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Published in:
Clinical Endocrinology

DOI (link to publication from Publisher):
[10.1111/cen.14750](https://doi.org/10.1111/cen.14750)

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Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Dal, J., Rosendal, C., Karmisholt, J., Feldt-Rasmussen, U., Andersen, M. S., Klose, M., Feltoft, C., Heck, A., Nielsen, E. H., & Jørgensen, J. O. L. (2023). Sex difference in patients with controlled acromegaly-A multicentre survey. *Clinical Endocrinology*, 98(1), 74-81. <https://doi.org/10.1111/cen.14750>

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Sex difference in patients with controlled acromegaly—A multicentre survey

Jakob Dal^{1,2}  | Christian Rosendal¹ | Jesper Karmisholt¹  |
 Ulla Feldt-Rasmussen^{3,4} | Marianne S. Andersen⁵ | Marianne Klose³ |
 Claus feltoft⁶ | Ansgar Heck⁷ | Eigil H. Nielsen¹ | Jens O. L. Jørgensen⁸

¹Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark

²Steno Diabetes Centre North Jutland, Aalborg, Denmark

³Department of Endocrinology and Metabolism, National University Hospital Rigshospitalet, Copenhagen, Denmark

⁴Department of Clinical Medicine, Faculty of Health and Medical Sciences, Copenhagen University, Copenhagen, Denmark

⁵Department of Endocrinology, Odense University Hospital, Odense, Denmark

⁶Department of Endocrinology, Herlev University Hospital, Herlev, Denmark

⁷Section of Specialized Endocrinology, Oslo University Hospital and Faculty of Medicine, University of Oslo, Oslo, Norway

⁸Department of Endocrinology, Aarhus University Hospital, Aarhus C, Denmark

Correspondence

Jakob Dal, Department of Endocrinology, Aalborg University Hospital, 9000 Aalborg, Denmark.
 Email: jakob.dal@dadnet.dk

Abstract

Objective: Active acromegaly is subject to sex differences in growth hormone (GH) and Insulin like growth factor 1 (IGF-I) patterns as well as clinical features but whether this also pertains to controlled disease is unclear.

Design: In a cross-sectional, multi-centre study, 84 patients with acromegaly ($F = 43$, $M = 41$), who were considered controlled after surgery alone ($n = 23$) or during continued somatostatin receptor ligand (SRL) treatment ($n = 61$), were examined.

Methods: Serum concentrations of GH, insulin, glucose and free fatty acid (FFA) were measured during an oral glucose tolerance test (OGTT) together with baseline serum IGF-I and completion of two HR-QoL questionnaires (acromegaly quality of life questionnaire [AcroQoL] and Patient-assessed Acromegaly Symptom Questionnaire [PASQ]).

Results: The mean age at the time of the study was 57 (± 1.1) years and the majority of females (were postmenopausal. Females had significantly higher fasting GH but comparable IGF-I standard deviation scores (SDS). Using fasting GH $< 1.0 \mu\text{g/L}$ as cut off, disease control was less prevalent in females ($F: 56\%$ vs. $M: 83\%$, $p = .007$) whereas a comparable figure was observed using IGF-I SDS < 2 ($F: 79\%$ vs. $M: 76\%$, $p = .71$). Compared with males, female patients showed impaired AcroQoL physical score ($p = .05$), higher fasting FFA ($p = .03$) and insulin concentrations during the OGTT ($p = .04$).

Conclusion: In patients with acromegaly considered controlled, postmenopausal females exhibited higher GH levels than males despite comparable IGF-I levels, which also translated into impaired metabolic health and well-being. Our findings point to the relevance of including GH measurements in the assessment of disease control and suggest that disease-specific sex differences prevail after treatment.

KEYWORDS

acromegaly, age, FFA, GH, IGF-I, insulin, pituitary adenoma, quality of life, sex

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1 | INTRODUCTION

Acromegaly is a rare but debilitating disease, which in most cases originates from a benign somatotroph adenoma from the anterior pituitary gland.¹ The phenotype is caused by excess production of growth hormone (GH) and Insulin like growth factor 1 (IGF-I) in addition to a mass effect of the pituitary adenoma.² If left untreated, the disease is associated with excess morbidity and mortality.² Surgical adenomectomy is a first-line treatment and effective in 50%–60%, and medical treatment with somatostatin receptor ligand (SRL) is a second-line treatment used in approximately 50% of patients.²

