Age- and Sex-Specific Differences as Predictors of Surgical Remission Among Patients With Acromegaly

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Context: Sex and age are factors conferring resistance to medical treatment in patients with acromegaly. However, their impact on outcomes of transsphenoidal-selective adenomectomy (TSA) has not been evaluated.

Objective: To analyze age- and sex-related differences concerning surgical outcomes of growth hormone (GH)-secreting pituitary adenomas.

Design: Retrospective.

Setting: Single-center tertiary hospital.

Participants: Patients with acromegaly (n = 463) who underwent TSA between January 2000 and July 2014.

Intervention: TSA.

Main Outcome Measurements: Tumor characteristics and surgical outcomes.

Results: Sex differences existed in the baseline insulinlike growth factor-1 levels and the mean tumor size. Overall, surgical remission rates were 89.7% and 76.5% in male and female patients, respectively ($P < 0.001$). Total tumor tissue resection was performed in 92.6% and 85.8% of male and female participants, respectively ($P = 0.021$). Premenopausal women had a higher proportion of pituitary adenoma with cavernous sinus invasion than did men aged <50 years (35.3% vs 21.7%, $P = 0.007$). In immediate postoperative, 75-g oral glucose tolerance tests, fewer premenopausal women reached <1 ng/dL nadir GH levels than did men aged <50 years (59.9% vs 87.7%, $P < 0.001$). Surgical results were similar in both sexes among older patients (≥50 years). However, premenopausal women had significantly lower long-term remission rates than did men aged <50 years (69.3% vs 88.0%, $P < 0.001$).

Conclusion: Premenopausal women with acromegaly tend to have larger tumors, more aggressive tumor types, and lower remission rates than do men. However, further studies on the clinical implications are needed. (***J Clin Endocrinol Metab*** **103: 909–916, 2018)**

Acromegaly is defined as the chronic hypersecretion of growth hormone (GH) and consequently, insulinlike growth factor-1 (IGF-1) into the circulation. This disease is most commonly caused by GH-secreting pituitary adenomas. Patients with acromegaly have increased premature mortality (1) because of insulin resistance,

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 18 August 2017. Accepted 15 December 2017.
First Published Online 20 December 2017

Abbreviations: CI, confidence interval; CV, coefficient of variation; GH, growth hormone; IGF-1, insulinlike growth factor-1; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; OR, odds ratio; TSA, transsphenoidal-selective adenomectomy.

myocardial hypertrophy, hypertension, diastolic dysfunction, ventilatory dysfunction, and sleep apnea (2, 3). Transsphenoidal-selective adenomectomy (TSA) is the treatment of choice among patients with acromegaly. Resection is performed, not only for resectable somatotroph adenomas but also for those that cause visual impairment (4), even if complete resection of the tumor is impossible. The surgical success rate is known to be associated with tumor size and invasiveness. Patients with small and noninvasive tumors are more likely to achieve surgical remission than large and invasive tumors (5, 6). The complete resection rate of microadenomas is ~80% to 90%; however, the cure rate with surgery drops to 50% in the cases of macroadenomas (7). Additionally, some studies showed that the recurrence rate after the initial surgical remission may reach up to 10% (6, 8, 9).

Several studies have been conducted on the prognostic factors of acromegaly (10, 11). Fernandez-Rodriguez *et al.* (10) demonstrated that the main prognostic factors of acromegaly were increasing tumor size, tumor volume, high baseline GH/IGF-1 levels, a >3% Ki-67 level, young age, magnetic resonance imaging (MRI) T2 hyperintensity, and sparsely granulated tumors. Meanwhile, several studies focused on the sex differences associated with these factors but have not shown consistent results. Some authors reported that female patients had higher circulating baseline GH levels and more aggressive and larger pituitary tumors than male patients. Furthermore, a stronger correlation between tumor volume and GH levels was observed among female patients than among male patients (12). However, another study found that the nadir GH levels did not differ between sexes in any participant group (13). Additionally, although the normal IGF-1 level is known to decline with age, data available regarding age-related changes in tumor size, invasiveness, and surgical outcomes among patients with acromegaly are scarce. Despite the fact that many studies have been conducted, data on selection of patients who are more likely to benefit from available therapies, show resistance to treatments, and have a higher probability of tumor recurrence remain sparse.

