The Metabolic Profile in Active Acromegaly is Gender-Specific

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Context: The sexual dimorphism of the somatotroph axis has been documented, but whether the acromegaly-related metabolic alterations are gender-dependent has never been investigated.

Objective: The aim of the study was to evaluate the impact of gender on the metabolic parameters in acromegaly.

Design: We conducted a retrospective, comparative, multicenter study.

Patients: The 307 newly diagnosed acromegalic patients included in the study were grouped by gender: 157 men (aged 48.01 $\pm$ 14.28 yr), and 150 women (aged 48.67 $\pm$ 14.95 yr; of which 77 were premenopausal and 73 postmenopausal).

Outcome Measurements: We measured each component of the metabolic syndrome (MS), hemoglobin A1c, the areas under the curve (AUCs) of glucose and insulin during 2-h oral glucose tolerance test, basal insulin resistance using the homeostasis model assessment of the insulin resistance index, stimulated insulin sensitivity using the insulin sensitivity index, early insulin-secretion rate using the insulinogenic index, β-cell function relative to insulin sensitivity using the oral disposition index and the visceral adiposity index (VAI) as the surrogate of visceral fat function.

Results: Women showed a higher prevalence of MS ($P < 0.001$), higher fasting insulin levels ($P < 0.001$), AUC for insulin ($P = 0.002$), homeostasis model assessment of the insulin resistance index ($P < 0.001$), and VAI ($P < 0.001$) and a lower insulin sensitivity index ($P = 0.002$) than men, whereas no difference was found in fasting glucose, AUC for glucose, hemoglobin A1c, insulinogenic index, and oral disposition index. In women, fasting glucose and fasting insulin showed a significant trend toward increase ($P < 0.001$) and decrease ($P = 0.004$), respectively, from the first to the fourth quartiles of age, whereas VAI showed a trend toward increase in both groups ($P < 0.001$). A significantly higher prevalence of MS ($P < 0.001$), increased waist circumference ($P < 0.001$), low high-density lipoprotein cholesterol ($P < 0.001$), and overt diabetes mellitus ($P < 0.001$) was found in postmenopausal women compared with premenopausal women, as well as with men.

Conclusions: The majority of metabolic features in acromegaly are gender-specific. Active acromegaly in women is strongly associated with higher visceral adiposity dysfunction, insulin resistance, and the features of MS. We suggest more accurate metabolic management in acromegalic women, especially in the postmenopausal years. **(*J Clin Endocrinol Metab* 98: E51–E59, 2013)**

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Abbreviations: AUC, Area under the curve; AUC_{GH}, AUC for GH; AUC_{GLU}, AUC for glucose; AUC_{INS}, AUC for insulin; BMI, body mass index; DIo, oral disposition index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; Homa-IR, homeostasis model assessment of the insulin resistance index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; mTOR, mammalian target of rapamycin; OGTT, oral glucose tolerance test; ULN, upper limit of normal; VAI, visceral adiposity index; WC, waist circumference.

Gender may affect the GH and IGF-I secretory pattern both in healthy subjects and in patients with acromegaly through mechanisms not fully understood and with discordant evidence. Spontaneous GH secretion seems to be higher in healthy women than in men (1, 2), whereas IGF-I levels are similar or higher in men (3, 4). Due to the lower sensitivity to GH, women affected by GH deficiency or hypopituitarism and receiving estrogen replacement need a higher GH dose than men to achieve normal IGF-I levels (5, 6). On the other hand, in acromegaly, higher GH or IGF-I levels have been found both in men and in women in different cohorts of patients analyzed. Some authors showed lower serum IGF-I levels and IGF-I/GH ratio in women than in men, particularly in younger patients, without any difference in GH levels, suggesting that gender, presumably sex steroids in women, may only partially modulate the relationship between circulating IGF-I and GH levels in patients with acromegaly (7). Indeed, Edèn Engström *et al.* (8) demonstrated that women with acromegaly need lower doses of octreotide than men to normalize IGF-I levels.

Conversely, basal GH was found to be higher in *de novo* women than in men with acromegaly by Colao *et al.* (9), and both basal and nadir GH levels were found to be significantly higher in women when GH was measured by different immunoassays (10). By contrast, a retrospective analysis of the data in the German Acromegaly Register, including 1485 patients, demonstrated significantly higher GH levels in men than women, and sex was considered an independent risk factor for biochemical activity in acromegaly (11). However, although gender has been considered by some authors a relevant determinant of hormonal levels in acromegaly, crucial to appropriately evaluating the activity of the disease, whether acromegaly-related metabolic alterations are gender-dependent has not been investigated so far.

The aim of this study was to evaluate the impact of gender on hormonal and metabolic parameters in a large Italian series of newly diagnosed patients with acromegaly.