Sex differences in the clinical presentation of newly diagnosed acromegaly have been reported.³ Female patients experience a longer diagnostic delay⁴ and are more prone to develop metabolic complications,^{3,5–7} whereas males are more prone to develop skeletal changes.⁸ Female patients also exhibit elevated GH relative to IGF-I,^{3,4} which is ascribed to a suppressive effect of oestrogen on hepatic IGF-I production, but additional underlying mechanisms may exist.^{9,10} Sex differences in the regulation of GH secretion in postmenopausal women and males in the general population have also been suggested.^{11,12}

It is unclear whether sex differences persist in patients with controlled disease, but discordantly elevated GH levels with normalised IGF-I in female patients across all age groups are reported.¹³ This could indicate that the relationship between GH and IGF-I persists in postmenopausal females during treatment.

In this multi-centre study, we further evaluated sex-specific differences in patients with acromegaly, who were considered controlled by either surgery alone or with SRL treatment.

2 | PATIENTS AND METHODS

2.1 | Patients and design

Eighty-four patients with acromegaly ($F = 43$, $M = 41$) were examined in a cross-sectional manner. By definition, all patients were considered controlled after either surgery alone ($F = 13$, $M = 10$) or during continued *first-generation* SRL treatment ($F = 30$, $M = 31$) for at least >6 months after either surgery alone or during continued SRL treatment. The definition of disease control was made by the attending endocrinologist and based on hormone levels as well as the clinical presentation, rather than using a specific cut-off level.

All patients were examined with serum GH profiles and concomitant insulin, glucose and free fatty acid (FFA) levels, a single IGF-I measurement, and two different HR-QoL questionnaires. Blood was sampled between 8:00 and 11:00 AM, after overnight fast with 10-min intervals during the first hour ($t = -60$ min to $t = 0$ min), followed by an oral glucose load (75 g) at $t = 0$ and sampling at $t = 30$, 45, 60, 90, and 120 min. All laboratory measurements were performed centrally (Medical Research Laboratory, Aarhus University Hospital, Denmark).

The data originate from a prospective study (DANSG) where SRL-treated patients were randomised to biochemical monitoring according to either IGF-I or GH levels during a 12-month period.¹⁴ In the current paper, only baseline data are included. The DANSG study was registered at Clinical Trials (ID:SOM-2012-01), and approved by the Danish Ethical Committee (no. 1-10-72-284-12), the Danish Data Protection Agency (no. 2012-41-0668), and the Regional Ethical Committee Southeast Norway (REK 2012/1383).

2.2 | Hormones and metabolites

All serum IGF-I and GH concentrations were determined centrally using the automated IDS-iSYS chemiluminescence immunoassays, as previously described.¹⁴ IGF-I standard deviation scores (SDS) at the time of acromegaly diagnosis were calculated post hoc based on IGF-I data from each patient record using the corresponding sex and age-related cut-off levels. Serum levels of insulin, glucose, and FFA were measured as previously described.¹⁴ Homeostatic model assessment (HOMA) was used to calculate b-cell function (HOMA-b) and insulin resistance (HOMA-IR) based on fasting levels of insulin and glucose.¹⁵ The adipose tissue insulin resistance (Adipo-IR) was calculated by multiplying fasting serum insulin concentration (pmol/L) by fasting serum FFA concentration (mmol/L).¹⁶

2.3 | Patient-reported symptoms and health related quality of life (HR QoL)

The Patient-assessed Acromegaly Symptom Questionnaire (PASQ) and the Acromegaly quality of life questionnaire (AcroQoL) questionnaires were applied. The latter comprises 22 questions each of which has 5 possible answers scored 1–5, with a total maximum score of 110 and expressed as a percentage. The questions are divided into two main categories: physical and psychological functions. The psychological dimension is subdivided into appearance and personal relationships. The score of 110 reflects the best possible QoL.¹⁷ The PASQ is a disease-specific questionnaire, which consists of six questions scoring 0–8 and a seventh question addressing the overall health status, based on the other six questions, scoring 0–10. The first six questions measure the following symptoms: headache, excessive sweating, joint pain, fatigue, soft tissue, swelling, and numbness or tingling of the extremities. A high PASQ score reflects a large symptom burden.¹⁸

2.4 | Statistical analysis

Histogram and qq-plot were used to examine continuous variables for normal distribution. If data were not normally distributed, log transformation was applied to obtain a normal distribution. Data are expressed as mean \pm SE or as median (interquartile range) for log-transformed data. Nonparametric data as HR-QoL were expressed as

median (range). Student's unpaired *t* tests were used to compare variables between groups. Correlation analyses were performed using Pearson's correlation coefficient. Wilcoxon rank-sum test were used to compare nonparametric data between groups. Fischer's exact test was used to test differences in cross tables. Area under the curve (AUC) was calculated by the trapezoidal rule. A *p*-value <.05 was considered statistically significant. Unless otherwise stated, the analyses were not stratified according to treatment modality.

