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ORIGINAL ARTICLE

Adrenal morphology and function in acromegalic patients in relation to disease activity

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Abstract Visceromegaly is a common consequence of acromegaly. However, few studies investigated the chronic effects of growth hormone on adrenal glands. Our aim was to evaluate adrenal morphology and function in a cohort of acromegalic patients in relation to disease activity. Twenty-six acromegalics (10 males and 16 females) and 21 healthy subjects were investigated. Gland morphology was evaluated by computerized axial tomography, measuring central, lateral, and medial adrenal segments. Uncontrolled acromegalics showed increased volume of all adrenal segments, higher urinary free cortisol (UFC), and lower morning adrenocorticotropic hormone in comparison with healthy subjects. However, normal cortisol levels after low-dose dexamethasone suppression test indicated a preserved regulation of the hypothalamic–pituitary–adrenal axis. In addition, uncontrolled patients showed greater medial segment of right gland, higher UFC, and aldosterone levels with respect to controlled patients. All acromegalics did not show any difference in adrenal size when grouped according to UFC/24 h levels. In addition, no difference was found in any of the parameters between normotensive and hypertensive patients. In conclusion, our findings confirm that acromegaly affects adrenal size as well as other organs. In addition, we report a stimulatory effect of growth hormone on adrenal function, although the regulation of the hypothalamic–pituitary–adrenal axis is preserved.

Keywords Acromegaly · Growth hormone · Adrenal gland · Cortisol

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Introduction

Acromegaly is a slow-developing, insidious disease, so that diagnosis is delayed by a number of years. It is known that visceromegaly is a common clinical feature of acromegaly due to the growth-promoting chronic effects of growth hormone (GH) on many tissues [1–3]. It is also acknowledged that growth hormone–insulin-like growth factor (IGF) system plays an important role in the regulation of adrenocortical function. Coyne demonstrated that steroid production of primary cultures of rat adrenocortical cells is significantly higher and better maintained in presence of corticotropin and GH rather than corticotropin alone [4]. In addition, IGFs induce adrenal steroidogenic secretion in adult human adrenocortical cells [5], although apparently GH is unable to directly stimulate cortisol secretion [6].

Few clinical studies evaluated adrenal function and morphology in acromegaly. Altered renin–angiotensin–aldosterone system, metanephrine, and catecholamine levels were proposed as potential explanation of hypertension in acromegalic patients, although with conflicting results [7–12]. Recently, high frequency of adrenal lesions has been documented in acromegalics; however, the correlation with duration of disease, GH, and IGF-1 levels was not investigated [13].

The aim of this study was to evaluate adrenal morphology and function in a cohort of acromegalic patients, with or without hypertension, in relation to disease activity.

Subjects and methods

Patients

Twenty-six acromegalic patients (10 males and 16 females, age 54.5 ± 10.4 years) were included in the study: 2 subjects were recruited at diagnosis, before starting any medical therapy; 8 subjects were treated with first-line therapy with SST-A (5 with octreotide LAR 20 mg/month; 3 with lanreotide LA 60 mg/month; duration of treatment: 10.3 ± 3.5 months); and 16 subjects were recruited after neurosurgical therapy, among them 6 were without medical treatment (time from surgery 3.2 ± 0.6 months), 8 were treated with long-acting somatostatin analogues (SST-A) (octreotide LAR 20 mg/month; duration of treatment 36.6 ± 12.5 months), and 2 patients were treated with pegvisomant (10 mg/day; duration of treatment: 13.1 ± 3.2 months). Mean duration of disease was 4.7 years for controlled and 3.5 years for uncontrolled acromegalics. Clinical characteristics of acromegalic patients are shown in Table 1. Based on nadir GH after oral glucose load (OGTT) and age-matched IGF-1 levels, patients were divided into two groups: controlled ($n = 14$) and uncontrolled ($n = 12$). Cut-off level for controlled subjects was 1 μg/l for GH after OGTT, together with normal IGF-1 for age [14]. GH levels of the two patients treated with pegvisomant were not considered. We excluded from the study all patients affected by secondary hypopituitarism, with mixed adenomas and those using antidiabetic drugs. Twenty-one voluntary healthy subjects were included as controls. The three groups (controlled acromegalics, uncontrolled acromegalics, and control subjects) were matched for age, body mass index (BMI), and body surface area (BSA) (Table 2). Informed consent was obtained from all subjects. The Institutional Review Board at the Faculty of Medicine of the University of Palermo approved the retrospective study.

