ORIGINAL ARTICLE

Sex and age differences among patients with acromegaly

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KEY WORDS

acromegaly, age, pituitary neuroendocrine tumor, sex

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ABSTRACT

INTRODUCTION Acromegaly is a chronic, slowly progressive disorder caused mostly by growth hormone (GH)-producing pituitary neuroendocrine tumors (PitNETs). Recently, the associations between sex and age at the time of diagnosis and the course of acromegaly have been a focus of debate.

OBJECTIVES The aim of our study was to evaluate the association between sex and age at the time of diagnosis of acromegaly and the clinical features, biochemical status, severity of the disease, and comorbidities.

PATIENTS AND METHODS This was a single-center study conducted in a group of consecutive patients with acromegaly and no family history of PitNETs. The participants were divded into 2 subgroups according to sex (male, female) and 3 subgroups according to age at the time of diagnosis: i) younger (≤40 years), ii) middle-aged (41–59 years), and iii) elderly patients (≥60 years).

RESULTS Our study included 101 patients (41 men, 60 women) who met the eligibility criteria. The mean (SD) age at the time of diagnosis was 47.3 (14.1) years and the median diagnostic delay was 5 years (interquartile range, 3–10). Age at the time of diagnosis and diagnostic delay were not statistically different in men and women. Levels of insulin-like growth factor 1 (IGF-1) above the upper limit of age-adjusted normal range (%ULN IGF-1) were greater in men than in women (mean [SD], 174.8% [98.9%] vs 109.4% [66.6%]; $P = 0.002$), while there was no significant difference in terms of %ULN IGF-1 between the age groups. Median basal and nadir GH levels did not differ between the sexes. Men presented with hypogonadism more frequently than women (54% vs 26%; $P = 0.005$). Hyperprolactinemia, hypogonadism, and macroadenoma were more frequently observed in the younger patients than in the middle-aged and elderly individuals (all $P < 0.05$).

CONCLUSIONS According to our results, hypogonadism and greater IGF-1 values were more frequently observed in men with acromegaly. Hyperprolactinemia, hypogonadism, and macroadenoma were more frequent in patients with acromegaly aged 40 years or younger.

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INTRODUCTION Acromegaly is a chronic, slowly progressive disorder, most often caused by growth hormone (GH)-producing pituitary neuroendocrine tumors (PitNETs).[1] The prevalence of acromegaly varies from 5.3 to 6.9 per 100 000 inhabitants with a slight female predominance, and the disease is most often diagnosed in the fifth decade of life.[2,3] Common clinical manifestations include changes in external appearance as well as serious systemic complications, such as cardiovascular, metabolic, and osteoarticular comorbidities, and an elevated risk of malignancy. Cardiovascular diseases and malignancies are mostly responsible for the increased mortality in patients with acromegaly.[4] In biochemically controlled individuals, the risk of complications or death is similar to that observed in the healthy population.[5] If the GH excess occurs during infancy, childhood, or adolescence, when the epiphyseal plates are still open, abnormally tall stature is observed. Despite major progress in the diagnosis and therapy of acromegaly in recent years, the diagnostic delay remains too long and ranges between 5 and 10 years. Wide spectrum of

WHAT'S NEW?

Some diseases show sexual dimorphism. In this study, we investigated whether the patient's sex had any effect on the course of acromegaly. Additionally, we evaluated the association between age at the time of diagnosis and the clinical features of somatotroph adenomas. A better understanding of the natural history of acromegaly would allow the implementation of personalized therapy. This would lead to improved efficacy of biochemical control, which remains the strongest predictor of the patient's outcome. In our population, male patients had greater insulin-like growth factor 1 values and more often presented with hypogonadism, whereas hyperprolactinemia, hypogonadism, and macroadenoma were more frequent in younger patients (≤40 years) with acromegaly. We believe that focusing on additional factors related to acromegaly would help internal medicine specialists, general practitioners, as well as clinical endocrinologists improve the diagnosis and treatment of acromegaly in everyday practice.

clinical outcomes that may develop in the course of the disease depends on multiple factors. A better understanding of the natural history of acromegaly would allow the implementation of personalized therapy. This would lead to improved efficacy of biochemical control, which remains the strongest predictor of a patient's outcome.[6,7] Some diseases show sexual dimorphism, and in this study, we investigated if sex was associated with the course of acromegaly. It was suggested that estrogens and androgens may have an impact on the GH–insulin-like growth factor 1 (IGF-1) axis.[8-10] An age-related phenotype of acromegaly has also been observed.[11-14] Younger patients present more often with an aggressive form of the disease that is resistant to medical therapy. Other factors known to be associated with a worse prognosis include the sparsely granulated subtype of somatotroph tumor, greater IGF-1/GH bioactivity, T2 hyperintensity on magnetic resonance imaging (MRI), or larger tumor size.[15] The aim of this study was to evaluate the association between sex and age at the time of diagnosis and the clinical features, comorbidities, biochemical status at the time of diagnosis, and disease severity.

