ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TURKEY

ORIGINAL ARTICLE
Endocrinol Res Pract. 2024. [epub ahead of print]

The Relationship Between Serum Growth Hormone, Seminal Plasma Growth Hormone, and Sperm Parameters in Patients with Acromegaly in Remission

ABSTRACT

Objective: The influence of serum insulin-like growth factor-1 (IGF-1) and growth hormone (GH) on sperm parameters has been previously described in patients with acromegaly. However, the relationship between local GH/IGF-1 with systemic levels and sperm parameters in patients with acromegaly has not been established. In this study, we investigated the effects of seminal plasma hormone levels on sperm parameters in patients with acromegaly.

Methods: This cross-sectional study was conducted on 24 patients with acromegaly in remission and 16 men without chronic disease and/or hypogonadism. Seminal plasma GH and IGF-1 were measured. Semen parameters and seminal plasma hormone levels were compared.

Results: The acromegaly group had higher levels of serum GH (0.475 IQR (0.245-0.770) ng/mL) compared to the control group (0.08 IQR (0.03-0.159) ng/mL) ($P < .001$). Although seminal plasma GH levels were higher in the acromegaly (114 ± 82 pg/mL) than in the control group (61 ± 39 pg/mL) ($P = .004$), seminal plasma IGF-1 levels were similar ($P = .203$). Serum GH was positively correlated with seminal plasma GH ($r = 0.489$, $P = .001$) and negatively correlated with sperm count ($r = -0.337$, $P = .039$) and fast-forward motility ($r = -0.360$, $P = .023$). There was no correlation between seminal plasma hormone levels and semen parameters ($P > .05$ for all).

Conclusion: The findings suggested that sperm count may be adversely affected in patients with acromegaly despite an intact hypothalamic–pituitary–gonadal axis and disease control. The seminal plasma hormone levels seemed not to be correlated with semen alterations.

Keywords: Acromegaly, growth hormone, sperm count, seminal plasma, insulin-like growth factor-1

Ebru Cicek[1]

Cem Sulu[2]

Hande Mefkure Ozkaya[2]

Serdar Sahin[2]

Dildar Konukoglu[3]

Hamdi Ozkara[4]

Rosario Pivonello[5,6]

Pinar Kadioglu[2]

[1]*Department of Internal Medicine, İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye*
[2]*Division of Endocrinology, Metabolism, and Diabetes, Department of Internal Medicine, İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye*
[3]*Department of Biochemistry, İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye*
[4]*Department of Urology, İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye*
[5]*Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Diabetologia ed Andrologia, Unità di Andrologia e Medicina della Riproduzione, Sessualità e Affermazione di Genere (FERTISEXCARES), Università Federico II di Napoli, Naples, Italy*
[6]*Unesco Chair for Health Education and Sustainable Development, Federico II University, Naples, Italy*

Corresponding author:
Pinar Kadioglu
✉ kadioglup@yahoo.com

Received: July 17, 2024
Revision Requested: September 2, 2024
Last Revision Received: September 30, 2024
Accepted: October 14, 2024
Publication Date: November 11, 2024

Cite this article as: Cicek E, Sulu C, Mefkure Ozkaya H, *et al*. The relationship between serum growth hormone, seminal plasma growth hormone, and sperm parameters in patients with acromegaly in remission. *Endocrinol Res Pract*. Published online November 11, 2024. doi 10.5152/erp.2024.24525.

DOI: 10.5152/erp.2024.24525

Introduction

Acromegaly is characterized by physical, metabolic, rheumatological, respiratory, and cardiac impairments.[1] It is also well-acknowledged that patients with acromegaly may experience reproductive abnormalities. Male patients with acromegaly can present with sexual dysfunction and infertility.[2]

The presence of growth hormone (GH) receptors in the testicles and hypothalamus supports the notion that male fertility is under the control of GH.[3] Since GH can act on multiple levels of the hypothalamus–pituitary–testicular axis, patients with acromegaly may suffer from sexual dysfunction stemming from various causes.[4] In our recent study, we found that testosterone levels were lower and sperm parameters were impaired in patients with acromegaly.[5] We also showed that the impairments in testicular functions become more evident with increasing serum GH and insulin-like growth factor (IGF-1), suggesting their detrimental effect on male fertility. Similar to the serum, seminal plasma contains a wide range of bioactive molecules that can directly influence sperm function and fertilization. Based on previous studies that showed the presence of seminal plasma GH and IGF-1, as well as their potential effect on male fertility,[6,7] we aimed to investigate the relations among serum GH and IGF-1 levels, seminal plasma GH and IGF-1 levels, and semen indices in patients with acromegaly.