Therefore, this study aimed to investigate the effect of sex and age on GH and IGF-1 concentrations, tumor size and invasiveness, and surgical outcomes among patients with acromegaly.

Materials and Methods

Study populations

A total of 491 Korean patients with acromegaly underwent TSA between January 2000 and July 2014 in Severance Hospital, Seoul, South Korea. The operations were performed by one neurosurgeon (S.H.K.). Twenty-eight out of 491 patients were excluded from the study because appropriate endocrinological evaluations were not performed. We reviewed the data of 463 patients with acromegaly who underwent appropriate endocrinological evaluations and were followed up for at least 3 years after TSA until July 2014. The endocrinological evaluations included 75-g oral glucose tolerance tests (OGTTs), along with measurement of IGF-1; OGTTs and measurement of IGF-1 were performed every 6 months during the first 3 years after surgery and then annually. The combined pituitary function test was also performed. These patients were divided into four groups based on their sex and age: men aged <50 years, premenopausal women, men aged ≥50 years, and postmenopausal women.

Pituitary tumors were classified based on radiological findings, using MRI of the sella and parasellar regions, as previously described (14). In brief, classification I refers to tumors that are <1 cm in diameter and limited within the sella. Classification II pertains to adenomas that extend into the suprasellar region to <1 cm from the diaphragmatic border. Classification IIIA includes tumors extending into the suprasellar space to >1 cm from the diaphragmatic border, whereas classification IIIB consists of adenomas extending into the sphenoid sinus, encroaching on the internal carotid arteries. Lastly, classification IV refers to adenomas with obvious invasion into the cavernous sinus, as shown on the MRI, and the medial dural wall of the cavernous sinus, as confirmed during the operation.

Immediate postoperative dynamic MRI of the sella was conducted within 48 hours after TSA to determine whether surgical resection was complete, which was then compared with that conducted 1 year following TSA. Subsequently, MRI was performed annually to find any evidence of recurrence and every 2 or 3 years if the patients reached biochemical remission at 4 years after TSA. Surgical remission is defined as <1 ng/mL nadir serum GH level based on the result of the 75-g OGTTs, age- and sex-matched normal IGF-1 level, and absence of a remnant tumor, as shown in the postoperative MRI. Long-term remission refers to a remission status that is maintained for >3 years. This study was approved by the Institutional Review Board of the Yonsei University College of Medicine (4-2017-0568). In accordance with the Institutional Review Board approval for reviewing the medical records of the patients, we collected and analyzed data through the electronic medical records system of Yonsei University College of Medicine.

Endocrinological evaluation

Before the surgery, the serum GH level was measured from sera obtained during a 75-g OGTT using a previously described protocol (5). OGTT was performed 1 week after TSA, every 6 months for 3 years, and then annually. Suppression of GH to <1 ng/mL in the 75-g OGTT was considered representative of biochemical remission. Before February 2010, GH levels were measured using an immunoradiometric assay (hGH 100T Kit; Nichols Institute, San Juan Capistrano, CA) with a sensitivity of 0.02 ng/mL. The within-assay coefficient of variation (CV) ranged from 2.8% to 4.2%, and the interassay CV varied from 3.5% to 7.2%.

After February 2010, GH levels were measured using an immunoradiometric assay (hGH-RIACT; CIS Bio International, Gif-sur-Yvette, France) with 0.03 μIU/mL sensitivity. The within-assay CV ranged from 1.3% to 2.1%, and the interassay CV varied from 3.8% to 5.0%. The World Health Organization's international standard (98/574) was used to measure the

GH level. Before July 2005, IGF-1 levels were measured using an immunoradiometric assay system (DSL-5600 Active; Diagnostic Systems Laboratories, Webster, TX) with 0.80 ng/L sensitivity. The within-assay CV ranged from 1.5% to 3.4%, and the interassay CV varied from 1.5% to 8.2%. After July 2005, IGF-1 levels were measured using an immunoradiometric assay system (IGF-1 NEXT IRMA CT; Biocode Hycel, Liège, Belgium), with a minimum detectable IGF-1 concentration of 1.25 ng/L. The interassay and within-assay CV ranges of IGF-1 were 7.4% to 9.1% and 2.6% to 4.4%, respectively (14).