Patients and Methods

Patients

We retrospectively reviewed the data from consecutive patients with active acromegaly recruited and diagnosed at the Departments of Endocrinology of the Universities of Palermo, Naples, and Genoa between 2000 and 2010. Of 390 newly diagnosed patients, 307 (157 men aged 48 ± 14.2 yr, and 150 women aged 48.6 ± 14.9 yr, of which 77 were premenopausal and 73 were postmenopausal) were included in the study. Exclusion criteria were: mixed GH/prolactin-secreting adenomas, any previous specific treatment for acromegaly (surgery, somatostatin analogs, dopamine agonist, or radiotherapy), and the presence of concomitant overt hypogonadism, to avoid the potential impact of hormonal deficit or gonadal replacement therapy on GH, IGF-I, as well as metabolic parameters. No women receiving estrogens and/or progesterone as contraceptives or postmenopausal hormone in replacement therapy were included. The 157 men and 150 women were divided into the following groups in line with quartiles of age: first quartile (39 men, <38.5 yr; 41 women, <37 yr), second quartile (45 men, 38.5–49 yr; 35 women, 37–47 yr), third quartile (38 men, 50–59 yr; 38 women, 48–63 yr), and fourth quartile (35 men, >59 yr; 36 women >63 yr).

Disease activity at the time of the study was confirmed by altered serum GH during morning profile and/or nonsuppressible GH below 1 μg/liter after oral glucose tolerance test (OGTT), elevated age, and gender-corrected plasma IGF-I levels (12). In 28 subjects with a previous diagnosis of overt diabetes mellitus (DM), OGTT was not performed, and the diagnosis was made by high serum GH, calculated as the mean of a 6-h blood sampling (0800–1400 h with 30-min sampling), IGF-I levels, and adequate clinical context. As regards hypoglycemic therapy of the whole cohort of patients, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) subjects were treated with diet alone (68%) or metformin (32%); diabetic patients were treated with metformin alone (70%) or in combination with other hypoglycemic drugs (sulfonylureas or glinides) (30%). All patients with a previous diagnosis of DM, IFG, or IGT and already receiving dietary or pharmacological therapy suspended the treatment for at least 3 d before metabolic evaluation to avoid an effect on insulin sensitivity and secretion indexes (13). In all patients, magnetic resonance imaging revealed the presence of a pituitary tumor. Tumor volume was calculated in line with the Di Chiro and Nelson formula (volume = height × length × width × π/6) and was expressed as cubic millimeters. The mean duration of the disease was established by patient interview, patients' clinical pictures, and onset of osteoarticular symptoms. At the time of hospitalization, all patients signed an informed consent for the scientific use of their data. The identity of the participants remained anonymous during database analysis.

Study design

This is a retrospective, comparative, multicenter cohort study. All patients at diagnosis underwent complete clinical and metabolic evaluation. Body mass index (BMI), systolic and diastolic blood pressure were measured in all patients. Waist circumference (WC) was measured at the midpoint between the lower rib and the iliac crest. Patients were analyzed according to each criterion of the metabolic syndrome (MS) (14) and each category of glucose tolerance (15). After an overnight fast, lipid profile [total, high-density lipoprotein (HDL), and low-density lipoprotein-cholesterol, triglycerides], hemoglobin A1c (HbA1c), mean fasting plasma GH (at least three blood samples at 30-min intervals), and IGF-I levels were measured. To normalize IGF-I for age in individual patients, we calculated the ratio between the IGF-I level and the upper limit of the normal (ULN) range for age (normal = ≤1), and the data were presented as IGF-I ULN. OGTT was performed by measuring plasma blood glucose, insulin levels, and GH every 30 min for 2 h after a 75-g oral glucose load. The areas under the curve of glucose (AUC_{GLU}), insulin (AUC_{INS}) and GH (AUC_{GH}) during 2-h OGTT were calculated. Basal insulin resistance was assessed

using homeostasis model assessment of the insulin resistance index (Homa-IR) (16), whereas insulin sensitivity was measured using the insulin sensitivity index (ISI), a composite index derived from the OGTT and validated by Matsuda and DeFronzo (17). The early insulin-secretion rate was evaluated using the insulinogenic index (18). The total insulin secretion was assessed by AUC_{INS}, whereas the β-cell function relative to insulin sensitivity was assessed by the oral disposition index (DIo) (19).

As the surrogate of visceral fat function in all patients, we calculated the visceral adiposity index (VAI), an index of adipose tissue distribution and function associated with cardiometabolic risk (20) and already demonstrated to be strongly associated with active acromegaly (21, 22).

VAI was calculated using the following formulas differentiated according to sex, where TG is triglycerides levels expressed in millimoles per liter and HDL is HDL-cholesterol levels expressed in millimoles per liter: Males, VAI = [WC/39.68 + (1.88 × BMI)] × (TG/1.03) × (1.31/HDL); and Females, VAI = [WC/36.58 + (1.89 × BMI)] × (TG/0.81) × (1.52/HDL).