3 | RESULTS

3.1 | Clinical characteristics including GH and IGF-I levels

Demographic and clinical variables including the use of pituitary surgery, SRL treatment and treatment of hypopituitarism were comparable between males and females (Table 1). Seven patients (M:4, F:3) had type 2 diabetes mellitus (T2D). At the time of diagnosis, females showed significantly lower IGF-I_{SDS} compared with males (Table 2). After disease control, females showed significantly higher GH_{fasting}, GH_{AUC}, and GH_{delta} levels but comparable IGF-I_{SDS} and GH_{nadir} levels (Table 2 and Figures 1 and 2). This pattern was present in patients controlled by surgery alone as well as in SRL-treated patients (Table 2).

According to a GH_{fasting} cut-off level <1 µg/L, significantly fewer female patients achieved disease control (F: 56% (24 of 43) vs. M:83% (34 of 41), *p* = .007, Figures 3 and 4). A comparable number of females and males achieved disease control defined by IGF-I_{SDS} < 2 [F:79% (34 of 43) vs. M:76% (31 of 41), *p* = .71] or GH_{nadir} < 0.4 µg/l [F:47% (20 of 43) vs. M:61% (25 of 41), *p* = .18].

3.2 | Glucose tolerance and insulin sensitivity

HOMA-IR, HOMA-beta, glucose measurements, and Adipo-IR levels were comparable for females and males (Table 3). During the OGTT, females showed significantly higher Insulin_{AUC} and insulin_{120 min} levels. Fasting FFA levels were significantly higher in females but decreased to a lower level after glucose suppression. When multiplying Insulin_{AUC} by FFA_{AUC} during the OGGT, females showed significantly higher levels than males (*p* = .047).

3.3 | HR-QOL

Overall HR-Qol scores were comparable between females and males (Table 4), but female patients showed a significantly worse HR-QOL score in the AcroQol physical domain. The questions with

	All	Sex		<i>p</i> value
		Male	Female	
Patients (<i>n</i>)	84	41	43	N.S.
At diagnosis				
Age (year)	44 (±11)	43 (±11)	44 (±11)	N.S.
Adenoma size (mm)	17 (±1.1)	15 (±1.3)	19 (±1.8)	N.S.
Macro adenoma (%)	77	80	74	N.S.
Time of study				
Age (year)	57 (±1.1)	56 (±1.6)	58 (±1.4)	N.S.
Acromegaly duration	13 (±1.0)	13 (±1.5)	14 (±1.4)	N.S.
Treatment				
Long-acting SRL (<i>n</i>)	61	31	30	
- Duration (years)	9.2 (3.4–14)	8.9 (3.7–13)	9.6 (2.7–11)	N.S.
- Dosage (mg/month)	30 (20–40)	30 (20–40)	20 (10–30)	N.S.
- Pituitary surgery (<i>n</i>)	55	27	28	N.S.
Pituitary surgery only (<i>n</i>)	23	10	13	N.S.
Irradiation (<i>n</i>)	15	6	9	N.S.
Pituitary insufficiency (<i>n</i>)	26	13	13	N.S.
- Hypogonadism (<i>n</i>)	9	7	2	N.S.
- Hypothyroidism (<i>n</i>)	19	9	10	N.S.
- Adrenal insufficiency (<i>n</i>)	12	8	4	N.S.
- Diabetes insipidus (<i>n</i>)	3	1	2	N.S.