Statistical analysis

Continuous variables are expressed as means ± standard deviation. Independent *t* tests were used for the analysis of continuous variables to compare the groups based on sex and age. Categorical variables, such as the tumor characteristics or remission rate of each group, were analyzed using χ^2 tests. A linear mixed model was used to analyze the immediate surgical outcomes. Meanwhile, multivariate binary logistic regression analysis was used to predict the factors associated with surgical failure among patients with acromegaly. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 23 (IBM, Armonk, NY).

Results

Clinical and biochemical characteristics

A total of 463 patients (203 men, 260 women) with acromegaly underwent TSA, and the mean age of the participants was 42.9 ± 11.3 years. The mean follow-up duration after TSA was 61.4 ± 40.4 months. The mean preoperative random serum GH and IGF-1 levels were 26.5 and 716.5 ng/mL, respectively. Furthermore, the mean maximal tumor diameter was 17 ± 7.9 mm (range: 3–47 mm). Among the 463 patients, 117 (25.3%) had adenomas with cavernous sinus invasion. Total tumor resection was performed in 411 patients (88.8%). The long-term surgical remission rate was 82.3% (381 out of 463 patients; Table 1).

Table 1. Clinical and Biochemical Characteristics of Patients With Acromegaly

Article I. Parameters	Article II. Total Patients
Number of patients	463
Age, y	42.9 ± 11.3
Female sex, n (%)	260 (56.2)
Premenopausal women, n (% of women)	107 (41.2)
Follow-up duration, months	61.4 ± 40.4
Preoperative random GH, ng/mL	26.5 ± 29.6
Preoperative OGTT nadir GH, ng/mL	19.8 ± 20.9
Preoperative IGF-1, ng/mL	716.5 ± 230.8
Maximal diameter of tumor, mm	17.0 ± 7.9
Tumor classification, n (%)/remission, n (%)	
I	134 (28.9)/129 (96.3)
II	80 (17.3)/75 (93.8)
IIIA	40 (8.6)/32 (80.0)
IIIB	92 (19.9)/82 (89.1)
IV	117 (25.3)/63 (53.8)
Total resection of tumor, n (%)	411 (88.8)
Long-term surgical remission (≥1 y), n (%)	381 (82.3)

Data are presented as means ± standard deviation or number (%).

Sex differences in clinical characteristics

Supplemental Table 1 presents the differences in the clinical characteristics of the participants based on sex. Women with acromegaly tended to be older than men with acromegaly (45.2 ± 11.4 vs 39.9 ± 10.3 years, $P < 0.001$). Additionally, women had a lower preoperative IGF-1 level (667.1 ± 197.4 vs 781.7 ± 254.8 ng/mL, $P < 0.001$) than did men, although statistically, different random, preoperative GH levels were not observed between sexes. Women also had a larger tumor size than did men (18.0 ± 8.2 vs 15.7 ± 7.3 mm, $P = 0.002$). Moreover, women had a higher proportion of tumors with cavernous sinus invasion (29.2% vs 20.2%, $P = 0.026$) than did men. Given these reasons, women had a significantly lower total tumor resection rate than did men (85.8% vs 92.6%, $P = 0.021$). As a result, women had a lower long-term surgical remission rate (76.5% vs 89.7%, $P < 0.001$).