Hormone and biochemical assays

Glycemia, HbA1c, and lipid levels were measured in centralized accredited laboratories with standard methods. During the study period, GH levels were assayed by immunoradiometric and immunoenzymatic assays according to availability. The sensitivity of the assays ranged from 0.05–0.02 μg/liter. Serum IGF-I was measured using immunoradiometric assays (Diagnostic Systems Laboratories Inc., Webster, TX). The normal ranges (for age) were: 180–625 and 151–530 (≤20 yr), 118–475 and 118–450 (21–30 yr), 102–400 and 100–390 (31–40 yr), 100–306 and 96–228 (41–50 yr), 95–270 and 90–250 (51–60 yr), 88–250 and 82–200 (61–70 yr), and 78–200 and 68–188 μg/liter (≥70 yr) for men and women, respectively. The sensitivity of the assay was 0.8 μg/liter. The intra- and interassay coefficients of variation were 3.4, 3.0, and 1.5%, and 8.2, 1.5. and 3.7% for low, medium, and high points on the standard curve, respectively. Serum insulin was measured by ELISA (DRG Instruments GmbH, Marburg, Germany). The sensitivity of the method was 1 IU/ml. The normal insulin range (IU/ml) was 5–19. The assays for the assessment of IGF-I and insulin were constant during this entire period. We decided to analyze the data of patients recruited in the decade 2000–2010 because in that period we did not change assay.

Statistical analysis

The Statistical Packages for Social Sciences SPSS version 17 (SPSS Inc., Chicago, IL) was used for data analysis. Baseline characteristics were presented as mean ± SD for continuous variables; rates and proportions were calculated for categorical data. Normality of distribution for quantitative variables was assessed by the Kolmogorov-Smirnov test. Because age, BMI, and AUC_{GLU} did not show normal distribution, these variables were log-transformed. Differences between groups in univariate analysis were detected by the unpaired Student's t test for continuous variables and by the χ^2 test and Fisher's exact test (when appropriate) for categorical variables. Differences in metabolic parameters between men and women were corrected for AUC_{GH} through a logistic regression model. The ANOVA trend analysis was used to assess means of metabolic and hormonal parameters across the age quartiles. A P value of <0.05 was considered statistically significant.

Results

The clinical and biochemical features of all patients, grouped for gender, are listed in Table 1.

No difference in age (48.01 ± 14.28 *vs.* 48.67 ± 14.95 yr; $P = 0.693$), BMI (25.54 ± 3.43 *vs.* 25.80 ± 3.59 kg/m^2; $P = 0.512$), duration of disease (85.39 ± 66.46 *vs.* 88.35 ± 68.28 months; $P = 0.701$), and tumor volume (1664 ± 1699 *vs.* 2087 ± 2166 mm^3; $P = 0.137$) was observed between men and women.

Biochemical parameters of acromegaly according to gender

The basal serum GH levels (31.38 ± 24.21 *vs.* 26.78 ± 22.26 μg/liter; $P = 0.085$), post-OGTT GH nadir (21.66 ± 17.91 *vs.* 17.98 ± 17.79 μg/liter; $P = 0.081$), AUC_{GH} (3150 ± 2333 *vs.* 2645 ± 2328; $P = 0.059$), and IGF-I ULN (2.31 ± 0.79 *vs.* 2.43 ± 0.89; $P = 0.207$) did not significantly differ between men and women. We found a trend toward decrease on basal GH ($P < 0.001$ and $P = 0.002$, respectively), post-OGTT GH nadir ($P = 0.001$ and $P = 0.016$, respectively), and AUC_{GH} ($P < 0.001$ and $P = 0.004$, respectively) from the first to the fourth quartile of age in both men and women. In addition, in women a trend toward decrease in tumor volume from the first to the fourth quartile of age ($P = 0.013$) was found. No significant trend toward variation in IGF-I levels was found in either group ($P = 0.170$ and $P = 0.411$ in men and women, respectively). The biochemical parameters of all patients, grouped for quartiles of age, are listed in Tables 2 and 3 for men and women, respectively.

Metabolic parameters of acromegaly according to gender

MS was found in 107 patients (34.9%), and its prevalence was higher in women than in men (51.3 *vs.* 19.1%; $P < 0.001$). Sixty-eight (22.1%) patients had increased WC according to the above-mentioned Adult Treatment Panel III criteria, 57 (38%) of whom were women and 11 (7%) were men ($P < 0.001$). Low HDL-cholesterol was found in 120 (39.1%) patients, 93 (62%) of whom were women and 27 (17.2%) were men ($P < 0.001$). No gender difference was found in the prevalence of hypertriglyceridemia (31.2 *vs.* 35.3%; $P = 0.443$). A total of 107 women and 95 men (71.3 *vs.* 60.5%; $P = 0.046$) showed increased systolic blood pressure, whereas no significant difference was found in the prevalence of diastolic blood pressure (46 *vs.* 40.8%; $P = 0.355$).