PATIENTS AND METHODS The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Jagiellonian University (1072.6120.58.2020).

This was a single-center, epidemiological study conducted between January 1, 2019 and May 31, 2020. It included 101 consecutive adult patients with acromegaly who were diagnosed at the Department of Endocrinology, Jagiellonian University Medical College in Kraków, Poland. Biochemical confirmation of acromegaly was based on IGF-1 concentration above the normal range for age and sex with a lack of GH suppression (<1 μIU/ml) during the oral glucose tolerance test.[7,16] Exclusion criteria were ectopic growth hormone–releasing hormone (GHRH) production[17] or/and a positive family history of PitNETs. Baseline data regarding the biochemical status at the time of diagnosis and radiographic data were collected retrospectively, whereas information concerning the diagnostic delay and age at the onset of symptoms were collected during routine visits to an outpatient clinic. The data were analyzed in 2 subgroups divided by sex (male, female) and 3 subgroups divided by age at the time of diagnosis: i) younger patients (≤40 years), ii) middle-aged patients (41–59 years), and iii) elderly patients (≥60 years). Age at the onset of symptoms was estimated based on the patient case files and was confirmed with the patient and their family. Age at the time of diagnosis was defined as the age at which biochemical confirmation of acromegaly and a radiographic diagnosis of pituitary tumor were established. Hyperprolactinemia was defined as a prolactin concentration above the normal range (>400 μIU/ml). Hypogonadism was defined as amenorrhea in premenopausal women, low estradiol level with low or inappropriate but within-reference-range serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in postmenopausal women, or low serum testosterone level in men with low or inappropriate but within-reference-range serum levels of FSH and LH. Remission of the disease following the first surgery was defined as suppression of the GH concentration below 1 μg/l (2.5 μIU/ml) in the 75-g oral glucose suppression test and normalization of IGF-1.[7] Radiographic data were collected at the time of the first confirmation of pituitary abnormality or during follow-up, using MRI. Body height was assessed using a stadiometer. Body mass index (BMI) was calculated as the body mass divided by the square of the body height. Plasma IGF-1 concentration was measured with the RIA-ELISA (DIAsource ImmunoAssays SA, Louvain-la-Neuve, Belgium). The intra-assay coefficient of variation (CV) was 12.9%, while the inter-assay CV was 6.1%. The sensitivity of the assay was 4.5 ng/ml. Plasma GH concentration was measured with the IRMA assay (DIAsource ImmunoAssays SA). The intra-assay CV was 2.7%, while the inter-assay CV was 7.2%. The sensitivity of the assay was 0.04 μIU/ml.

The level of IGF-1 was expressed as a baseline value (ng/ml) and as percentage of IGF-1 of the upper limit of age-adjusted normal range (%ULN IGF-1).

Normal IGF-1 ranges in female patients were 191–478 ng/ml (for the age group of 21–30 years), 180–437 ng/ml (31–50 years), 123–406 ng/ml (41–50 years), 122–327 ng/ml (51–60 years), and 91-320 ng/ml (>60 years). Normal IGF-1 ranges in male patients were 235–408 ng/ml, 154–270 ng/ml, 160–318 ng/ml, 144–286 ng/ml, and 94-245 ng/ml, respectively, for the same age groups.

Statistical analysis Statistical analysis was performed using the Statistica software, version 13.3 (StatSoft Inc., Tulsa, Oklahoma, United States).