Comparison of characteristics by age group

Supplemental Table 2 demonstrates the differences in the clinical characteristics of participants based on age group. The result of the analysis showed that younger age groups (premenopausal women and men aged <50 years) had higher preoperative, random GH (29.7 ± 30.1 vs 19.2 ± 27.3 ng/mL, $P = 0.001$), OGTT nadir GH (22.4 ± 22.5 vs 14.2 ± 15.8 ng/mL, $P < 0.001$), and IGF-1 (735.1 ± 229.6 vs 675.6 ± 228.9 ng/mL, $P = 0.02$) levels than did older groups (postmenopausal women and men aged ≥50 years). Furthermore, younger groups had a longer mean maximal tumor diameter than did older groups (17.9 ± 8.3 vs 15.2 ± 6.8 mm, $P < 0.001$). The younger age groups also had a higher proportion of adenomas with cavernous sinus invasion than did older age groups (28.2% vs 18.8%, $P = 0.03$). On the contrary, younger age groups showed a lower total tumor resection rate than did older age groups (85.6% vs 95.8%, $P = 0.001$). Given these findings, long-term surgical remission is more difficult to achieve in younger age groups than in older age groups (79.0% vs 89.6%, $P = 0.006$).

Age- and sex-matched comparison of the clinical parameters and characteristics of tumor

As shown previously, the clinical features differed depending on the age and sex of the participants. Table 2 shows the age-matched and sex-matched comparison of

clinical parameters. Premenopausal women had a lower preoperative IGF-1 level (673.9 ± 167.9 vs 793.6 ± 263.7 ng/mL, $P < 0.001$) and larger tumor size (19.7 ± 8.6 vs 16.2 ± 7.6 mm, $P < 0.001$) than did men aged <50 years. The premenopausal female group had the highest proportion of macroadenoma or tumor with cavernous sinus invasion among all groups. Therefore, premenopausal female patients displayed a lower total tumor resection rate than did men aged <50 years (Table 2). Regarding anterior pituitary function, measured via preoperative and postoperative combined pituitary function tests, the proportion of worsened hypopituitarism after surgery was also found to be higher in premenopausal women than in men aged <50 years (11.6% vs 3.8%, $P = 0.009$). However, there was no significant difference in surgical remission rate among the patients with tumors with cavernous sinus invasion from all groups (Supplemental Table 3).

Comparison of surgical outcomes

Figures 1 and 2 present the immediate changes in GH levels after surgery and immediate surgical outcomes in each group, respectively. Premenopausal women tended to have higher serum GH levels over time after surgery than did the other groups. Furthermore, premenopausal women were more likely to have remnant mass, as shown in the postoperative MRI than did the other groups (Fig. 2). Consequently, premenopausal women achieved less immediate postoperative biochemical remission than the other groups. In immediate postoperative OGTTs, fewer premenopausal women reached <1 ng/dL nadir GH levels than did men aged <50 years (59.9% vs 87.7%, $P < 0.001$). A similar trend was observed, even in the long-term remission rate. Premenopausal women also had the lowest long-term remission rate among all groups (Fig. 3).

Factors associated with surgical failure among patients with acromegaly

Multivariate logistic regression analysis was used to determine the factors associated with surgical failure among patients with acromegaly. The results showed that younger age [premenopausal women and men aged <50 years; odds ratio (OR), 3.48; 95% confidence interval (CI), 1.21 to 10.03, $P = 0.021$], female (OR, 3.63; 95% CI, 1.37 to 9.60, $P = 0.009$), large tumor size (OR, 1.16;