Materials and Methods

This study was conducted in Endocrinology, Metabolism, and Diabetes and Urology outpatient clinics of a tertiary care university hospital between 2021 and 2022. The present study was approved by the Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine

(approval number: 2021-90-273; date: May 05, 2021.). All participants provided written informed consent.

Subjects

Patients with acromegaly and control men were included. The eligible patients with acromegaly were recruited between September 2021 and February 2022 during their routine follow-up visits. The control subjects were selected among healthy volunteers (healthy controls, HCs).

The diagnosis of acromegaly was confirmed in all patients. The inclusion criteria for all participants were: i) age 18-65 years, ii) having a regular sexual partner, iii) consent to participate. The exclusion criteria for all participants included the presence of i) history of hypogonadism or testosterone and/or gonadotropin replacement therapy, ii) hyperprolactinemia, iii) previous conditions that could affect semen parameters (such as orchiectomy, infections, varicocele, or trauma), iv) neurological and/or psychiatric diseases, substance or alcohol abuse, v) overt hypothyroidism or hyperthyroidism, vi) acute medical conditions (such as sepsis or acute coronary syndrome) and major organ failure (hepatic, renal, cardiac), vii) active malignancy or previous history of chemotherapy, viii) presence of genetic diseases affecting sexual development (such as Klinefelter syndrome), and ix) alcoholism.

Procedures

Clinical and Laboratory Assessments: A study visit was planned for each eligible participant at 8:00 AM. During the study visit, relevant demographic and clinical data were collected. Fasting blood samples were obtained at 8:30 AM, and serum levels of GH, IGF-1, follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid hormones, and testosterone levels were determined. Serum levels of these hormones were measured using the electrochemiluminesc ence immunoassay method.

Semen analyses were performed after 72 hours of sexual abstinence based on the last edition of the "WHO Laboratory Handbook Examining and Processing Human Semen."[8] The details of macroscopic and microscopic examination were provided elsewhere.[5]

After the semen analysis, the seminal samples were centrifuged twice at 3000 rpm for 10 minutes each time. The plasma portion was then collected in Eppendorf tubes and stored at −80°C until analyses.

MAIN POINTS

- This study provided the first piece of data on the seminal plasma growth hormone and insulin—like growth factor-1 levels in patients with acromegaly.
- The findings of this study suggested that sperm parameters may be negatively affected in patients with acromegaly despite an intact hypothalamic–pituitary–gonadal axis and disease control.
- The sperm alterations in patients with acromegaly appear to be related to elevated serum growth hormone levels.
- Seminal plasma growth hormone and insulin-like growth factor levels did not appear to have a major impact on sperm alterations.
- The effects of seminal plasma hormones on testicular function merit further attention.

Seminal plasma GH and IGF-1 levels were measured by enzyme-linked immunoassays using commercially available kits (Quantikine ELISA, catalog no.: DGH00 and Rockville, catalog no.: EA102183, respectively).

Endocrinological Definitions

Endocrinological definitions and treatment protocols for acromegaly were based on internationally agreed guidelines.[9] Remission was determined by the presence of basal GH < 1 μg/L and normal IGF-1.[10] The definition of hypogonadism was made according to the presence of clinical symptoms and signs of testosterone deficiency with unequivocally and consistently low serum testosterone levels (<300 ng/dL).[11,12]

Statistical Analyses

Statistical analyses were performed using SPSS version 29.0 (IBM SPSS Corp.; Armonk, NY, USA). Continuous data were presented as means and standard deviations, or median and interquartile range (IQR) (25%-75%) based on the distribution. Independent samples *t*-test and Kruskal–Wallis test were used to evaluate differences in continuous parameters. Differences in categorical parameters were analyzed using the Pearson chi-square test. Correlation analyses were performed with Spearman's rank correlation test.