TABLE 1 Effect of sex on the biochemical and clinical features of acromegaly

Parameter	Women (n = 60)	Men (n = 41)	*P* value
Age at the time of diagnosis, y	47.7 (13.8)	46.7 (14.7)	0.72
Diagnostic delay, y	6 (3.5–10)	5 (3–7)	0.60[a]
Baseline GH level, μIU/ml	25.4 (18.4–67)	31.6 (20–66.2)	0.49[a]
Nadir GH level, μIU/ml	30.1 (13.4–61.2)	30.2 (21.5–72.4)	0.60[a]
Baseline IGF-1 level, ng/ml	778.7 (267.3)	831.4 (292.4)	0.42
%ULN IGF-1, %	109.4 (66.6)	174.8 (98.9)	0.002
Hyperprolactinemia, %	27.1	20.0	0.46
Tumor size, mm	12 (9.5–19)	16 (11.5–24)	0.09[a]
Macroadenoma, %	74.4	83.9	0.33
Hypogonadism, %	25.5	54.1	0.006
BMI, kg/m^2	27.5 (4.93)	29.2 (4.4)	0.10
Body height, cm	164.6 (7.6)	179.5 (9.2)	<0.001

Data are shown as percentage of affected patients, mean (SD), or median (interquartile range).

P values were derived from the χ^2 test or the *t* test unless indicated otherwise. A *P* value <0.05 was considered significant.

a Calculated using the Mann–Whitney test

Abbreviations: BMI, body mass index; GH, growth hormone; IGF-1, insulin-like growth factor 1; %ULN IGF-1, IGF-1 above the upper limit of age-adjusted normal range

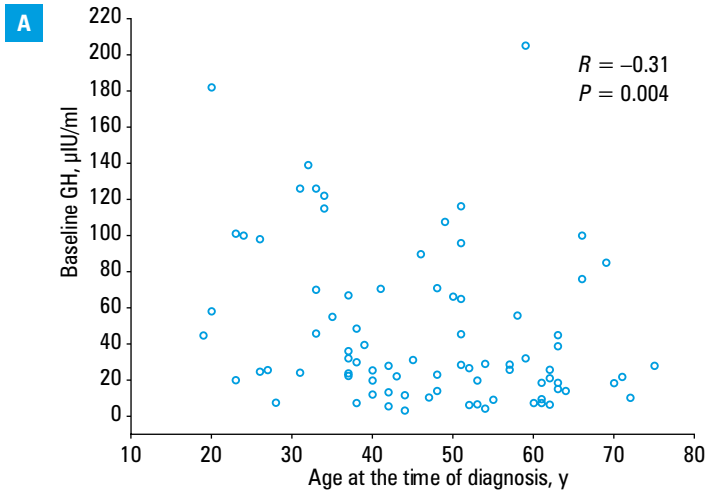

FIGURE 1 **A** – correlation between the age at the time of acromegaly diagnosis and the baseline GH level
Abbreviations: see TABLE 1

The significance level was set at 0.05. Categorical variables were expressed as frequencies. Quantitative variables were presented as mean with SD or median with interquartile range (IQR), depending on whether they followed a normal distribution. In order to confirm the normal distribution of variables, the Shapiro–Wilk test was applied. The differences in quantitative variables between the 2 groups divided by sex were analyzed using the *t* test for independent values if the assumption of normality of distribution was met. The equality of variances assumption was verified with the *F* test. In the case of the heterogeneous variances, the unequal variances *t* test (Cochran–Cox) was used (for %ULN IGF-1). If the conditions for the *t* test were not met, the Mann–Whitney test was applied.

Similarly, analysis of variance (ANOVA) and the Kruskal–Wallis test were used to compare variables between the 3 defined age groups, as appropriate. If the results were significant, post-hoc tests (Dunn test) were used to identify the groups that differed.

The χ^2 test was applied to analyze the relationship between sex and age groups with categorical variables. Spearman correlation coefficients (*R*) were calculated to measure the relationships between parameters.

RESULTS A total of 101 unselected, consecutive adult patients with somatotroph PitNETs (out of 104 patients who were interviewed in the outpatient clinic) met the eligibility criteria. Among the excluded individuals, 1 patient did not consent to participate in the study, 1 had a positive family history of PitNETs, and 2 patients were suspected to have ectopic GHRH/GH production. The study group comprised 60 women and 41 men at a mean (SD) age at the time of diagnosis of 47.3 (14.1) years, and a median (IQR) delay in diagnosis of 5 (3–10) years. There were no significant differences between the sexes in terms of the age at the time of diagnosis or diagnostic delay (TABLE 1).

Effect of age and sex on growth hormone concentration

Median baseline and nadir GH concentrations did not differ between the sexes. In the entire study group, the baseline GH level correlated inversely with age ($R = -0.31$; $P = 0.004$) (FIGURE 1A). Greater GH concentrations were observed in the younger subgroup as compared with the middle-aged and elderly patients: median (IQR), 44.7 (24.1–100) μIU/ml vs 28.2 (12.5–65.6) μIU/ml vs 19.9 (12.1–33.4) μIU/ml, respectively ($P = 0.04$) (TABLE 2). The post-hoc test showed a significant difference in the GH level between the younger and the elderly group ($P = 0.01$).