Table 2. Age- and Sex-Matched Comparison of Clinical Parameters

	Younger Group (M < 50 Y; F, Premenopause)			Older Group (M ≥ 50 Y; F, Postmenopause)		
	Male	Female	*P*	Male	Female	*P*
Number of patients	166	153		37	107	
Age, y	36.2 ± 6.9	37.9 ± 8.1	0.051	56.6 ± 5.4	55.7 ± 6.1	0.397
Follow-up duration, mo	61.4 ± 41.3	62.9 ± 42.2	0.744	55.0 ± 42.2	61.6 ± 35.8	0.359
Preoperative random GH, ng/mL	28.8 ± 30.1	30.8 ± 30.1	0.592	23.6 ± 43.2	17.8 ± 19.4	0.487
Preoperative OGTT nadir GH, ng/mL	20.9 ± 19.7	24.1 ± 25.2	0.230	14.3 ± 16.1	14.2 ± 15.8	0.962
Preoperative IGF-1, ng/mL	793.6 ± 263.7	673.9 ± 167.9	<0.001	729.3. ± 206.5	657.4 ± 234.3	0.138
Maximal diameter of tumor, mm	16.2 ± 7.6	19.7 ± 8.6	<0.001	13.7 ± 5.3	15.7 ± 7.1	0.117
Macroadenoma, n (%)	130 (79.8)	134 (89.3)	0.02	25 (67.6)	79 (75.2)	0.365
Tumor classification, n (%)/remission, n (%)						
I	55 (33.1)/55 (100)	24 (15.7)/21 (87.5)		19 (51.4)/19 (100)	36 (33.6)/34 (94.4)	
II	37 (22.3)/35 (94.6)	27 (17.6)/24 (88.9)		1 (2.7)/1 (100)	15 (14.0)/15 (100)	
IIIA	4 (2.4)/3 (75.0)	24 (15.7)/20 (83.3)		2 (5.4)/2 (100)	10 (9.3)/7 (70.0)	
IIIB	34 (20.5)/31 (91.2)	24 (15.7)/19 (79.2)		10 (27.0)/9 (90.0)	24 (22.4)/23 (95.8)	
IV	36 (21.7)/22 (61.1)	54 (35.3)/22 (40.1)	0.007[a]	5 (13.5)/5 (100)	22 (20.6)/14 (58.3)	0.344[a]
Total resection of tumor, n (%)	151 (91.0)	122 (79.7)	0.004	37 (100.0)	101 (94.4)	0.141
Long-term surgical remission, n (%)	146 (88.0)	106 (69.3)	<0.001	36 (97.3)	93 (86.9)	0.075
Change in pituitary function, n (%)						
Normal to normal	43 (27.0)	56 (38.4)		11 (30.6)	54 (53.5)	
Normalized	62 (39.0)	43 (29.5)		12 (33.3)	22 (21.8)	
Improved	33 (20.8)	18 (12.3)		9 (25.0)	11 (10.9)	
Persisted	15 (9.4)	12 (8.2)		4 (11.1)	5 (5.0)	
Worsened	6 (3.8)	17 (11.6)		0 (0)	9 (8.9)	

Data are presented as means ± standard deviation or number (%). Student *t* test and χ^2 test were performed.

Abbreviations: F, female; M, male.

[a] *P* for the proportion of tumor classification IV in each group.

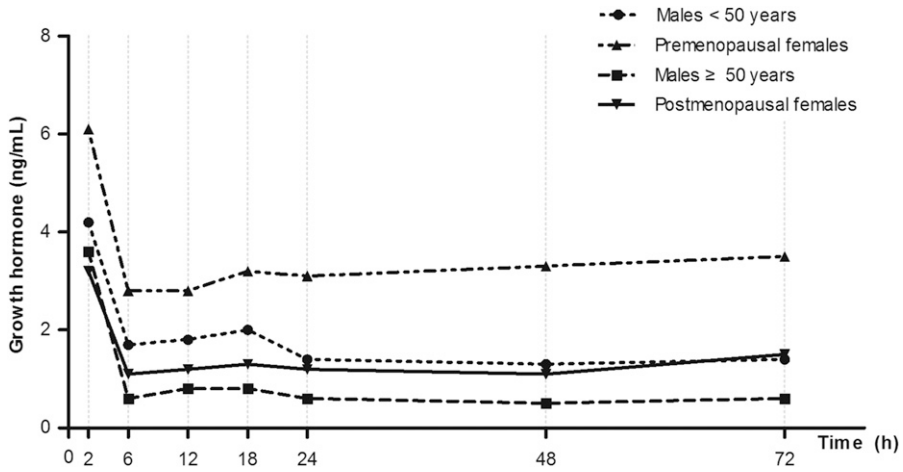

Figure 1. Immediate hormonal changes after TSA. Mean immediate postoperative serial, random GH levels of each group. Premenopausal women had higher immediate serial GH after TSA than did the other groups ($P = 0.026$ and <0.001 for group and time, respectively; $P = 0.788$ for group and time interaction).