TABLE 1 Baseline characteristic data are presented as the total number of mean ± S.E or median (interquartile range)

TABLE 2 GH and IGF-I levels in acromegaly

	Male	Female	p value
Diagnosis			
IGF-I (SDS)	5.8 (± 0.4)	4.7 (± 0.3)	.01
GH nadir ($\mu\text{g/L}$)	10 (5.4–18)	14 (3.6–41)	N.S.
Time of study			
IGF-I (SDS)	1.3 (± 0.1)	1.3 (± 0.2)	N.S.
GH fasting ($\mu\text{g/L}$)	0.7 (0.4–1.1)	1.1 (0.7–1.8)	.001
GH nadir ($\mu\text{g/L}$)	0.3 (0.1–0.6)	0.4 (0.2–0.8)	N.S.
GH delta ($\mu\text{g/L}$)	0.2 (0.1–0.6)	0.7 (0.2–1.2)	<.001
GH AUC	123 (94–152)	178 (145–211)	.01
Somatostatin treated (n)			
	31	30	N.S.
IGF-I (SDS)	1.2 (± 0.2)	1.4 (± 0.2)	N.S.
GH fasting ($\mu\text{g/L}$)	0.7 (0.4–1.3)	1.1 (0.7–1.8)	.01
GH nadir ($\mu\text{g/L}$)	0.3 (0.2–0.7)	0.6 (0.2–0.9)	N.S.
GH delta ($\mu\text{g/L}$)	0.2 (0.1–0.6)	0.4 (0.1–1.1)	.04
Surgery only (n)			
	10	13	N.S.
IGF-I (SDS)	1.1 (± 0.4)	1.3 (± 0.1)	N.S.
GH fasting ($\mu\text{g/L}$)	0.7 (0.1–0.9)	1.3 (0.9–1.9)	.002
GH nadir ($\mu\text{g/L}$)	0.2 (0.01–0.4)	0.3 (0.1–0.3)	N.S.
GH delta ($\mu\text{g/L}$)	0.3 (0.07–0.5)	1.1 (0.6–1.5)	.007

Abbreviations: AUC, Area under the curve; SDS, standard deviation scores.

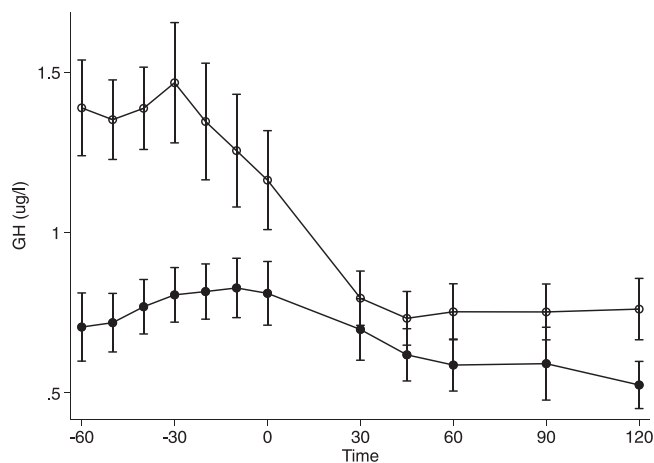


FIGURE 1 Mean + SE serum levels of GH during an oral glucose tolerance test (OGTT) in females (hollow circle) and males (filled circle) with acromegaly. OGTT, oral glucose tolerance test.

significantly worse scores in females were, “I have problems carrying out my usual activities” (No 9), “I have little sexual appetite” (No 21), and “I feel weak” (No 22). In male patients, one question showed a worse outcome than in females, “People stare at me because of my appearance” (No 10). There were no significant differences in HR-

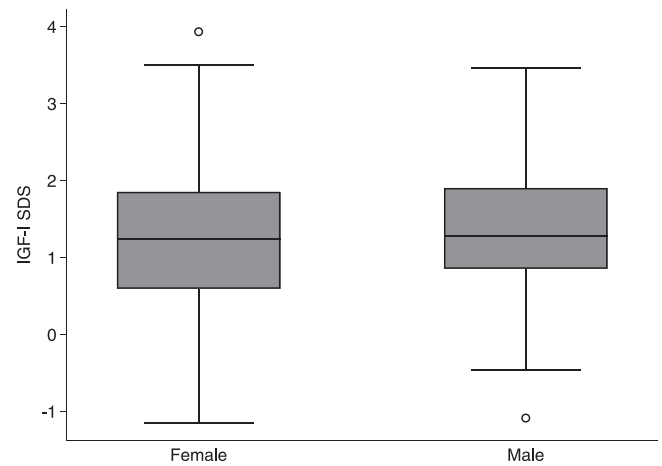


FIGURE 2 Boxplots showing IGF-I SDS in females and males with acromegaly. SDS, standard deviation scores.