Results

Participant Characteristics

A total of 24 acromegaly patients and 16 control men were enrolled. The general features of the acromegaly and control groups are shown in Table 1. The groups were comparable in terms of age, marital status, body mass index, and smoking status. The age at presentation was 38 ± 8.9 years in patients with acromegaly, and median duration of the disease was 73 months (IQR: 45.5-99.5 months).

In the acromegaly group, 22 patients (91.6%) had a history of transsphenoidal surgery, 1 patient (4.2%) had received additional pituitary radiotherapy, and 1 patient (4.2%) refused transsphenoidal surgery and received somatostatin receptor ligand as primary therapy. At the time of assessment, 18 patients with acromegaly (75%) were using somatostatin receptor ligand, and no patient was on pegvisomant. All patients with acromegaly were in remission. In the acromegaly group, 4 patients had diabetes (16.7%) and 2 patients had hypertension (8.3%).

Comparison of Laboratory Parameters

Patients with acromegaly had higher levels of serum GH and IGF-1, and lower total testosterone levels compared to HCs (Table 1). Other laboratory features are shown Table 1.

Comparisons of Semen Parameters and Semen Hormone Levels

The semen parameters of study groups are revealed in Table 2. Patients with acromegaly had lower total sperm count, sperm concentration, and percentage of sperm with normal morphology compared to HCs (Figure 1). The sperm motility showed no difference among the groups.

Patients with acromegaly had higher levels of seminal plasma GH compared to HCs (Table 2, Figure 2). Seminal plasma IGF-1 levels were similar (Table 2).

In this study, 18 patients with acromegaly (75%) were on SLAR treatment. The comparison between SLAR users and non-users was presented in Table 3. The subgroups did not differ in sperm parameters, seminal plasma GH and IGF-1 levels.

Table 1. Demographic and Laboratory Parameters of the Study Groups

Features	Acromegaly (n = 24)	Control (n = 16)	*P*
Age (years)	44.2 ± 8.9	42.5 ± 9.4	.573
Marital status, n (%)			1.0
Married	20 (83.3)	14 (87.5)	
Single	3 (12.5)	2	
Divorced	1 (4.2)	0 (0)	
Child(ren), n (%)	19 (79.2)	12 (75)	1.0
Smoking, n (%)	10 (41.7)	4 (25)	.329
Body mass index (kg/m^2)	27.6 ± 3.3	25.7 ± 5.5	.184
GH (µg/L)	0.475 [0.245-0.770]	0.08 [0.03-0.159]	<.001
IGF-1 (µg/L)	173 [146-236]	146 [123-183]	.034
IGF-1 upper limit of normal	0.7 [0.5-0.9]	0.5 [0.4-0.6]	.040
FSH (U/L)	4.1 [3.3-6.3]	3.2 [2.7-4.2]	.149
LH (U/L)	4.3 ± 1.7	4.8 ± 2.7	.433
Total testosterone (ng/dL)	359 ± 50	436 ± 109	.016
Prolactin (µg/L), median (IQR)	10 [6-13]	11 [9-14]	.323

Continuous data were presented as mean ± standard deviation or median (interquartile range) according to normality.
GH, growth hormone; IGF-1, insulin-like growth factor 1; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Table 2. Seminal Plasma Hormone Levels and Sperm Parameters

	Acromegaly (n = 24)	Healthy Controls (n = 16)	*P*
Seminal volume (mL)	2.3 [1.6-3.8]	3 [2.1-3.8]	.120
Sperm concentration (mil/mL)	30 [20-40]	45 [40-90]	.003
Total sperm count (mil/ejaculate)	60 [44-105]	120 [120-181]	<.001
Total motile sperm (%)	58 [50-58]	58 [51-65]	.436
Rapid progressive	25 [25-25]	25 [25-30]	.212
Slow progressive	30 [25.5-30]	29 [25-32.3]	.795
Non-progressive	3 [3-3]	3 [2.3-5]	.212
Sperms with normal morphology*, n (%)			.004
<1%	3 (12.5)	0 (0)	
1%-4%	15 (63.5)	4 (25.0)	
>4%	6 (25)	12 (75.0)	
Seminal plasma GH (pg/mL)	80 [56-174]	48 [33-86]	.027
Seminal plasma IGF-1 (pg/mL)	301 ± 152	412 ± 252	.129

*Normal morphology is was defined as 4% or higherContinuous parameters were presented as mean ± standard deviation or median [interquartile range].
GH, growth hormone; IGF-1, insulin-like growth factor-1.