95% CI, 1.09 to 1.24, $P < 0.001$), and cavernous sinus invasion (OR, 5.68; 95% CI, 1.11 to 29.08, $P = 0.037$) were significantly associated with surgical failure among patients with acromegaly (Table 3).

Discussion

Our study demonstrated that women with acromegaly tend to have relatively lower serum IGF-1 levels and more invasive and larger tumors than do men. Moreover, younger patients (premenopausal women and men aged <50 years) have a more biochemically hyperactive disease status and more aggressive adenomas than do older patients (postmenopausal women and men aged ≥50 years). Thus, there were fewer premenopausal women who achieved immediate improvement after surgery or long-term remission than did the other groups. Therefore, age, sex, and tumor size and invasiveness are associated with disease features and surgical outcomes of patients with acromegaly.

Although some studies have been conducted on sex-specific differences in acromegaly, they produced inconsistent results, and their findings were insufficient to suggest a clear conclusion (12, 13). Therefore, the results of the current study, where a single surgeon performed the surgery to reduce bias related to the surgical technique used, are important in clarifying the clinical features and prognosis after surgery of acromegaly based on sex. Our group has published several studies on surgical remission

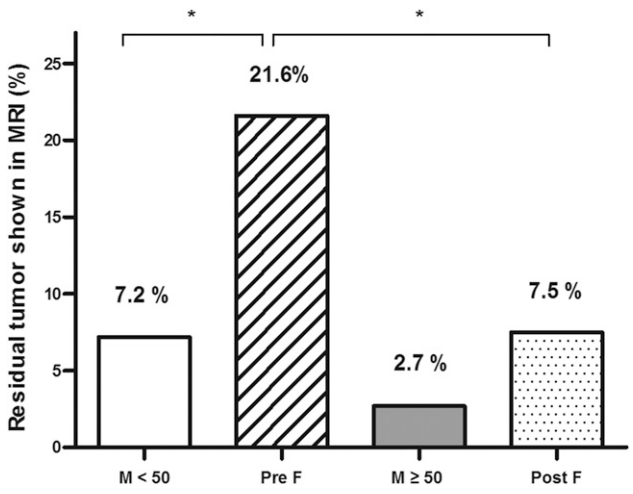

Figure 2. Proportions of subtotal resection of tumor. Residual pituitary tumor, as shown in the immediate postoperative MRI (*$P <$ 0.05). M < 50, males aged <50 years; M ≥ 50, males aged ≥50 years; Post F, postmenopausal females; Pre F, premenopausal females.

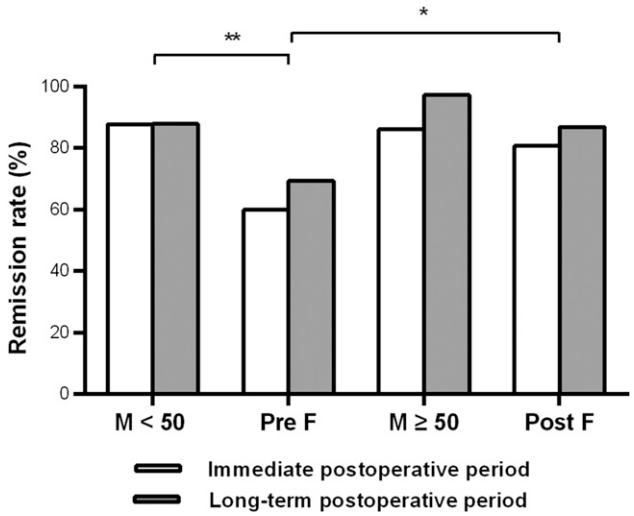

Figure 3. Immediate and long-term surgical remission in each group. Complete remission was evaluated through MRI and 75-g glucose tolerance tests within the first postoperative week and during the follow-up period. Fewer premenopausal women achieved both immediate postoperative and long-term surgical remissions. The white bars represent the immediate postoperative remission rate (%), whereas the gray bars represent the long-term surgical remission rate (%). *$P < 0.05$, **$P < 0.001$.