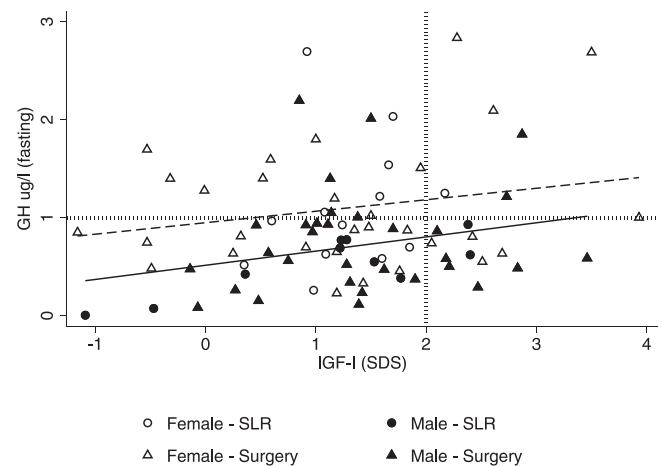


FIGURE 3 Correlations between fasting GH and IGF-I SDS. Females and males are depicted with hollow symbols and dashed regression line or filled symbols and full regression line, respectively. Patients with acromegaly treated with surgery (triangle) or a somatostatin receptor antagonist (circle). Reference lines for IGF-I SDS = 2 and fasting GH = 1 $\mu\text{g/L}$ is shown (dashed lines). SDS, standard deviation scores.

QOL outcomes between patients treated with SRL or surgery alone (data not shown). AcroQol physical domain score correlated negatively with IGF-I SDS in females only ($p = .038$, $R^2 = .10$).

4 | DISCUSSION

This study suggests that female patients with acromegaly are less well controlled after treatment compared with males despite comparable and normalised IGF-I levels. The sex difference was attributed to higher fasting GH levels measured over a 1 h period during strictly controlled conditions, which is superior to predicting disease activity as compared with a single fasting measurement.^{20,21} The difference in fasting GH concentrations was unexpected

inasmuch as healthy postmenopausal females and males were reported to have comparable GH levels.²¹ Also, a sex-independent cutoff level for nadir GH was recently recommended for males and postmenopausal females with acromegaly using the same ultrasensitive IDS-iSYS as in our study, which is similar to our finding.²² In acromegaly, a recommended cutoff level for disease control of both

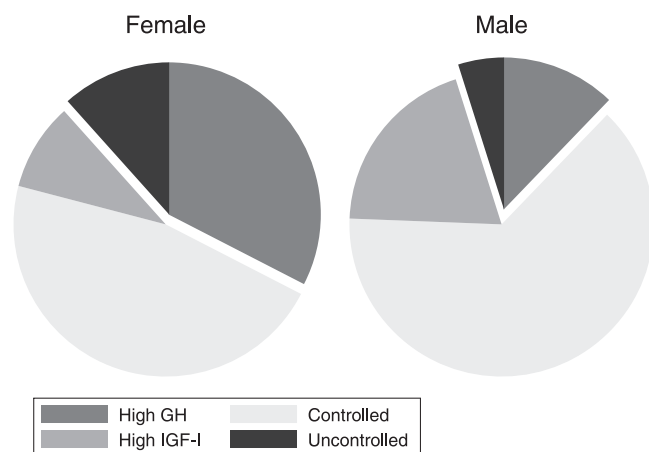


FIGURE 4 Distribution of females and males into one of the four predefined groups: concordantly elevated GH and IGF-I levels (black, uncontrolled), elevated GH and normalised IGF-I levels (dark grey, high GH), elevated IGF-I with normalised GH levels (light grey, high IGF-I) and concordantly normalised GH and IGF-I levels (white, controlled). Floating pie represents all cases with elevated GH levels and combines the group of high GH and uncontrolled persons.

males and females included a random GH < 1 µg/L is.¹ This value was based on an epidemiological study, suggesting that the overall increased mortality in acromegaly was attributed to patients of either sex exhibiting a GH level > 1 µg/L at their last follow-up.²³