A more marked family history for diabetes was shown in women than in men (48 *vs.* 33.8%; $P = 0.011$); 153 of 307 patients (49.8%) were classified as having normal glucose tolerance, 19 (6.2%) as IGT, and 33 (10.7%) as combined IFG and IGT, without gender difference in the

TABLE 1. Clinical and biochemical features of 307 newly diagnosed acromegalic patients grouped for gender

	All patients	Men	Women	*P*	*P*[a]
n	307	157	150		
Age (yr)	48.33 ± 14.59	48.01 ± 14.28	48.67 ± 14.95	0.693	
BMI (kg/m^2)	25.67 ± 3.51	25.54 ± 3.43	25.80 ± 3.59	0.512	
Duration of disease (months)	86.83 ± 67.26	85.39 ± 66.46	88.35 ± 68.28	0.701	
Tumor volume (mm^3)	1867 ± 1943	1664 ± 1699	2087 ± 2166	0.137	
Basal GH (μg/liter)	29.13 ± 23.35	31.38 ± 24.21	26.78 ± 22.26	0.085	
Nadir GH (μg/liter)	19.87 ± 17.91	21.66 ± 17.91	17.98 ± 17.79	0.081	
AUC_{GH}	2903 ± 2341	3150 ± 2333	2645 ± 2328	0.059	
IGF-I (ULN)	2.37 ± 0.84	2.31 ± 0.79	2.43 ± 0.89	0.207	
MS	107 (34.9)	30 (19.1)	77 (51.3)	<0.001	
Increased WC	68 (22.1)	11 (7)	57 (38)	<0.001	
Hypertriglyceridemia	102 (33.2)	49 (31.2)	53 (35.3)	0.443	
Low HDL-cholesterol	120 (39.1)	27 (17.2)	93 (62)	<0.001	
Increased systolic blood pressure or specific treatment	202 (65.8)	95 (60.5)	107 (71.3)	0.046	
Increased diastolic blood pressure or specific treatment	133 (43.3)	64 (40.8)	69 (46)	0.355	
Family history for diabetes	125 (40.7)	53 (33.8)	72 (48)	0.011	
Normal tolerance	153 (49.8)	80 (51)	73 (48.7)	0.688	
IFG	68 (22.1)	42 (26.8)	26 (17.3)	0.047	
IGT	19 (6.2)	10 (6.4)	9 (6.0)	0.893	
IFG + IGT	33 (10.7)	17 (10.8)	16 (10.7)	0.964	
DM	107 (34.9)	30 (19.1)	77 (51.3)	<0.001	
Fasting glucose (mmol/liter)	5.45 ± 0.91	5.44 ± 0.90	5.47 ± 0.92	0.755	
HbA1c (%)	5.32 ± 1.16	5.38 ± 1.17	5.29 ± 1.15	0.349	
Fasting insulin (IU/ml)	18.18 ± 11.04	15.14 ± 8.95	21.25 ± 12.08	<0.001	<0.001
Homa-IR	4.33 ± 2.66	3.59 ± 2.24	5.08 ± 2.84	<0.001	<0.001
ISI-Matsuda	3.45 ± 2.16	3.85 ± 2.15	3.05 ± 2.11	0.002	0.020
AUC_{INS}	8358 ± 4121	7578 ± 3383	9127 ± 4622	0.002	0.004
AUC_{GLU}	931 ± 259	908 ± 240	954 ± 273	0.140	
Insulinogenic index (ΔIns 30 min/ΔGlu 30 min)	47.40 ± 113	36.18 ± 52.76	58.43 ± 150.30	0.137	
DIo	3.67 ± 8.47	3.82 ± 9.90	3.42 ± 6.83	0.630	
VAI	2.03 ± 1.04	1.58 ± 0.75	2.51 ± 1.10	<0.001	<0.001

Data are expressed as number of subjects (percentage) or mean ± SD.

[a] *P* value corrected for AUC_{GH}.

prevalence of these categories of glucose tolerance. Women were more affected by overt DM than men (5.1.3 *vs.* 19.1%; $P < 0.001$), whereas men showed a higher prevalence of IFG (26.8 *vs.* 17.3%; $P = 0.047$).