Table 3. Factors Associated With Surgical Failure Among Patients With Acromegaly

Factor	OR (95% CI)	*P*
Age, y		
Male ≥50 y or postmenopausal female	Reference	
Male <50 y or premenopausal female	3.48 (1.21–10.03)	0.021
Female sex	3.63 (1.37–9.60)	0.009
Preoperative random GH, ng/mL	1.01 (0.99–1.03)	0.236
Preoperative OGTT nadir GH, ng/mL	0.99 (0.96–1.02)	0.372
Preoperative IGF-1, ng/mL	1.00 (0.999–1.003)	0.384
Maximal diameter of tumor, mm	1.16 (1.09–1.24)	<0.001
Tumor classification, n (%)		
I	Reference	
II	0.97 (0.16–5.92)	0.972
III	0.78 (0.13–4.81)	0.791
IV	5.68 (1.11–29.08)	0.037

of acromegaly that revealed surgical remission rates of ~75% to 84%, which is similar to that in the current study (14–16).

In the current study, baseline GH levels were not different between sexes, but the mean preoperative IGF-1 level was lower in women. Previous data regarding sex-specific differences in GH and IGF-1 levels in patients with acromegaly have not been consistent. This may be related to experiments showing that oral estrogens attenuate GH receptor signaling and IGF-1 production, as well as stimulate GH secretion by reducing negative feedback of IGF-1 (17, 18). Duarte *et al.* (19) reported that estrogens are capable of reducing IGF-1 production, possibly through suppressor of cytokine signaling 2 protein upregulation, which impairs the Janus kinase–signal transducer and activator of transcription pathway. In addition, in patients with acromegaly, for a given serum GH level, women were estimated to have lower serum IGF-I values than men (20). Furthermore, an analysis of 1485 patients from the German Acromegaly Register revealed higher random GH levels and IGF-1 levels in men (21). However, another study showed no sex differences in baseline GH and IGF-I levels in patients with acromegaly (13). A Japanese group showed that women had lower serum IGF-I levels, whereas GH levels did not differ from those in men (22). Consistent with the current study, serum IGF-I level was lower in women aged <50 years than in men aged <50 years; however, this sex difference was not observed in patients aged ≥50 years. In addition, another study reported comparable random GH levels with lower IGF-I levels in women (23). Our study also demonstrated that the preoperative OGTT nadir GH levels did not differ between women and men. Thus, our results, which are similar to those of Freda *et al.* (13), do not support the establishment of separate OGTT nadir GH criteria between men and women for diagnosis of acromegaly.

Previous reports show that with regard to tumor size, younger female patents tended to have larger adenomas or more macroadenomas; however, the difference was not statistically significant as a result of small sample sizes (23–25). Moreover, in an analysis of 18 patients with acromegaly, male sex was associated with a poor outcome; however, the study only included a small number of patients without cavernous sinus invasion (26). In addition, although several studies demonstrated the effect of sex on outcomes of treatment with somatostatin analog (12, 27), no study with a large sample size has provided evidence for a difference in surgical prognosis based on sex. The current study uses a large set of patients in suggesting that premenopausal women have larger and more aggressive GH-secreting adenomas than do men. Hence, women have a statistically, significantly higher probability of surgical failure from TSA than do men.