In our study sample, serum GH was positively correlated with seminal plasma GH ($r = 0.489$, $P = .001$) (Figure 3) and negatively correlated with sperm count ($r = -0.337$, $P = .039$) and fast-forward motility ($r = -0.360$, $P = .023$). On the contrary, there was no significant correlation between seminal plasma hormone levels and semen parameters ($P > .05$ for all).

Discussion

In the present study, eugonadal patients with acromegaly who had controlled disease exhibited lower sperm count and sperm concentration in comparison to control men. The percentage of sperm with normal morphology was also lower in the acromegaly group. These findings underpin the negative impact of acromegaly on male fertility despite disease control. We provided evidence regarding the seminal levels of GH and IGF-1 in patients with acromegaly. The patients had higher levels of seminal plasma GH compared to the control group. The positive association between serum and seminal plasma GH was noteworthy. The sperm count and fast forward motility were negatively affected by increasing levels of serum GH. Contrary to plasma growth hormone, seminal plasma GH and IGF-1 did not appear to affect semen parameters. These findings

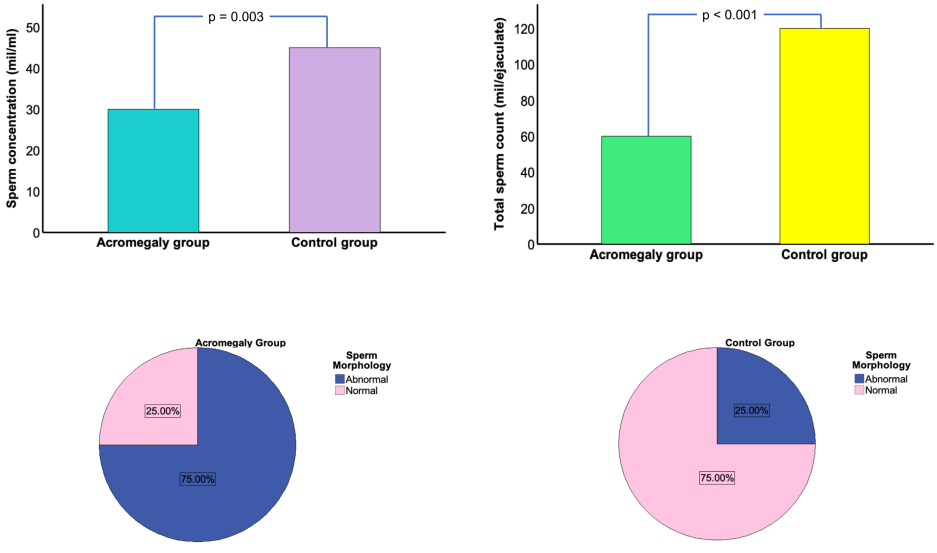

Figure 1. The comparison of sperm concentration, count, and motility between the acromegaly group and the control group.

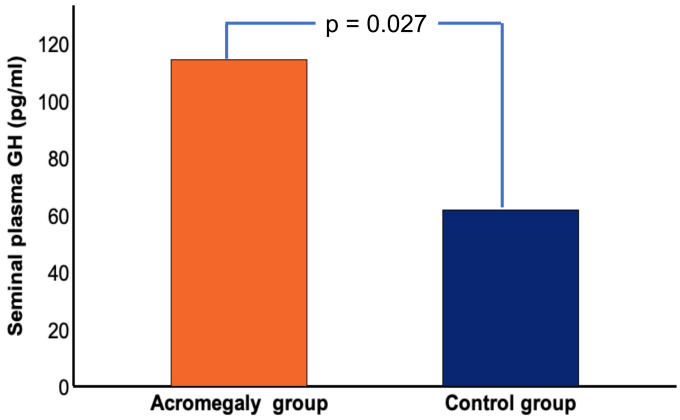

Figure 2. The comparison of seminal plasma growth hormone levels between study groups.

led to speculation that the impact of GH on male fertility appears to be primarily driven by its circulating concentrations rather than its seminal plasma levels.