Women showed significantly higher fasting insulin levels (21.25 ± 12.08 *vs.* 15.14 ± 8.95 IU/ml; $P < 0.001$), AUC_{INS} (9127 ± 4622 *vs.* 7578 ± 3383; $P = 0.002$), and Homa-IR (5.08 ± 2.84 *vs.* 3.59 ± 2.24; $P < 0.001$), and lower ISI Matsuda (3.05 ± 2.11 *vs.* 3.85 ± 2.15; $P = 0.002$) than men. These significances were confirmed when we corrected the *P* value for AUC_{GH}. No difference was found between men and women in fasting glucose (5.44 ± 0.90 *vs.* 5.47 ± 0.92 mmol/liter; $P = 0.755$), AUC_{GLU} (16,361 ± 4,324 *vs.* 17,182 ± 4,931; $P = 0.140$), HbA1c (5.38 ± 1.17 *vs.* 5.29 ± 1.15%; $P = 0.349$), insulinogenic index (36.18 ± 52.76 *vs.* 58.43 ± 150.30; $P = 0.137$), and DIo (3.82 ± 9.90 *vs.* 3.42 ± 6.83; $P = 0.630$). Women showed significantly higher VAI value than men (2.51 ± 1.10 *vs.* 1.58 ± 0.75; $P < 0.001$). This significance was confirmed when we corrected the *P* value for AUC_{GH}.

Analyzing the metabolic parameters according to quartiles of age, no significant trend toward variation in all parameters was found in men, with the exception of VAI, which showed a trend toward increase from the first to the fourth quartile ($P < 0.001$) (Fig. 1). Conversely, in women fasting glucose and fasting insulin showed a significant trend toward increase ($P < 0.001$) and decrease ($P = 0.004$), respectively (Fig. 2). No significant trend toward variation in other metabolic parameters was found, whereas VAI showed a trend toward increase from the first to the fourth quartile ($P = 0.001$) (Fig. 1). The metabolic parameters of all patients, grouped for quartiles of age, are listed in Tables 2 and 3 for men and women, respectively.

When we further analyzed each criterion of the MS and the categories of glucose tolerance, grouping women into two groups on the basis of the menopausal status, a significantly higher prevalence of MS ($P < 0.001$), increased WC ($P < 0.001$), low HDL-cholesterol ($P < 0.001$), and overt DM ($P < 0.001$) was found in postmenopausal women compared with premenopausal women, as well as with men. Conversely, a slightly higher prevalence of IFG

TABLE 2. Parameters of disease activity and metabolic features of 157 men with newly diagnosed acromegaly across quartiles of age

	First quartile	Second quartile	Third quartile	Fourth quartile	*P* for trend
n	39	45	38	35	
Tumor volume (mm^3)	1830 ± 1450	1720 ± 2110	1550 ± 1130	1410 ± 1750	0.352
Basal GH (μg/liter)	41.26 ± 22.58	40.16 ± 25.69	17.33 ± 17.39	24.33 ± 21.24	<0.001
Nadir GH (μg/liter)	26.97 ± 16.29	26.20 ± 17.90	14.76 ± 17.28	16.31 ± 17.14	0.001
AUC_{GH}	3890 ± 2108	3975 ± 2310	1942 ± 2087	2574 ± 2203	<0.001
IGF-I (ULN)	2.19 ± 0.42	2.34 ± 0.75	2.20 ± 0.82	2.51 ± 1.07	0.170
Fasting glucose (mmol/liter)	5.17 ± 0.88	5.56 ± 0.73	5.39 ± 0.71	5.62 ± 1.21	0.077
HbA1c (%)	5.13 ± 0.82	5.36 ± 0.96	5.65 ± 1.75	5.38 ± 0.92	0.216
Fasting insulin (IU/ml)	15.61 ± 7.42	16.82 ± 10.49	11.39 ± 6.29	16.30 ± 10.05	0.558
Homa-IR	3.63 ± 2.09	4.12 ± 2.63	2.65 ± 1.34	3.85 ± 2.40	0.576
ISI-Matsuda	3.33 ± 1.22	3.22 ± 1.22	4.53 ± 2.16	3.19 ± 1.33	0.256
AUC_{INS}	8620 ± 3091	8167 ± 2970	7060 ± 3281	7842 ± 3306	0.126
AUC_{GLU}	956 ± 139	948 ± 195	827 ± 325	944 ± 214	0.251
Insulinogenic index (ΔIns 30 min/ΔGlu 30 min)	24.47 ± 307.65	67.81 ± 107.35	42.52 ± 46.75	5.45 ± 279.94	0.738
DIo	0.18 ± 9.57	5.57 ± 10.09	7.08 ± 11.09	2.88 ± 6.18	0.101
VAI	1.22 ± 0.38	1.65 ± 0.59	1.48 ± 0.78	1.98 ± 1.00	<0.001

Data are expressed as mean ± SD.

($P = 0.006$) was found in men. No significant difference in the prevalence of hypertriglyceridemia ($P = 0.683$), increased systolic ($P = 0.054$) and diastolic ($P = 0.570$) blood pressure, IGT ($P = 0.528$), and IFG + IGT ($P = 0.505$) was found among the three groups (Table 4).