The nadir GH concentration after the oral glucose load test did not differ between the age groups. Additionally, the baseline GH level positively correlated with the tumor size ($R = 0.46$; $P < 0.001$).

Effect of age and sex on insulin-like growth factor 1 values

The mean (SD) value of %ULN IGF-1 was greater in men than in women: 174.8% (98.9%) vs 109.4% (66.6%) ($P = 0.002$). The %ULN IGF-1 values did not differ between the age groups. The baseline IGF-1 level was greater in the younger patients than in the middle-aged and elderly participants: median (IQR), 871 (756–1068) ng/ml vs 762. 5 (593–885) ng/ml vs 617 (483–765) ng/ml, respectively ($P = 0.003$). The post-hoc test showed a significant difference in the baseline IGF-1 level between the younger patients and the elderly group ($P = 0.003$) (TABLE 2).

The baseline IGF-1 level inversely correlated with age at the time of diagnosis ($R = -0.35$;

TABLE 2 Effect of age on the biochemical and clinical features of acromegaly

Parameter	Young; ≤40 years (n = 36)	Middle-aged; 41–59 years (n = 40)	Elderly; ≥60 years (n = 25)	*P* value	*P* value		
					Young vs middle-aged	Young vs elderly	Middle aged vs elderly
Baseline GH level, μIU/ml	44.7 (24.1–100)	28.2 (12.5–65.6)	19.9 (12.1–33.4)	0.04[a]	0.16[b]	0.01[b]	0.72[b]
Baseline IGF-1 level, ng/ml	871 (756–1068)	762.5 (593–885)	617 (483–765)	0.003[a]	0.10[b]	0.003[b]	0.59[b]
%ULN IGF-1, %	121 (77.5–204.5)	138.5 (71–196)	107 (73–139)	0.77[a]	>0.99[b]	>0.99[b]	>0.99[b]
Hyperprolactinemia, %	39.3	20.6	9.5	0.045	0.45[b]	0.31[b]	0.70[b]
Tumor size, mm	15 (12–23)	14.5 (9.3–18)	10.5 (8–15)	0.02[a]	0.13[b]	0.03[b]	>0.99[b]
Macroadenoma, %	93.1	74.1	61.1	0.02[a]	0.02[b]	0.005[b]	0.46[b]
Age at menarche, y (only women, n = 57)	13 (12–15)	13 (13–14)	13 (12–14)	0.87[a]	1.00[b]	1.00[b]	1.00[b]
Body height, cm	176.3 (11.5)	168.4 (10)	166.2 (8.8)	<0.001[c]	0.003[d]	0.001[d]	0.38[d]
BMI, kg/m^2	26.4 (23.8–28.1)	28.4 (24.8–30.2)	30.1 (26.8–31.3)	0.007[a]	0.17[b]	0.007[b]	0.43[b]
Diagnostic delay, y	4 (1.8–7)	6.5 (4–10)	7 (5–10)	0.04[a]	0.09[b]	0.09[b]	1.00[b]
Remission after the first surgery, %	50	57.5	60.1	0.68	0.66[b]	0.58[b]	0.85[b]
Hypogonadism, %	54.8	27.8	28.6	0.047	0.20[b]	0.96[b]	0.29[b]

Data are shown as percentage of affected patients, mean (SD) or median (interquartile range). *P* values were derived from the χ^2 test or the *t* test unless indicated otherwise. A *P* value <0.05 was considered significant.

