenomas can interfere with the hypothalamic-pituitary-gonadal (HPG) axis, leading to hypogonadotropic hypogonadism. This disruption occurs by interfering with the normal pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which subsequently leads to a decrease in the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. Persistent elevation of GH and IGF-1 can also diminish the pituitary's responsiveness to GnRH and directly impair gonadotropin release, ultimately resulting in hypogonadism, with clinical manifestations such as infertility and reduced libido.

Moreover, Testosterone levels show an obvious reduction between healthy control men and acromegaly men (Median = 430, Median= 277) respectively Table 1.

In their 2020 study, Rie Nishio *et al.*[20] found that excess GH was the primary factor contributing to hypogonadism in male acromegaly patients, while the total blood testosterone level showed the strongest correlation with GH in these patients. This goes along with our findings, see the correlation between GH and Testosterone levels in Table 4.

Older studies about age-related changes, obesity, and disease duration in men on testosterone levels show no significant differences[21,22], therefore, we did not consider it in our study.

As reported by Alexopoulou *et al.*, in 2014[23], glucose metabolism disorders are more common acromegaly patients compared to the general population, even when accounting for those at higher risk of developing diabetes due to prolonged exposure to elevated levels of GH and IGF-1. We measured the testosterone levels in male patients (acromegaly) with diabetes to evaluate the relation, and our finding revealed that testosterone levels are greatly lowered in acromegaly patients with diabetes (Median= 192) as compared to non-diabetic acromegaly men (Median=353) p-value= 0.000, Table 3.

Men with diabetes mellitus (DM) often have low testosterone levels due to several factors related to the disease and its metabolic effects. DM can disrupt the hormonal axis, leading to lower levels of sex hormone-binding globulin (SHBG), which increases the availability of free testosterone but may also result in a dysfunctional balance of hormones. Also, chronic hyperglycemia can lead to increased inflammation, oxidative stress, and changes in the hypothalamic-pituitary-gonadal (HPG) axis, impairing testosterone production. Additionally, obesity—common in men with diabetes and Acromegaly—leads to increased aromatase activity in adipose tissue, which converts testosterone into estrogen, further lowering testosterone levels. Finally, diabetic complications such as peripheral neuropathy, poor circulation, and increased prolactin levels can also negatively affect testicular function and the production of testosterone. As a result, low testosterone is relatively common in men with diabetes, contributing to symptoms like fatigue, reduced libido, and erectile dysfunction.

7. CONCLUSION

The study found that acromegaly patients have higher BMI, GH, and IGF-1 levels, which contribute to insulin resistance and metabolic problems. Elevated GH and IGF-1 disrupt the HPG axis, leading to hypogonadism and lower testosterone levels, which are linked to erectile dysfunction. Additionally, testosterone levels were significantly lower in acromegaly patients with diabetes compared to non-diabetic acromegaly patients, highlighting the negative impact of diabetes on testosterone production. These hormonal disruptions contribute to common symptoms like reduced libido and fatigue in affected men.

8. RECOMMENDATIONS

We recommend measuring total testosterone, sex-hormone binding Globulin (SHBG), and prolactin to assess gonadal function in men with acromegaly at the time of diagnosis, prior to treatment, after surgery, and annually thereafter. This will help determine whether recovery from acromegaly increasing the likelihood of recovery from low testosterone levels.

Authors Contribution

O.Y.S. and L.A.G. conceived and designed the work. L.A.G., K.G., and M.A.T. performed experiments, data processing, and collection. K.G. and L.A.G Analyzed and interpreted the results. L.A.G. and O.Y.S. prepared the manuscript draft and did the statistical analysis. J.A.K. and L.A.G edited the article. H.F. provided the supervision and approved the final version to be published.

Conflict of Interests: The authors stated that they have no conflicts of interest related to the authorship and publication of this article.

Funding: The authors declare that there is no funding.