Although impaired gonadal function is a frequent problem for acromegaly patients,[13] the scientific knowledge about sperm alterations in acromegaly patients is scant. In the last decade, only a few studies investigated semen alterations in acromegaly patients, and except for one, all studies reported impaired semen parameters.[5,14,15] The present study contributes to the growing body of evidence supporting the impaired sperm parameters in acromegaly patients.[5,15,16] Particularly, the observation of low sperm count and sperms with normal morphology despite disease control highlights the importance of addressing reproductive health issues in the management of acromegaly patients, even in the remission setting.

Table 3. Comparison of Seminal Plasma and Serum Parameters Between SLAR Users and Non-Users

	SLAR Users (n = 18)	SLAR Non-Users (n = 6)	*P*
Seminal volume (mL)	2.4 ± 1.4	2.9 ± 0.9	.396
Sperm concentration (mil/mL)	30 [20.8-40]	22 [6.5-37.5]	.199
Total sperm count (mil/ejaculate)	60 [43.5-110]	60 [30.5-40]	.880
Total motile sperm (%)	58 [53.3-58]	58 [36-59.8]	.820
Rapid progressive	25 [25-25]	25 [11.2-26.3]	.537
Slow progressive	30 [26.5-30]	30 [20-30.8]	.820
Non-progressive	3 [3-3]	3 [2.8-40]	.626
Sperms with normal morphology*, %	16.7	50	.378
Seminal plasma GH (pg/mL)	79.6 [59.7-193.6]	98.1 [47.8-165.7]	.871
Seminal plasma IGF-1 (pg/mL)	290.3 [170.5-362.6]	323.5 [267.6-467.9]	.310
Serum GH	0.520 [0.270-0.810]	0.250 [0.120-0.800]	.224
Serum IGF-1	184.6 ± 58	187.2 ± 84.8	.935

Continuous parameters were presented as mean ± standard deviation or median [interquartile range].
GH, growth hormone; IGF-1, insulin-like growth factor-1; SLAR, long acting somatostatin analog.
*Normal morphology is defined as >4%.

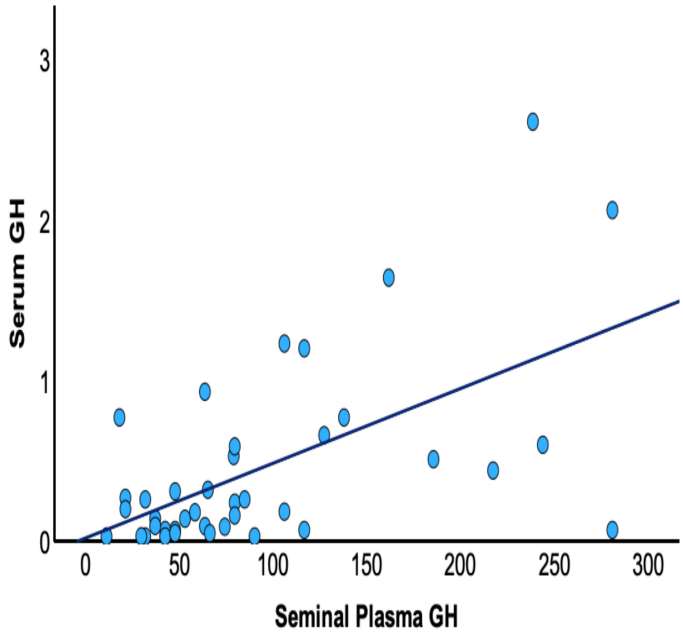

Figure 3. The correlation between serum and seminal plasma growth hormone levels.

The sperm abnormalities in acromegaly patients have been attributed to various factors, with low androgen levels being one of the primary considerations. However, none of the acromegaly patients in the present study had hypogonadism. This observation supports the unique impact of GH hypersecretion on sperm alterations observed in acromegaly patients. A plethora of evidence has suggested that Sertoli cells, Leydig cells, and spermatozoa are plausible targets for the actions of circulating GH and IGF-1.[17] On the other hand, the effects of local GH and IGF-1 found in seminal plasma on testicular functions remain to be established. To date, few studies have assessed the role of seminal plasma GH and IGF-1 in the reproductive system.[6,7,18] The majority of these studies have focused on men with decreased sperm motility, low sperm counts, or infertility. To our knowledge, there is no study that has evaluated the seminal plasma GH and/or IGF-1 levels and their relations with sperm parameters in acromegalic men.