One of the reasons why women have larger and more advanced pituitary tumors than do men is that women tend to be diagnosed later compared with men. The diagnosis of acromegaly typically takes several years because of the initially nonspecific and slow progression of clinical symptoms. In past studies, the diagnosis of acromegaly takes an average of 8 years (28, 29), although relatively recent studies reported a reduced period of 2.5 ± 4.6 years, as a result of the development of brain MRI images; however, the establishment of diagnosis still takes a long time (30). Kreitschmann-Andermahr *et al.* (31) showed that the mean duration for seeking medical advice for the diagnosis of acromegaly was 2.9 years, with women and men receiving a diagnosis of acromegaly at an average duration of 4.1 and 1.6 years, respectively ($P = 0.001$). Additionally, women consulted more doctors than did men in the process (4.0 vs 2.7 doctors, $P < 0.001$) (31). With the consideration that early diagnosis and appropriate treatment are key factors in the prognosis of acromegaly, the education of patients on the early manifestations of acromegaly is important so that they can visit the hospital as soon as possible. Moreover, clinicians should be aware of the possibility of the

existence of acromegaly in patients who present with symptoms, especially among women.

Several clinical factors have been suggested to be associated with the prognosis of acromegaly. Age, histological type, radiological findings, and several molecular factors, such as *Ras* oncogene, aryl hydrocarbon receptor-interacting protein gene, and pituitary tumor-transforming gene, were reported as either conditions or markers that are associated with the prognosis of acromegaly (10). Among them, age and sex are the basic clinical parameters that can be considered easily before surgery. However, how these factors influence the surgical outcome of patients with acromegaly remains to be elucidated. Besides the time of diagnosis already mentioned previously, hormonal status might be one of the reasons why more premenopausal women have more invasive tumors than do men aged <50 years. In rat studies, chronic estrogen administration induces the development of prolactin secretory tumors (32). Estrogen is also known to activate expression of genes implicated in pituitary tumorigenesis, such as pituitary tumor-transforming gene, transforming growth factor α and β, fibroblast growth factor β, and fibroblast growth factor β receptor. Another study that evaluated estrogen receptor expression in human pituitary adenomas demonstrated that some somatotrophinomas contain estrogen receptors. Somatotrophinomas, which express estrogen receptors, were large and aggressive tumor types (33). Based on these findings, the clinical features of tumors among premenopausal women might be attributed to estrogen. However, further studies are needed to validate this mechanism.

The existence of larger and more aggressive GH-secreting adenomas among women than men is also confirmed by the results of the subgroup analysis based on age. In the current study, younger patients presented with more biochemically hyperactive disease status and larger and invasive tumors than older patients. This finding is consistent with the results of several related studies (23, 34, 35). Additionally, the results of our age-based subgroup analysis revealed that women have lower IGF-1 levels and larger tumors than do men, and this trend is particularly pronounced in younger patients. In particular, premenopausal women had larger and more aggressive tumors than did the other groups, including postmenopausal women. Therefore, complete resection of the pituitary tumor mass through surgery is more difficult to achieve and results in a lower remission rate in premenopausal women than that in the other groups. Thus, premenopausal women displayed lower, long-term remission rates and worse postoperative pituitary function than did the other groups.

This study suggests the effect of sex and age on the surgical prognosis of acromegaly. The effect of sex on the prognosis was confirmed by the results of the subgroup analysis based on age. Nevertheless, this study has some limitations. With the consideration of the retrospective design of this study, potential bias during data collection might exist. Furthermore, the patients included in this study were all from a tertiary medical center in South Korea. Hence, prospective studies conducted among a large number of patients from multiple centers are needed. We also did not investigate the time duration since the patient developed symptoms nor the number of doctors they visited during that period. On average, the longer time from symptom onset to the diagnosis of acromegaly among women is associated with the increased aggressiveness of the disease. An investigation on these aspects would have strengthened the findings of this study.

In conclusion, the results of our study are consistent with those of previous studies, where younger age, long maximal tumor diameter, and presence of cavernous sinus invasion were significantly associated with surgical failure among patients with acromegaly (10, 11). Additionally, we found that women, especially premenopausal women, have larger, more aggressive tumors than do men, so the probability of surgical failure is higher in women. The findings of this study should be considered when treating patients with acromegaly.

Acknowledgments

Financial Support: This work was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (Grant HI15C1584 to E.J.L.).

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Disclosure Summary: The authors have nothing to disclose.

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