a Calculated using the Mann–Whitney test

b Calculated using the Kruskall–Wallis test

c Calculated using the analysis of variance

d Calculated using the Newman–Keuls test

Abbreviations: see TABLE 1

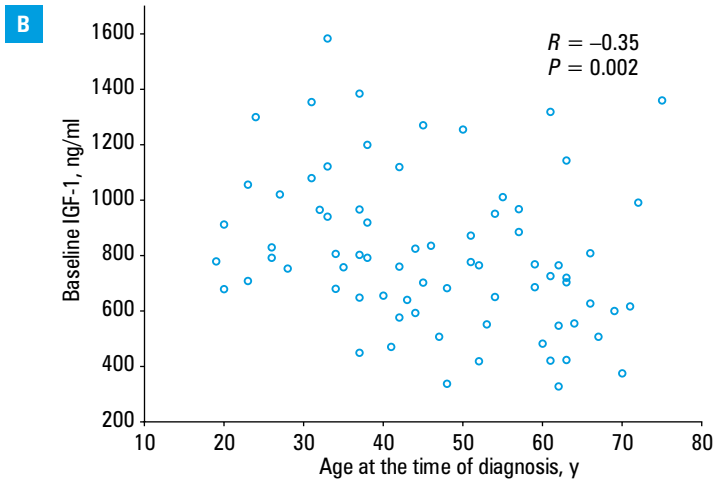

FIGURE 1 B – correlation between the age at the time of acromegaly diagnosis and the baseline IGF-1 level
Abbreviations: see TABLE 1

P = 0.002), while there was no correlation between %ULN IGF-1 and age (*R* = –0.02; *P* = 0.88) (FIGURE 1B and 1C). Baseline IGF-1 positively correlated with the body height (*R* = 0.27; *P* = 0.02).

Effect of age and sex on hyperprolactinemia The incidence of hyperprolactinemia was the greatest among the younger patients (39.4%), as compared with the middle-aged (20.6%) and elderly individuals (9.5%) (*P* = 0.003) (TABLE 2). The post-hoc test showed a significant difference in the frequency of hyperprolactinemia between the younger patients and the elderly group (*P* = 0.02) (TABLE 2).

In the entire study population, there was an inverse correlation between the prolactin level and age at the time of diagnosis (*R* = –0.33; *P* = 0.004) (FIGURE 1D). There was no significant difference in the frequency of hyperprolactinemia between men and women.

Effect of age and sex on tumor size The pituitary tumor size did not differ between female and male participants; however, a negative correlation between the tumor size and age was observed. The younger patients presented with a larger tumor size than the middle-aged and elderly individuals: median (IQR), 15 (12–23) mm vs 14.5 (9.3–18) mm vs 10.5 (8–15) mm, respectively (*P* = 0.045). The post-hoc test showed a significant difference in the tumor size between the younger patients and the elderly group (*P* = 0.03) (TABLE 2).

The frequency of macroadenoma was slightly greater in men than in women (84% vs 74%); however, the difference did not reach statistical significance. The tumor size positively correlated with the GH concentration (*R* = 0.46; *P* <0.001) and body height (*R* = 0.37; *P* = 0.001), but an inverse correlation was found for the age at the time of diagnosis (*R* = –0.33; *P* = 0.003) (FIGURE 1E).