We found that acromegaly patients had higher levels of seminal plasma GH compared to the other groups. The correlation of serum GH with seminal plasma GH levels implies an influence of serum GH on the hormonal environment within the male reproductive tract. It can be argued that seminal plasma GH may be a surrogate marker of serum GH or vice versa. Given the increased levels of seminal plasma GH with increasing levels of serum GH and low sperm count in acromegaly patients, we proposed that the negative effect of excess serum GH on sperm count may be mediated through increased seminal plasma GH in acromegaly patients. However, we did not find a relation between seminal plasma GH and sperm parameters. Previously, lower seminal plasma GH has been associated with decreased sperm motility.[6,19] In the present study, although the control group had lower seminal plasma GH than the acromegaly group, sperm motility showed no difference. Overall, our results implied that the negative impact of GH excess on male fertility is related to its systemic levels

rather than local concentrations. Further investigations with larger sample sizes and more comprehensive assessments of male reproductive health may provide deeper insights into the potential role of seminal GH in acromegaly-related semen alterations.

Our study did not reveal a difference in seminal plasma IGF-1 levels between patients with acromegaly and control men. One possible explanation for this finding may be that serum GH has no effect on testicular IGF-1 production.[20] The absence of a correlation between serum GH and seminal IGF-1 in our study supports this notion. The extent to which systemic GH levels correlate with seminal IGF-1 levels might depend on the degree of disease control. In this study, all the patients in the acromegaly group had controlled disease. It can be speculated that serum GH might affect seminal plasma IGF-1 levels once it reaches a certain threshold. Therefore, mildly elevated serum GH levels in the acromegaly group might have fallen short of increasing seminal IGF-1, leading to comparable seminal IGF-1 levels. It is also possible that intratesticular production of IGF-1 induced by GH may be confined within the testicular cellular compartments and therefore may not be detectable in seminal plasma. The presence of IGF-1 production by the prostate gland could also influence the comparison of seminal plasma IGF-1 levels between acromegaly patients and others.[21] Previously, it has been shown that seminal plasma IGF-1 levels exhibit substantial random fluctuations within the same individual or are diluted distally due to fluid production by prostate.[22] If this is so, the similar levels of seminal plasma IGF-1 cannot dispute the direct effect of GH on testicular IGF-1 production in acromegaly patients.

Another finding of our study was the lack of correlation between seminal plasma IGF-1 levels and semen parameters. Indeed, evidence regarding the association between seminal plasma IGF-1 levels and semen parameters is conflicting. Some studies conducted on infertile men have proposed that elevated seminal plasma IGF-1 levels may be associated with infertility, suggesting a possible detrimental effect on sperm quality and function.[18,23] Conversely, animal models and studies conducted on patients with fertility problems and healthy men have reported a potential beneficial impact of seminal plasma IGF-1 on sperm parameters.[24,25] Additionally, no association was documented in men with abnormal sperm motility and/or morphology.[6,26] The discordant findings concerning the relation of seminal plasma IGF-1 and semen parameters may be related to local factors that such as IGF-2 and IGF-binding proteins that can alter the bioactivity and bioavailability of seminal plasma IGF-1. There is no study that has investigated the seminal plasma IGF-1 levels in acromegaly patients. Given the conflicting data in the literature, reported fluctuations in its seminal plasma levels, and the findings from our study, it is reasonable to assume that seminal plasma IGF-1 might not be a reliable marker for assessing gonadal function in acromegaly patients.