In addition, we compared the metabolic features of acromegalic patients with a group of 301 Caucasian healthy nonacromegalic subjects matched for age and BMI. For this purpose, we used the collected data from Genoa, Naples, and Palermo. Metabolic parameters were significantly poorer in acromegalic patients than in control subjects. Acromegalic men and pre- and postmenopausal women showed a higher prevalence of hypertriglyceridemia, low HDL-cholesterol, increased systolic and diastolic blood pressure, and higher VAI. Acromegalic patients showed a significantly greater prevalence of DM compared with nonacromegalic subjects. A lesser degree of insulin sensitivity was also evident in acromegalic patients regardless of gender, as demonstrated by higher fasting insulin levels and Homa-IR and by lower ISI-Matsuda compared with nonacromegalic subjects. These data are shown in Supplemental Table 1, pub-

TABLE 3. Parameters of disease activity and metabolic features of 150 women with newly diagnosed acromegaly across quartiles of age

	First quartile	Second quartile	Third quartile	Fourth quartile	*P* for trend
Tumor volume (mm^3)	2720 ± 2500	2,100 ± 1,710	1,990 ± 2,570	940 ± 1000	0.013
Basal GH (μg/liter)	30.85 ± 21.17	34.46 ± 20.63	23.82 ± 20.75	17.82 ± 23.60	0.002
Nadir GH (μg/liter)	21.87 ± 17.63	20.14 ± 15.68	16.21 ± 17.01	11.84 ± 20.40	0.016
AUC_{GH}	3,171 ± 2,296	3,249 ± 2,163	2,267 ± 2,017	1,857 ± 2,594	0.004
IGF-I (ULN)	2.22 ± 0.66	2.59 ± 0.69	2.55 ± 1.32	2.39 ± 0.69	0.411
Fasting glucose (mmol/liter)	5.12 ± 0.66	5.07 ± 0.73	5.44 ± 0.81	6.29 ± 0.94	<0.001
HbA1c (%)	5.11 ± 0.98	5.35 ± 1.38	5.45 ± 1.44	5.12 ± 0.64	0.817
Fasting insulin (IU/ml)	23.48 ± 12.77	24.84 ± 13.61	20.03 ± 11.05	16.32 ± 8.94	0.004
Homa-IR	5.39 ± 3.06	5.52 ± 3.05	4.82 ± 2.64	4.57 ± 2.55	0.141
ISI-Matsuda	2.77 ± 1.60	2.50 ± 1.02	3.12 ± 1.93	2.58 ± 1.49	0.852
AUC_{INS}	9,631 ± 4,123	10,559 ± 5245	9,247 ± 4,568	8,998 ± 2,521	0.380
AUC_{GLU}	956 ± 216	982 ± 218	962 ± 235	1,068 ± 218	0.087
Insulinogenic index (ΔIns 30 min/ΔGlu 30 min)	67.45 ± 178.65	40.80 ± 91.11	95.72 ± 206.09	59.87 ± 120.84	0.749
DIo	2.83 ± 5.77	1.36 ± 1.09	5.99 ± 10.59	3.22 ± 4.47	0.204
VAI	2.13 ± 0.80	2.47 ± 0.94	2.47 ± 1.11	3.02 ± 1.34	0.001

Data are expressed as mean ± SD.

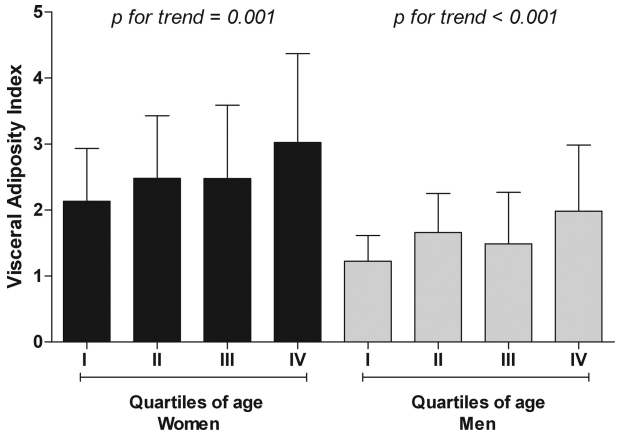

FIG. 1. VAI for trend according to quartiles of age in acromegalic women and men.

lished on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Discussion

In this multicenter retrospective study, we analyzed the hormonal and metabolic parameters in a large series of men and women affected by active untreated acromegaly. Women showed a worse metabolic profile than men, regardless of the hormonal data, indicating that gender may independently affect the metabolic parameters in acromegaly.