REFERENCES

1. Corathers S, Williford DN, Kichler J, *et al*. Correction: Implementation of Psychosocial Screening into Diabetes Clinics: Experience from the Type 1 Diabetes Exchange Quality Improvement Network. Curr Diab Rep., 2023; 23: 29. https://doi.org/10.1007/s11892-023-01500-8.
2. Zhang L, Zhang L, Li S, Zhang Q, Luo Y. Overexpression of mm9_circ_013935 alleviates renal inflammation and fibrosis in diabetic nephropathy via the miR-153-3p/NFIC axis. Canadian journal of physiology and pharmacology, 2021; 99(11): 1199-1206.
3. Clemmons DR. Roles of insulin-like growth factor-I and growth hormone in mediating insulin resistance in acromegaly. Pituitary, 2002; 5: 181–3.
4. Barbour LA, Mizanoor Rahman S, Gurevich I, Leitner JW, Fischer SJ, Roper MD, et al. Increased P85alpha is a potent negative regulator of skeletal muscle insulin signaling and induces *in vivo* insulin resistance associated with growth hormone excess. J Biol Chem., (2005); 280: 37489–94. 10.1074/jbc.M506967200.
5. Frara S, Maffezzoni F, Mazziotti G, Giustina A. Current and emerging aspects of diabetes mellitus in acromegaly. Trends Endocrinol Metab., 2016; 27: 470–83. 10.1016/j.tem.2016.04.014.
6. Kasayama S, Otsuki M, Takagi M, Saito H, Sumitani S, Kouhara H, et al. Impaired β-cell function in the presence of reduced insulin sensitivity determines glucose tolerance status in acromegalic patients. Clin Endocrinol, 2000; 52: 549–55. 10.1046/j.1365-2265.2000.00986.x.
7. Zhang D, Guo X, Feng M, Bao X, Deng K, Yao Y, Lian W, Xing B, Wang H. Preoperative and postoperative blood testosterone levels in patients with acromegaly: a prospective study. Front Endocrinol (Lausanne), 2023 Oct 11; 14: 1259529. doi: 10.3389/fendo.2023.1259529.
8. Caputo M, Ucciero A, Mele C, De Marchi L, Magnani C, Cena T, et al. Use of administrative health databases to estimate incidence and prevalence of acromegaly in Piedmont Region, Italy. J Endocrinol Invest, 2019; 42(4): 397–402. doi: 10.1007/s40618-018-0928-7.
9. Salvio G, Martino M, Balercia G, Arnaldi G. Acromegaly and male sexual health. Rev Endocrine Metab Disord., 2022; 23(3): 671–8. doi: 10.1007/s11154-022-09721-0.
10. Gadelha MR, Kasuki L, Lim DS, Fleseriu M. Systemic complications of acromegaly and the impact of the current treatment landscape:an update. Endocr Rev., 2019; 40: 268–332. doi: 10.1210/er.2018-00115.
11. Melmed S, Casanueva FF, Klibanski A, Bronstein MD, Chanson P, Lamberts SW, *et al*. A consensus on the diagnosis and treatment of acromegaly complications. Pituitary, 2013; 16(3): 294–302. doi: 10.1007/s11102-012-0420-x.
12. Palacios JD, Komotar RJ, Kargi AY. Successful Treatment of Acromegaly and Associated Hypogonadism with First-Line Clomiphene Therapy. Case Rep Endocrinol, 2018 Jun 26; 2018: 7925019. doi: 10.1155/2018/7925019. PMID: 30046497; PMCID: PMC6038655.
13. Basaria S. Male hypogonadism. Lancet, 2014; 383(9924): 1250–63. doi: 10.1016/S0140-6736(13)61126-5.
14. Bhasin S, Basaria S. Diagnosis and treatment of hypogonadism in men. Best Pract Res Clin Endocrinol Metab., 2011; 25(2): 251–70. doi: 10.1016/j.beem.2010.12.002.
15. Yan Z, Lei T. Hypogonadism in male patients with pituitary adenoma and its related mechanism: A review of literature. Brain Sci., 2022; 12(6): 796. doi: 10.3390/brainsci12060796.
16. Katznelson L, Laws ER, Melmed S, *et al.* Acromegaly: an endocrine society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism, 2014; 99(11): 3933–3951. doi: 10.1210/jc.2014-2700.
17. Zhang J, Wang Y, Xu X, Gu Y, Huang F, Zhang M. Postoperative complications and quality of life in patients with pituitary adenoma. Gland Surg., 2020; 9: 1521–1529. doi: 10.21037/gs-20-690.
18. Weir CB, Jan A. BMI classification percentile and cut off points. In: StatPearls. Treasure Island (FL: StatPearls Publishing, 2022.
19. Mercado M, Ramırez-Renter´ ıa C. Metabolic complications of acromegaly.´ Front Hormone Res., 2018; 49: 20–8. doi: 10.1159/000486001.
20. Nishio R, Takeshita A, Uchida T, Herai T, Sakamoto K, Shimizu Y, et al. GHinduced LH hyporesponsiveness as a potential mechanism for hypogonadism in male patients with acromegaly.

Endocrine J., 2021; 68(8): 953–68. doi: 10.1507/endocrj.EJ20- 0596.
21. Allan CA, McLachlan RI. Age-related changes in testosterone and the role of replacement therapy in older men. Clin Endocrinol, (2004); 60: 653–70. doi: 10.1111/ j.1365-2265.2004.02002.x.
22. Mah PM, Wittert GA. Obesity and testicular function. Mol Cell Endocrinol, 2010; 316(2): 180–6. doi: 10.1016/j.mce.2009.06.007.
23. Alexopoulou O, Bex M, Kamenicky P, Mvoula AB, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: a study in 148 patients. Pituitary, 2014; 17: 81–9. 10.1007/s11102-013-0471-7.