In the present study, the impaired sperm parameters in patients with acromegaly, despite an intact hypothalamo-gonadal axis and biochemical control of the disease, suggest that other factors, such as comorbidities and treatments, may play a role. The negative effects of diabetes mellitus and hypertension on semen quality are well-established.[27] In this study, only 16% of patients had diabetes and 8% had hypertension. The relatively low prevalence of these comorbidities might minimize the impact that diabetes or hypertension could have had on sperm quality, leaving other factors to be explored. Therefore, we also considered the plausible effects of acromegaly treatment. In this study, 75% of patients with acromegaly were on SLAR therapy. The specific effects of SLAR treatment on sperm parameters remain unclear, and scientific knowledge on its impact in animal studies is limited. In animal models, octreotide has been shown to affect testicular function, evidenced by reduced semen motility.[28] This reduction has been linked to the octreotide-induced decrease in GH levels. Nevertheless, it is uncertain whether the same effect occurs in humans when excess GH is normalized with SLAR treatment. In this study, sperm parameters and seminal plasma GH/IGF-1 levels did not differ between acromegalic patients receiving SLAR therapy and those who were not. A body of literature has shown that both low and high GH levels have been shown to negatively affect gonadal function. Therefore, SLAR therapy, by bringing elevated GH levels back to the normal range, might not have impacted sperm parameters adversely as anticipated. This hypothesis is further supported by a study demonstrating improved sperm count and motility in acromegalic men after short-term suppression of GH and IGF-1 following somatostatin analogue treatment.[15] Overall, it can be proposed that the effect of SLAR on reproductive health might be more complex than initially expected, underpinning the need for future research.

Some limitations of our study need to be acknowledged. The small sample size might have smoothened the differences in studied outcomes; a larger sample size might have improved the power of analysis. Another limitation would be the cross-sectional design. We also acknowledge that the selection of fertile men as a control group may not perfectly represent the broader population. On the other hand, we provided preliminary evidence about the information on seminal plasma GH and IGF-1 levels in patients with acromegaly. We acknowledge that multiple semen analyses, instead of one, would provide more accurate information about reproductive biology.

We found that sperm count may be negatively affected in patients with acromegaly, even in the presence of an intact hypothalamic–pituitary–gonadal axis and disease control, highlighting the multifaceted nature of sperm abnormalities in acromegaly. The sperm alterations in patients with acromegaly appear to be correlated with elevated serum GH levels rather than increased seminal plasma GH. While our study provided important preliminary data on the seminal plasma GH and IGF-1 levels, the effects of seminal plasma GH and IGF-1 on the testicular function of acromegaly patients require more in-depth research.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine (approval no: 2021-90-273; date: May 05, 2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.K.; Design – P.K., S.S.; Supervision – P.K., H.O.; Resources – H.O., P.K., H.M.O.; Materials – C.S., E.C.; Data Collection and/or Processing – C.S., E.C.; Analysis and/or Interpretation – C.S., P.K., S.S., H.O., R.P.; Literature Search – C.S., E.C., R.P.; Writing – C.S.; Critical Review – R.P., P.K.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The present study was funded by Scientific Research Projects Coordination Unit of İstanbul University-Cerrahpaşa (Grant No: 35933).