Study design

All subjects enrolled had been investigated for BMI, BSA, nadir GH after OGTT, IGF-1 levels (the average value of three measurements assessed during the previous 6 months, expressed as IGF-1 standard deviation (SD)), lipid profile (total cholesterol, HDL, LDL, triglycerides), fasting glucose, and fasting insulin. Insulin resistance had been evaluated by Homeostasis Model Assessment Insulin Resistance Index (HOMA-IR), applying Matthews formula [fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5] [15]. Systolic and diastolic blood pressure profile had been assessed in supine position after 2 weeks of washout from hypertensive drugs (during this period patients changed their treatment to calcium channel blockers). ECG, cardiac ultrasonography parameters (% of ejection fraction, left ventricular parietal size, telediastolic ventricular volume, and valvular morphology) [16], and 24-h urinary albumin excretion had been also evaluated. Adrenal size and morphology were measured with computerized axial tomography (CT). Measurements of central, lateral, and medial adrenal segments were taken (values expressed as mean ± SD). "Brilliance 64 Philips" CT machine with "Work Station Philips" program and 4-mm scanning intervals was used. Diagnosis of hyperplastic adrenal glands was done when the sum of central, lateral, and medial adrenal segments was >97° percentile of control population. Morning and midnight plasma cortisol and adrenocorticotropic hormone (ACTH), cortisol after single dose (1 mg) overnight dexamethasone suppression test (Nugent's Test), and 24-h urinary free cortisol (UFC) had been assessed in all subjects. Plasma aldosterone/renin activity ratio, plasma and urinary normetanephrine, and metanephrine levels had been measured after 2 weeks of hypertensive drug washout and appropriate diet regimen.

Hormone and biochemical assays

Glycemic, lipid (HDL, LDL, total cholesterol, and triglycerides), and microalbuminuria levels were measured with standard methods. Serum GH was assessed by ELISA (BioSource hGH-EASIA kit, Nivelles, Belgium). Sensitivity of the method was 0.07 μg/l. Inter- and intra-assay coefficients of variation (CV values) were 3.6–4.4 and 3.7–9.8%, respectively, for GH levels of 6.4–21.2 and 1.9–13.1 μg/l, respectively. Serum total IGF-1 was assessed by ELISA (OCTEIA IGF-1 kit, IDS Inc., Fountain Hills, AZ, USA). Sensitivity was 1.9 μg/l. Inter- and intra-assay CV values were 7–7.1 and 2.3–3.5%, respectively, for IGF-1 levels of 90.7–186 and 66.7–120.9 μg/l, respectively. Normal range of total IGF-1 levels (μg/l) was 150–350 (adults). Serum insulin was measured by ELISA (DRG Instruments GmbH, Germany). Sensitivity of the method was 1 μUI/ml. Normal range of insulin (μUI/ml) was 5–19. ACTH, cortisol, and UFC were measured by ELISA (DRG Instruments GmbH, Germany). Normal range of ACTH was 7.9–65.1 pg/ml (with sensitivity of 0.46 pg/ml); normal range of cortisol was 5–23 μg/dl (day time) and 3–15 μg/dl (night time); and normal range of UFC was 9–18 μg/24 h (with sensitivity of 0.2 μg/dl). Cortisol values after Nugent's Test were considered normal when <1.8 μg/dl. Aldosterone was measured by RIA (Immunotech, France); normal range was 0.8–17 ng/dl, with sensitivity of 0.6 ng/dl. Plasma renin activity was measured by RIA method (Immunotech, France); normal range was 1.5–5.7 ng/ml/h. Cut-off value for suspected primary hyperaldosteronism was aldosterone (ng/dl)/renin activity ratio >40. Plasma and urinary metanephrine were measured by RIA (Immunotech, France), with sensitivity of 99 and 77%, respectively.

Table 1 Medical treatment of controlled and uncontrolled acromegalic patients

	Controlled acromegalics ($n = 14$) Mean ± SD	Uncontrolled acromegalics ($n = 12$) Mean ± SD	p
Nadir GH levels (μg/l)[a]	0.8 ± 0.2	3.8 ± 2.1	<0.001
IGF-1 levels (μg/l)	182 ± 12	462 ± 36	<0.001
Duration of disease (years)	4.7 ± 8.4	3.5 ± 2.2	0.176
	n (%)	*n* (%)	*p*
Neurosurgery	3 (21)	3 (25)	1
First-line octreotide LAR 20 mg/month	3 (21)	2 (16)	1
First-line lanreotide LA 60 mg/month	2 (14)	1 (0.8)	1
Pegvisomant 10 mg/day after neurosurgery	2 (14)	0	0.483
Octreotide LAR 20 mg/month after neurosurgery	4 (28)	4 (33)	1
At diagnosis	0	2 (16)	0.203

[a] GH levels of patients under treatment with pegvisomant were not considered

Conversion factors for the International System (SI) were: glucose (mg/dl vs. mmol/l: 0.0555), insulin (μUI/ml vs. pmol/l: 6.945), total cholesterol (mg/dl vs. mmol/l: 0.0259), triglycerides (mg/dl vs. mmol/l: 0.0113), ACTH (pg/ml vs. pmol/l: 0.22), cortisol (μg/dl vs. nmol/l: 27.59), and aldosterone (ng/dl vs. nmol/l: 0.0277).