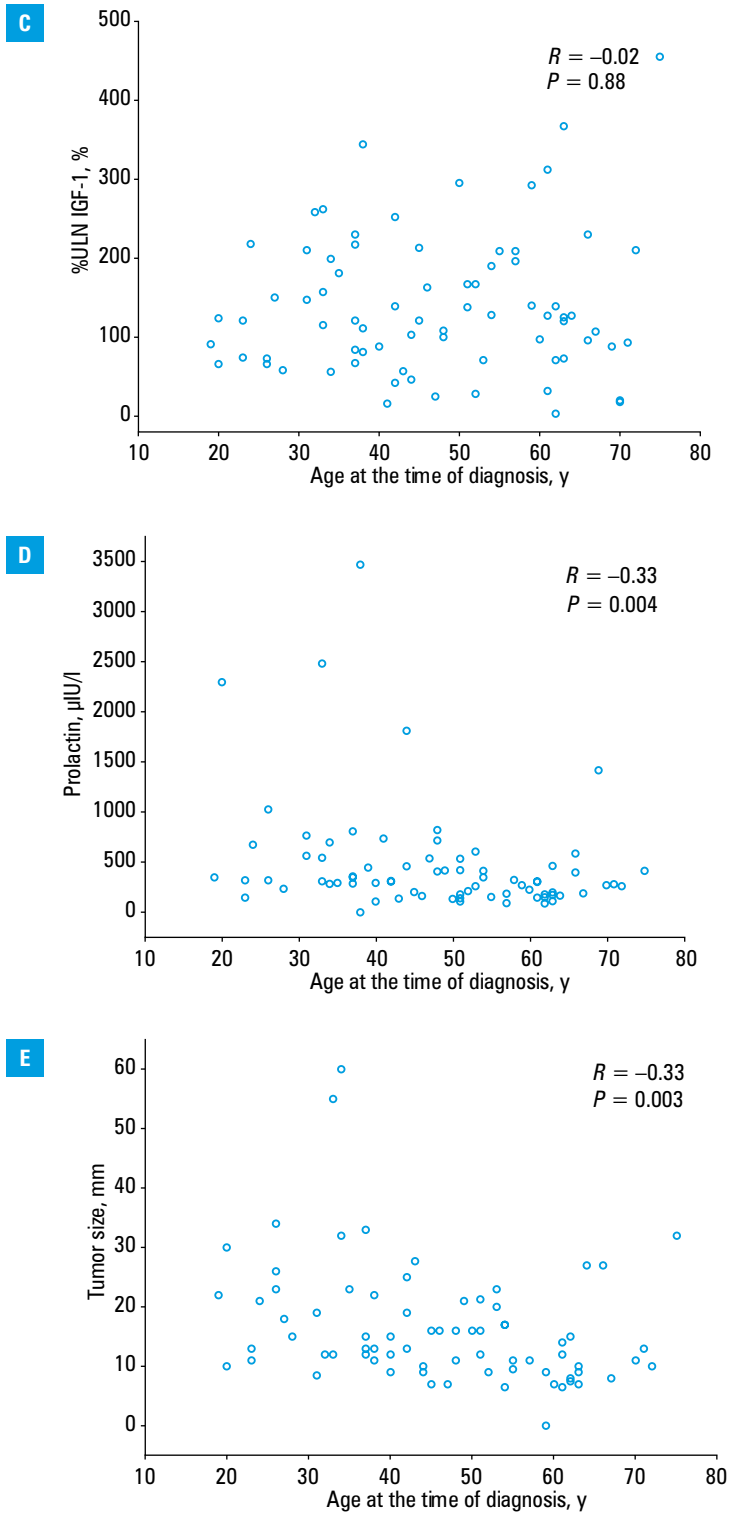

FIGURE 1 Correlation between the age at the time of acromegaly diagnosis and the %ULN IGF-1 (**C**), prolactin level (**D**), and pituitary tumor size (**E**)
Abbreviations: see TABLE 1

Effect of age and sex on hypogonadism Male patients presented with hypogonadism more frequently than female participants (54% vs 26%; $P = 0.005$). Hypogonadism at the time of diagnosis was also more common in the younger patients (54.8%) than in the middle-aged (27.8%) and elderly individuals (28.6%) ($P = 0.047$). The post-hoc test showed a significant difference in the frequency of hypogonadism between the younger patients and the middle-aged group ($P = 0.024$) (TABLE 2).

Effect of age and sex on BMI In female and male patients with acromegaly, median BMI values were similar. However, BMI inversely correlated with age in the entire population: the values were lower in the younger patients than in the middle-aged and elderly participants; median (IQR), 26.4 (23.8–28.1) vs 28.4 (24.8–30.2) vs 30.1 (26.8–31.3), respectively ($P = 0.007$). The post-hoc test showed a significant difference in BMI between the younger patients and the elderly group ($P = 0.007$) (TABLE 2). Moreover, BMI positively correlated with age at the time of diagnosis ($R = 0.32$; $P = 0.001$) (FIGURE 1F).

Effect of age and sex on body height Younger patients with acromegaly presented with a significantly greater mean body height than the middle-aged and elderly individuals: 176.3 (11.5) cm vs 168.4 (9.8) cm vs 166.2 (8.8) cm, respectively ($P < 0.001$). The post-hoc test showed a significant difference in body height between the younger patients and the middle-aged group ($P = 0.004$), and between the younger patients and the elderly group ($P = 0.001$) (TABLE 1). The body height positively correlated with the tumor size ($R = 0.37$; $P = 0.001$) and %ULN IGF-1 ($R = 0.34$; $P = 0.004$), but negatively correlated with the age at the time of diagnosis ($R = –0.37$; $P < 0.001$) (FIGURE 1G). Male patients presented greater height than the female group.

Effect of age and sex on remission of the disease following the first surgery The impact of a patient's sex on the remission rate following the first surgery was not significant. The elderly patients presented with a higher rate of successful treatment following transsphenoidal surgery (60.1%) than the middle-aged (57.5%) and younger patients (50%); however, these differences did not reach statistical significance.

Comorbidities Arterial hypertension, nodular goiter, and diabetes mellitus with glucose intolerance were more common among the elderly patients with acromegaly than in the middle-aged and younger participants ($P < 0.05$). There were no sex-related differences.

DISCUSSION

The results of our study, which involved a Polish cohort of unselected adult patients with somatotroph PitNETs, showed sex- and age-related differences in the disease presentation, prevalence of comorbidities, biochemical status, and severity of acromegaly.