However, sex differences in GH secretory patterns in active acromegaly and in healthy young subjects have been well described.^{3,4,11,21,24} Healthy premenopausal women show two-fold higher basal and pulsatile GH levels compared with men.²¹ Females with active acromegaly have a higher GH/IGF-I ratio due to a low IGF-I,⁴ which according to our study seems to persist posttreatment regardless of age and type of treatment. Indications of these sex differences have previously been reported in studies focusing on biochemical discordance where only GH or IGF-I reached the predefined cutoff level. In these studies, a consistent pattern of females prone to exhibiting elevated GH levels and normalised IGF-I is present.^{13,20,25-27} It has been suggested that the discordant high GH phenotype is predominantly found in younger oestrogen-sufficient females, implying a possible role for age and oestrogens driving this biochemical divergence.¹³ However, in most of these studies, the mean age among the female patients is close to the average age of menopause.^{13,25-27} In one study, the group of discordant elevated GH concentrations consisted of 72% postmenopausal females with a mean age of 70 years.²⁰ The clinical implication is uncertain, although females have an increased risk of comorbidities related to increased GH levels.²

The mechanism driving the sex differences in GH secretion is mainly ascribed to the action of circulating oestrogen. In premenopausal females, oestrogen reduces the hepatic IGF-I production

	Sex		p value
	Male	Female	
FFA (mmol/L)			
FFA AUC	22 (17-31)	26 (16-37)	N.S.
FFA fasting	0.37 (0.22-0.48)	0.44 (0.34-0.59)	.03
FFA 120 min	0.05 (0.03-0.09)	0.03 (0.01-0.07)	.02
Glucose (mmol/L)			
Glucose AUC	910 (800-1122)	882 (773-1152)	N.S.
Glucose fasting	5.5 (5.1-5.9)	5.0 (4.7-5.7)	N.S.
Glucose 120 min	6.3 (5.2-8.5)	6.8 (5.2-8.8)	N.S.
Insulin (pmol/L)			
Insulin AUC	15863 (9210-23996)	20303 (15473-29265)	.04
Insulin fasting	25 (20-48)	25 (18-39)	N.S.
Insulin 120 min	129 (82-203)	173 (122-342)	.01
Homa-Beta	46 (30-81)	54 (35-85)	.72
Homa-IR	1.2 (0.8-2.1)	0.9 (0.6-1.5)	.09
Adipo-IR	10 (6-19)	11 (5-20)	.76

Abbreviations: AUC, area under the curve; FFA, free fatty acids; HOMA, homeostatic model assessment.

TABLE 3 FFA, glucose, and insulin levels presented as median (interquartile range)

TABLE 4 Quality of life questionnaire data presented as median (range)

	All	Sex		p Value
		Male	Female	
AcroQol				
Global health status (%)	74 (50–96)	77 (50–95)	71 (50–96)	N.S.
Physical (%)	73 (33–100)	78 (33–100)	68 (40–100)	.05
- No. 9 (1–5)		5 (1–5)	4 (1–5)	.01
- No. 22 (1–5)		4 (1–4)	3 (2–5)	.02
Psychological (%)	73 (44–99)	74 (44–97)	71 (49–99)	N.S.
- No. 10 (1–5)		4 (1–5)	5 (1–5)	.02
Appearance (%)	63 (37–100)	69 (37–100)	63 (37–97)	N.S.
- No. 21 (1–5)		3 (2–5)	3 (1–5)	.03
Personal relationships (%)	83 (49–100)	89 (49–100)	83 (49–100)	N.S.
PASQ				
Headache (0–8)	1 (0–8)	1 (0–8)	1 (0–8)	N.S.
Excessive sweating (0–8)	1 (0–7)	1 (0–7)	1 (0–7)	N.S.
Joint pain (0–8)	4 (0–8)	3 (0–8)	4 (0–8)	N.S.
Fatigue (0–8)	4 (0–8)	3 (0–8)	4 (0–7)	N.S.
Soft tissue swelling (0–8)	1 (0–7)	1 (0–6)	1 (0–7)	N.S.
Numbness or tingling (0–8)	1 (0–7)	1 (0–6)	1 (0–7)	N.S.
Overall health status (0–10)	3 (0–9)	3 (0–9)	4 (0–8)	N.S.