Statistical analysis

SPSS 13 software and GraphPad InStat version 3.06, Windows Edition, were used for all statistical analyses. Continuous variables were shown as mean values ± SD. Rates and proportions were calculated for categorical data. Differences between the two groups were analyzed by Mann–Whitney test (nonparametric test), as they were continuous variables without normal distribution. For categorical variables, differences were analyzed with χ^2-test and Fisher's exact test when appropriate. Differences among the three groups (control subjects, controlled, and uncontrolled acromegalic patients) were analyzed with a nonparametric post hoc test (Dunn's Multiple Comparison Test), after Kruskal–Wallis analysis. The variables age, BMI, and BSA had normal distribution, therefore they were analyzed with one-way ANOVA Bonferroni adjustment. P values <0.05 were considered significant.

Results

Metabolic and cardiovascular parameters

Clinical characteristics, metabolic, and cardiovascular parameters are shown in Table 2. As expected, all acromegalic patients, regardless of disease activity, had higher prevalence of metabolic syndrome features compared with controls, including hypertension [17] and diabetes mellitus [18], higher total cholesterol and triglycerides, lower HDL-cholesterol, greater left ventricular parietal size, lower telediastolic left ventricular volume, and higher prevalence of valvular fibrosis. In particular, uncontrolled acromegalics showed also increased waist circumference [19], higher fasting glycemic values, insulin concentrations, HOMA-IR, and microalbuminuria/24 h. Comparing uncontrolled to controlled patients, uncontrolled subjects showed higher total cholesterol, triglycerides, microalbuminuria and insulin levels, systolic and diastolic blood pressure, greater left ventricular parietal size, and lower telediastolic left ventricular volume.

Grouping patients according to blood pressure, hypertensive subjects showed significantly higher levels of fasting glycemia and microalbuminuria/24 h. No significant difference was found regarding age, duration of illness from diagnosis, BMI, prevalence of metabolic syndrome, total cholesterol, insulin levels and HOMA-IR, ejection fraction, left ventricular parietal size, telediastolic left ventricular volume, and prevalence of valvular fibrosis (Table 3).

Grouping patients according to UFC/24 h levels, increased waist circumference values, microalbuminuria/24 h levels, and left ventricular parietal size were found in acromegalic patients with UFC values above the median (Table 4).

Adrenal morphology and function

Abdominal CT showed adrenal alterations in 8 (30.7%) acromegalic patients: 4 of them (15%) had unilateral hyperplasia, 2 (7.6%) bilateral hyperplasia, and 2 (7.6%)