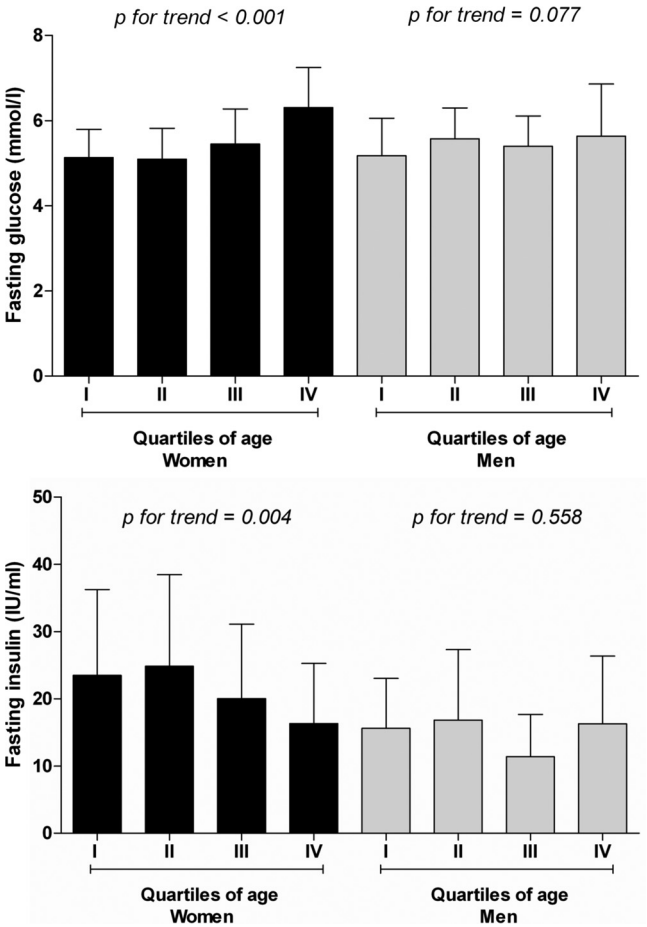

FIG. 2. Fasting glucose (*top*) and fasting insulin (*bottom*) for trend according to quartiles of age in acromegalic women and men.

The sexual dimorphism of the somatotroph axis and the lower sensitivity to GH in women have already been documented (23, 24), although with discordant results. Higher mean GH concentrations have frequently been found in both healthy and acromegalic women than in men (1, 7, 8), but these data are not confirmed by other studies (25). Lower IGF-I levels with concomitant higher GH nadir during OGTT have also been documented in 79 newly diagnosed acromegalic women compared with 72 men (4). In contrast with previous studies, some authors demonstrated higher IGF-I levels in men, because of the potential androgen role in stimulating GH secretion (26). Our data, showing a similar hormonal profile in men and women in terms of basal GH, nadir of GH during OGTT, AUC of GH and IGF-I levels, are in agreement with those of Freda *et al.* (27), which demonstrated in 92 subjects with acromegaly no significant gender difference in basal and nadir GH levels, thus not supporting separate criteria for treatment in men and women with acromegaly.

We found that GH levels showed a similar trend toward decrease from younger to older patients in both sexes, and these data confirm the evidence that in elderly subjects the disease seems to be less aggressive in terms of biochemical parameters. In two previous studies, the severity of acromegaly was reported to be milder in elderly patients than in young ones because it was associated with lower GH values and smaller tumor at presentation (28, 29). It is known that GH and IGF-I levels physiologically decrease with aging (25, 30), and our findings are partially in line with those of Colao *et al.* (4) showing that age is negatively correlated with basal and nadir GH in *de novo* acromegalic patients of both sexes. We also found that the tumor size did not significantly differ between men and women. In addition, among women, elderly patients had smaller adenomas than young patients. These data are in agreement with previous papers showing the maximal tumor diameter inversely correlated with age in women but not in men (4).

Beyond the hormonal and tumor parameters, already thoroughly studied, whether the metabolic alterations in acromegaly are dependent on gender has never previously been investigated.

A few years ago, a partial gender dimorphism in body composition abnormalities in acromegaly was hypothesized, with the evidence that acromegalic males had more total mass, lean body mass, and bone mineral content than controls and that the anabolic effect of GH on bone re-

TABLE 4. MS and glucose tolerance categories in men and pre- and postmenopausal women

	Men	Premenopausal women	Postmenopausal women	*P*
n	157	77	73	
MS	30 (19.1)	31 (40.3)	46 (63)	<0.001
Increased WC	11 (7)	22 (28.6)	35 (47.9)	<0.001
Hypertriglyceridemia	49 (31.2)	26 (33.8)	27 (37)	0.683
Low HDL-cholesterol	27 (17.2)	46 (59.7)	47 (64.4)	<0.001
Increased systolic blood pressure or specific treatment	95 (60.5)	51 (66.2)	56 (76.7)	0.054
Increased diastolic blood pressure or specific treatment	64 (40.8)	37 (48.1)	32 (43.8)	0.570
IFG	42 (26.8)	7 (9.1)	19 (26)	0.006
IGT	10 (6.4)	3 (3.9)	6 (8.2)	0.528
IFG + IGT	17 (10.8)	6 (7.8)	10 (13.7)	0.505
DM	8 (5.1)	7 (9.1)	19 (26)	<0.001

Data are expressed as number of subjects (percentage).

verted in cured males but not in females (32). For these reasons, we aimed to compare all MS features, the categories of glucose tolerance, and all indexes of insulin sensitivity and resistance, grouping the entire cohort of patients according to gender.