References

1. Melmed S. Medical progress: acromegaly. *N Engl J Med*. 2006;355(24):2558-2573. [CrossRef]
2. Vilar L, Vilar CF, Lyra R, Lyra R, Naves LA. Acromegaly: clinical features at diagnosis. *Pituitary*. 2017;20(1):22-32. [CrossRef]
3. Tenuta M, Carlomagno F, Cangiano B, et al. Somatotropic-Testicular Axis: a crosstalk between GH/IGF-I and gonadal hormones during development, transition, and adult age. *Andrology*. 2021;9(1):168-184. [CrossRef]
4. Melmed S, Colao A, Barkan A, et al. Guidelines for acromegaly management: an update. *J Clin Endocrinol Metab*. 2009;94(5):1509-1517. [CrossRef]
5. Yilmaz MK, Sulu C, Ozkaya HM, Kadioglu A, Ortac M, Kadioglu P. Evaluation of sex hormone profile and semen parameters in acromegalic male patients. *J Endocrinol Invest*. 2021;44(12):2799-2808. [CrossRef]
6. Simopoulou M, Philippou A, Maziotis E, et al. Association between male Infertility and seminal plasma levels of growth hormone and insulin-like growth factor-1. *Andrologia*. 2018;50(7):e13048. [CrossRef]
7. Fu L, Yuen KCJ, Tint AN, Hoffman AR, Bongso AT, Lee KO. Association of decreased sperm motility and increased seminal plasma IGF-I, IGF-II, IGFBP-2, and PSA levels in infertile men. *Endocrine*. 2021;74(3):698-706. [CrossRef]
8. Organization WH. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. Geneva: World Health Organization; 2021.
9. Katznelson L, Laws ER, Jr, Melmed S, et al. Acromegaly: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(11):3933-3951. [CrossRef]
10. Giustina A, Barkan A, Beckers A, et al. A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. *J Clin Endocrinol Metab*. 2020;105(4), [CrossRef]
11. Corona G, Goulis DG, Huhtaniemi I, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males: endorsing organization: European Society of Endocrinology. *Andrology*. 2020;8(5):970-987. [CrossRef]
12. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(5):1715-1744. [CrossRef]
13. Salvio G, Martino M, Balercia G, Arnaldi G. Acromegaly and male sexual health. *Rev Endocr Metab Disord*. 2022;23(3):671-678. [CrossRef]
14. Andreassen M, Juul A, Feldt-Rasmussen U, Jørgensen N. Semen quality in hypogonadal acromegalic patients. *Pituitary*. 2020;23(2):160-166. [CrossRef]
15. Colao A, De Rosa M, Pivonello R, et al. Short-term suppression of GH and IGF-I levels improves gonadal function and sperm parameters in men with acromegaly. *J Clin Endocrinol Metab*. 2002;87(9):4193-4197. [CrossRef]
16. Katznelson L, Kleinberg D, Vance ML, et al. Hypogonadism in patients with acromegaly: data from the multi-centre acromegaly registry pilot study. *Clin Endocrinol (Oxf)*. 2001;54(2):183-188. [CrossRef]
17. Lobie PE, Breipohl W, Aragón JG, Waters MJ. Cellular localization of the growth hormone receptor/binding protein in the male and female reproductive systems. *Endocrinology*. 1990;126(4):2214-2221. [CrossRef]
18. Colombo JB, Naz RK. Modulation of insulin-like growth factor-1 in the seminal plasma of infertile men. *J Androl*. 1999;20(1):118-125. [CrossRef]
19. Biswas S, Ferguson KM, Stedronska J, Baffoe G, Mansfield MD, Kosbab MH. Fructose and hormone levels in semen: their correlations with sperm counts and motility. *Fertil Steril*. 1978;30(2):200-204. [CrossRef]
20. Puche JE, Castilla-Cortázar I. Human conditions of insulin-like growth factor-I (IGF-I) deficiency. *J Transl Med*. 2012;10:224. [CrossRef]
21. Cohen P, Peehl DM, Rosenfeld RG. The IGF axis in the prostate. *Horm Metab Res*. 1994;26(2):81-84. [CrossRef]
22. Anapliotou MG, Evagellou E, Kastanias I, Liparaki M, Psara P, Goulandris N. Effect of growth hormone cotreatment with human chorionic gonadotropin in testicular steroidogenesis and seminal insulin-like growth factor-1 in oligozoospermia. *Fertil Steril*. 1996;66(2):305-311. [CrossRef]
23. Naderi G, Mohseni Rad H, Tabassomi F, Latif A. Seminal insulin-like growth factor-I may be involved in the pathophysiology of infertility among patients with clinical varicocele. *Hum Fertil (Camb)*. 2015;18(2):92-95. [CrossRef]
24. Sánchez-Luengo S, Fernández PJ, Romeu A. Insulin growth factors may be implicated in human sperm capacitation. *Fertil Steril*. 2005;83(4):1064-1066. [CrossRef]
25. Glander HJ, Kratzsch J, Weisbrich C, Birkenmeier G. Insulin-like growth factor-I and alpha 2-macroglobulin in seminal plasma correlate with semen quality. *Hum Reprod*. 1996;11(11):2454-2460. [CrossRef]
26. Lee HS, Park YS, Lee JS, Seo JT. Serum and seminal plasma insulin-like growth factor-1 in male infertility. *Clin Exp Reprod Med*. 2016;43(2):97-101. [CrossRef]
27. La Vignera S, Condorelli R, Vicari E, D'Agata R, Calogero AE. Diabetes mellitus and sperm parameters. *J Androl*. 2012;33(2):145-153. [CrossRef]
28. Aurich JE, Kranski S, Parvizi N, Aurich C. Somatostatin treatment affects testicular function in stallions. *Theriogenology*. 2003;60(1):163-174. [CrossRef]