Several diseases show sexual dimorphism. This phenomenon is observed in autoimmune diseases as well as in pituitary tumorigenesis. Some studies suggest the role of estrogens as a potential trigger, especially in prolactinomas.[10,18-20] In most studies of patients with acromegaly, women were slightly more frequently affected than men

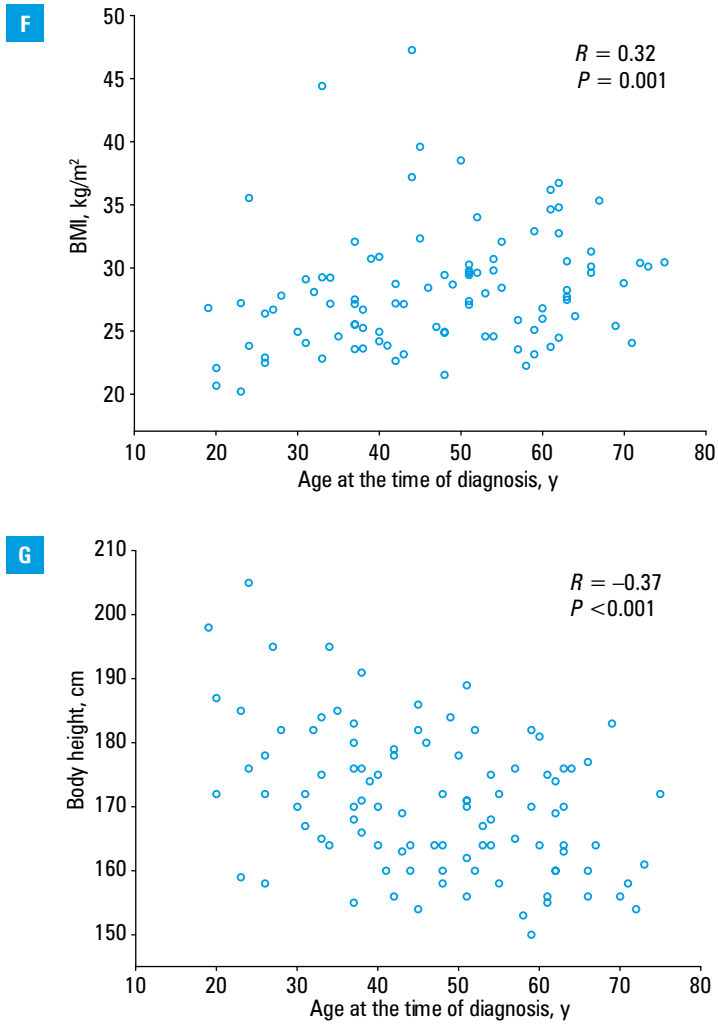

FIGURE 1 Correlation between the age at the time of acromegaly diagnosis and the BMI (**F**) and body height (**G**)
Abbreviations: see **TABLE 1**

(1.24:1).[2,3] However, there are also studies showing a balanced sex distribution or male predominance.[10,14,21,22] According to recently published data from a Denmark-based nationwide cohort study including all incident cases of acromegaly from 1978 to 2010, a balanced sex distribution and comparable age at the time of diagnosis were noted.[10] However, in that study, the sex distribution was associated with the calendar year during which acromegaly was confirmed (changing from initial female predominance to a more even sex balance). The authors suggested that this phenomenon may be associated with improvements in the diagnostic methods of somatotroph tumors (increased availability of MRI and IGF-1 assays in routine clinical practice), which led to an increasing incidence of milder cases of acromegaly.[10]

In our cohort, there were no relationships between the age at the time of diagnosis, sex, and the length of diagnostic delay. However, a recent meta-analysis by Dal et al[10] showed that women were older at the time of diagnosis and had a longer delay in diagnosis. In contrast, other studies demonstrated no sex-specific differences in the age at diagnosis of acromegaly.[10,21,23-26]

Based on several studies, there is strong evidence that gonadal steroids have a modulating effect on the somatotropic axis.[27,28] Estrogens reduce the GH secretion, and therefore cause a decrease in the IGF-1 production in the liver.[29] In contrast, testosterone increases the GH concentration.[9,28,30] In our cohort, there was no sex-specific effect on the basal and nadir GH levels; however, %ULN IGF-1 was greater in male patients. In a meta-analysis by Dal et al,[10] including 3567 cases, the IGF-1 concentration was significantly lower among women (mean difference, 106 µg/l), whereas the nadir GH concentration was comparable between the sexes. A recent study[31] also showed that other factors affecting the nadir GH level after glucose load include the BMI, sex, and estrogen in oral contraceptives. Moreover, the nadir GH concentration was significantly lower among healthy individuals than the cutoff values used in the current acromegaly guidelines.[31]