The acromegalic women, although displaying GH and IGF-I levels similar to men, showed a worse global metabolic profile, with a higher overall prevalence of MS. We found a lower degree of insulin sensitivity and greater basal and total hyperinsulinism in women than in men, demonstrated by lower ISI-Matsuda and higher fasting and AUC_{INS} levels, regardless of GH levels, whereas no difference was found in early and relative insulin secretion indexes (insulinogenic index and DIo). The BMI, which was comparable between men and women, did not affect these data. A possible explanation can be the higher visceral adipose dysfunction in acromegalic women, shown by higher VAI, than in men. We recently demonstrated that active acromegaly is strongly associated with visceral adiposity dysfunction, and both somatostatin analogs and surgical therapies were able to improve it, as demonstrated by the significant VAI decrease after 12 months of treatment (21). In addition, patients with high VAI show decreased insulin sensitivity because a significantly strong association between VAI and the rate of peripheral glucose utilization (M value) has been demonstrated (22). Therefore, the higher VAI levels in women with acromegaly could lead to a lower degree of insulin sensitivity than men. This finding seems to be in contrast with the well-known body composition differences between the sexes in the general population, where men tend to have central fat distribution and women tend to have peripheral fat distribution (33, 34). The higher visceral adiposity observed in healthy men is associated with elevated postprandial insulin, free fatty acid, and triglyceride levels (35). Conversely, the peripheral fat distribution typically found in healthy women is associated with improved insulin sensitivity, compared with central fat distribution (36). According to our results, women with acromegaly seem to have different behavior, in terms of visceral adiposity, compared with the existing data about healthy women. In our previous paper, although patients with high VAI were less insulin-sensitive, no significant difference in the glucose tolerance categories was reported between patients with normal and high VAI, supporting the hypothesis that VAI shows the early signs of metabolic risk, although a significant reduction in glucose tolerance has not yet occurred (22). This finding is apparently in contrast with these data because women showed a higher prevalence of overt DM. To explain this apparent discrepancy, the role of the higher family history for diabetes shown in women cannot be ruled out. Indeed, a direct and independent influence by family history for diabetes in VAI has already been demonstrated (22). Conversely, men only showed a higher prevalence of IFG, which disappeared when compared with women grouped according to menopausal status. In this connection, the fact that about half of the women were in the postmenopausal age group must be taken into account. Postmenopausal age in the general population is known to be associated with a higher prevalence of hypertension, diabetes, lipid alterations, and cardiovascular disease, likely due to the coincident increase in insulin resistance and in abdominal adiposity (37–44). Accordingly, a majority of postmenopausal women comply with the criteria defining MS, and cardiovascular disease is the first cause of morbidity and mortality in women, occurring even more frequently than in men (45). Similarly, when we grouped women in line with menopausal status, a higher prevalence of MS, increased WC, low HDL-cholesterol, and overt DM was found in postmenopausal women. Whether these changes are due to aging or to menopause itself is unknown. In this connection, age seems to influence metabolic parameters in acromegaly more in women than in men. The evidence that fasting

glucose showed a trend toward increase parallel to age increase in women only, together with a trend toward a decrease in fasting insulin, could be associated with the trend toward increase in VAI from the first to the fourth quartile of age, mainly in women. The visceral adipose dysfunction seems to act on basal insulin secretion and consequently on hepatic glucose output. In this connection, the increase in visceral adipose tissue is reported to contribute to enhanced gluconeogenesis and insulin resistance (46, 47). Therefore, in agreement with these findings, the higher VAI values in women could explain this different trend in the two groups of patients. In addition, a role of the mammalian target of rapamycin (mTOR) pathway, known to promote hyperinsulinism and insulin resistance and, by a feedback loop, to be overactivated by insulin and other growth factors, cannot be ruled out (48–50). In fact, a stronger activation of mTOR signaling in women than in men was recently demonstrated (31). Therefore, a more pronounced activation of mTOR pathway in women that could favor a greater degree of insulin resistance is not to be ruled out.

In conclusion, these data demonstrated that the majority of metabolic features in acromegaly are gender-specific, regardless of hormonal parameters. Active acromegaly in women is strongly associated with higher visceral adiposity dysfunction, insulin resistance, and the features of MS. Therefore, more careful metabolic management is suggested in acromegalic women. In addition, increased attention to risk factor modification in the postmenopausal years can help prospectively reduce cardiovascular disease risk in women with acromegaly.

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