Note: A high AcroQol score indicates a better Qol with few signs and symptoms of acromegaly, whereas PASQ is opposite graded. No. 9: I have problems carrying out my usual activities. No. 10: People stare at me because of my appearance. No. 21: I have little sexual appetite. No. 22: I feel weak.

which reduces the negative feedback on GH secretion.^{10,28} However, a paracrine action of oestrogen on the central stimulation of GH secretion in females has also been suggested.^{11,12} This mechanism is supported by the observation that a blockade of oestrogen action by tamoxifen reduces GH secretion in postmenopausal women but not in men.¹² High levels of oestrogen receptors are expressed in the hypothalamus and in the somatotroph cells of the pituitary gland.¹¹ Moreover, oestrogen is known to reduce somatostatin receptor expression and enhance ghrelin-induced increase in GH secretion in vitro.^{11,29} It is also proposed that local oestrogen in the pituitary mainly derive from local aromatisation of testosterone,¹² but further studies are needed to explore the underlying mechanisms.

The AcroQol scores were overall high, which is compatible with only few symptoms of active acromegaly. A recent meta-analysis including 52 studies showed a global AcroQol score of 63% among cross-sectional studies compared with a score of 74% in our cohort.³⁰ We observed only minor sex differences in the HR-Qol, but with worse outcomes in females. The AcroQol physical domain that showed a worse score in females included questions as: "I have problems carrying out my usual activities", "I feel weak" and "I have little sexual appetite". These findings support our previous publication on socioeconomic status in acromegaly. Females had increased use of social security benefits, early retirement, and a lower frequency of cohabitation and childbirth compared with males.³¹

Other studies have reported a worse outcome among females at the time of diagnosis,^{2,3,5} which could reflect a longer diagnostic delay.³³ It is less clear whether sex difference is a general phenomenon during disease remission, although other studies also support this notion.^{3,33}

Impaired glucose metabolism and diabetes mellitus are well-described complications in acromegaly² and are reported to be more prevalent in females.^{2,3} At the time of acromegaly diagnosis, female patients show a worse metabolic profile than males, despite comparable GH and IGF-I measures.⁵ This includes insulin resistance and several features of the metabolic syndrome which are ascribed to visceral fat dysfunction.⁵ Hence the underlying pathophysiology differs from that of type 2 diabetes mellitus since patients with acromegaly have a lean phenotype without increased visceral fat mass.³⁴ Insulin resistance in acromegaly is linked to the lipolytic effects of GH which causes insulin resistance in both muscle and fat.^{34–36} Our study suggested a subtle sex difference in the metabolic regulation, since female patients showed higher fasting FFA levels and a higher insulin response to glucose during the OGTT. Fasting insulin sensitivity measured by HOMA-IR and Adipo-IR, however, did not differ between females and males in our study. The use of SRL could affect the metabolic outcomes since somatostatin directly suppresses insulin secretion,³⁷ but this effect is not likely to be sex-dependent.

There are certain limitations to this study. First, the cross-sectional design prohibits the detection of causal mechanisms. Second, as the cohort is relatively small, we grouped the patients irrespective of treatment modality. In particular, a larger group of patients controlled by surgery only would have been a strength. On the other hand, males and females were matched on most variables including IGF-I, the treatment of acromegaly, and the prevalence of hypopituitarism. Third, no rigid criteria for disease control were applied, but it is noteworthy that IGF-I concentrations were within the upper limits of normal in most patients, which probably reflected common clinical practice across centres.

In summary, postmenopausal female patients with acromegaly exhibit increased GH concentrations despite normalised IGF-I levels. Female sex was also associated with slightly impaired quality of health, higher FFA levels despite higher insulin levels suggesting that disease-specific sex differences prevailed after treatment. Our findings support the relevance of including GH measurements in the routine assessment of disease control in acromegaly.

CONFLICTS OF INTEREST

Jakob Dal: unrestricted research grants and lecture fee from Pfizer and IPSEN, Jens O L Jørgensen: Grants and lecture fees from Pfizer, IPSEN and Novartis, Claus Feldttoft: Lecture fee from Bristol Myers Squibb, UFR: Grants, advisory board honoraria and lecture fees from Pfizer, IPSEN and Novartis, advisory board honoraria from Recordati, Ansgar Heck: speaker fees from Ipsen and Recordati.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Jakob Dal  <http://orcid.org/0000-0002-0610-7867>

Jesper Karmisholt  <https://orcid.org/0000-0001-6026-5834>

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How to cite this article: Dal J, Rosendal C, Karmisholt J, et al. Sex difference in patients with controlled acromegaly—a multicentre survey. *Clin Endocrinol (Oxf).* 2023;98:74-81. doi:10.1111/cen.14750