In our study population, both GH and IGF-1 concentrations inversely correlated with age. A variable age-dependent biochemical status was reported for the first time in 1992 by van der Lely et al.[32] This observation was later confirmed in several other studies, in which the older patients presented with lower GH and IGF-1 levels than the middle-aged and younger individuals.[12,32,33] In addition, our study showed that the basal GH level positively correlated with the tumor diameter.

Tumor size at the time of diagnosis is an important factor in the prediction of treatment outcomes. Larger pituitary tumors are associated with more aggressive behavior. In line with data from other studies, we observed no association between the sex and tumor diameter in our cohort.[3,14,21,24,34,35] However, some authors reported a larger tumor size in women.[12,13] Park et al[13] found that women (especially premenopausal) had larger and more aggressive tumors that were prone to surgical failure. In contrast, a multicenter study by Petrossians et al[36] found that male patients had larger tumors at the time of diagnosis. In our cohort, the younger patients presented with a larger tumor size at the time of diagnosis, which is consistent with previous studies showing a negative correlation between the tumor size and age.[9,34,37] Additionally, the tumor size positively correlated with GH levels, and this relationship has already been well established.[38] Age-related modulating factors, such as sex hormones or metabolic factors, may influence a more aggressive phenotype among young patients, indicated by a larger tumor size and higher GH concentration. This is in line with the results of our study, which showed that the younger patients demonstrated the highest recurrence rate of acromegaly following transsphenoidal surgery.

Hypogonadism in patients with acromegaly may result from the tumor mass effect or prolactin hypersecretion. However, hypogonadism was observed in patients with microadenoma in the absence of hyperprolactinemia.[39] In a study

of 363 patients, over half of the participants presented with hypogonadism, with a female predominance. In another study,[40] 38 out of 55 premenopausal patients with acromegaly presented with anovulatory cycles. In our analysis, hypogonadism was detected more frequently among men than women, and among the younger patients. Furthermore, Bhansali et al[11] observed hypogonadism in 23 out of 34 patients with adolescent acromegaly, especially in those with gigantism, as compared with the individuals of normal stature (90.9% vs 56.5%). Concomitant hypogonadism may also result in delayed closure of the epiphyses, and therefore lead to tall stature.[41,42] This is in line with our findings showing that the participants who were younger at the time of diagnosis were significantly taller than the middle-aged and elderly patients. Prolactin cosecretion or hyperprolactinemia due to stalk effect may contribute to greater body height, and in our cohort this phenomenon was most common among the younger patients. However, this observation was not sex-dependent.

Cardiovascular diseases, nodular goiter, and diabetes mellitus are more common in patients with acromegaly than in the general population.[43] In our study, the incidence of these comorbidities was greater in the older patients with acromegaly than in the younger participants. This is also observed in the general population. Although a milder acromegaly phenotype was observed in the older population, long-term exposure to excess GH/IGF-1 levels leads to irreversible effects. In addition, elderly patients with acromegaly need special attention and biochemical control, therefore, these factors should be the primary focus of patient management in this group.[43]

The main limitation of our epidemiological study was related to the fact that it used data from a single center; however, it did include over 100 consecutive patients. Regarding its retrospective design, a potential bias in data collection could exist. The radiographic data were assessed at various centers; however, the biochemical data at the time of diagnosis were analyzed locally in our department.

Conclusions The diagnosis of acromegaly is still challenging and knowledge about the disease among physicians is essential to early detection. According to our results, the course of acromegaly is influenced by the patient's sex and age at the time of diagnosis. Hypogonadism and greater IGF-1 values were more frequently observed in men, whereas hyperprolactinemia, hypogonadism, and macroadenoma were more common in the younger patients.

Additional efforts should be taken at the international level to facilitate early diagnosis in young patients presenting with an aggressive course of the disease as well as in older patients with a milder phenotype but significant comorbidities.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT AB and AGJ conceived to the concept of the study. AB, AGJ, MG, and AN searched for and extracted the data. AB, AGJ, and MG drafted the manuscript and contributed to data acquisition, analyses, and interpretation. AGJ, MG, JS, and AHD critically revised the manuscript and contributed to data interpretation. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

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