Table 2 Controlled and uncontrolled acromegalic patients vs. control group

	Controlled acromegalics (Group A) ($n = 14$)	Uncontrolled acromegalics (Group B) ($n = 12$)	Control group (Group C) ($n = 21$)	A vs. B	A vs. C	B vs. C
	Mean (SD)	Mean (SD)	Mean (SD)	p	p	p
Age	57.5 (11.3)	51 (8.2)	51.4 (12.7)	0.076	0.145	0.699
BMI (kg/m^2)	29.8 (2.8)	30.6 (5.2)	29.2 (3.5)	0.936	0.484	0.593
BSA (m^2)	1.94 (0.13)	1.89 (0.17)	1.87 (0.13)	1	0.459	1
	n (%)	n (%)	n (%)	p	p	p
Male	7 (50)	3 (25)	8 (38.1)	0.248	0.486	0.703
Female	7 (50)	9 (75)	13 (61.9)			
Diabetes mellitus[a]	4 (28.6)	6 (50)	0	0.422	0.019	0.001
Hypertension[b]	7 (50)	8 (66.7)	0	0.453	0.001	<0.001
Low HDL cholesterol[c]	2 (14.3)	4 (33.3)	0	0.365	0.153	0.012
Hypertriglyceridemia[c]	2 (14.3)	7 (58.3)	0	0.058	0.153	<0.001
Increased waist circumference[c]	6 (42.9)	10 (83.3)	7 (33.3)	0.051	0.568	0.010
Metabolic syndrome[c]	4 (28.6)	7 (58.3)	0	0.233	0.019	<0.001
	Metabolic parameters					
	Mean (SD)	Mean (SD)	Mean (SD)	p*	p*	p*
Total cholesterol (mmol/l)	4.4 (0.9)	5.1 (0.8)	3.6 (0.3)	n.s.	<0.05	<0.001
HDL cholesterol (mmol/l)	1.3 (0.3)	1.17 (0.2)	1.7 (0.2)	n.s.	<0.001	<0.001
Triglycerides (mmol/l)	1.4 (0.4)	1.72 (0.4)	1.0 (0.1)	n.s.	0.05	<0.001
Fasting glycemia (mmol/l)	5.8 (1.7)	6.8 (1.6)	4.8 (0.3)	n.s.	n.s.	<0.001
Insulin levels (pmol/l)	87.5 (35.4)	123.6 (59)	61.1 (9.7)	n.s.	n.s.	<0.001
HOMA-IR	3.1 (1.1)	5.6 (3.5)	1.9 (0.4)	n.s.	<0.01	<0.001
	Cardiovascular parameters					
	Mean (SD)	Mean (SD)	Mean (SD)	p*	p*	p*
Systolic blood pressure (mmHg)	122.5 (14.3)	142.9 (6.8)	114.6 (7.9)	<0.01	n.s.	<0.001
Diastolic blood pressure (mmHg)	73.2 (13)	85.5 (9.1)	67.1 (4.0)	<0.05	n.s.	<0.001
Microalbuminuria (mg/24 h)	9.3 (13.5)	28.1 (14.3)	9.3 (2.9)	0.001	n.s.	<0.01
Ejection fraction (%)	60 (3.3)	63.7 (4.4)	64.5 (3.8)	n.s.	<0.05	n.s.
Left ventricular parietal size (mm)	11.1 (1.9)	14.5 (2.3)	8.7 (0.8)	<0.001	<0.01	<0.001
Telediastolic ventricular volume (mm)	48.2 (3.8)	43.2 (3.6)	51.4 (1.6)	<0.05	<0.05	<0.001
	n (%)	n (%)	n (%)	p	p	p
Valvular fibrosis	4 (40)	6 (75)	0	0.188	0.039	<0.001
	Adrenal morphology and function					
	Mean (SD)	Mean (SD)	Mean (SD)	p*	p*	p*
Plasma aldosterone (nmol/l)	0.18 (0.08)	0.36 (0.25)	0.17 (0.05)	<0.05	n.s.	n.s.
Plasma renin activity (ng/ml/h)	2 (0.9)	1.3 (1.2)	1.5 (1.2)	n.s.	n.s.	n.s.
Plasma aldosterone/renin activity ratio	4.4 (5.4)	25.6 (23.5)	13.6 (15.3)	<0.05	n.s.	n.s.
Morning cortisol levels (nmol/l)	540.7 (361.4)	808.4 (587.6)	623.5 (110.3)	n.s.	n.s.	n.s.
Midnight cortisol levels (nmol/l)	377.9 (344.8)	626.3 (615.2)	383.5 (80)	n.s.	n.s.	n.s.
Morning ACTH levels (pmol/l)	6.07 (3.49)	5.61 (3.80)	9.46 (1.56)	n.s.	<0.01	<0.001
Midnight ACTH levels (pmol/l)	3.87 (3.19)	4.57 (3.19)	4.95 (1.60)	n.s.	n.s.	n.s.
Free cortisol in 24-h urine (nmol/24 h)	301.8 (131.6)	416.3 (110.9)	279.1 (32.5)	<0.05	n.s.	<0.001

Table 2 continued

	Controlled acromegalics (Group A) ($n = 14$)	Uncontrolled acromegalics (Group B) ($n = 12$)	Control group (Group C) ($n = 21$)	A vs. B	A vs. C	B vs. C
	Adrenal morphology and function					
	Mean (SD)	Mean (SD)	Mean (SD)	p*	p*	p*
Cortisol after Nugent's test (nmol/l)	24.8 (5.5)	28.9 (7.2)	22.0 (11.0)	n.s.	n.s.	n.s.
Medial adrenal segment (right) (mm)	21.3 (5.4)	27.2 (4.1)	17.7 (3.6)	<0.05	n.s.	<0.001
Lateral adrenal segment (right) (mm)	22.9 (6.4)	25.3 (4.6)	18.4 (4.4)	n.s.	n.s.	<0.001
Central adrenal segment (right) (mm)	20.11 (2.8)	22 (2.2)	13.8 (1.6)	n.s.	<0.001	<0.001
Medial adrenal segment (left) (mm)	21.2 (3.9)	25.3 (4.4)	17.6 (4.1)	n.s.	n.s.	<0.001
Lateral adrenal segment (left)(mm)	21.7 (4.2)	25.7(4.2)	17.6 (3.6)	n.s.	n.s.	<0.001
Central adrenal segment (left) (mm)	21.3 (2.1)	24.4 (3.1)	14.7 (2.8)	n.s.	<0.001	<0.001

Data are expressed as mean values ± SD

* Dunn's multiple comparison test after Kruskal–Wallis test; for BMI, age, BSA, and one-way ANOVA Bonferroni adjustment

[a] ADA criteria [18]

[b] ESH/ESC criteria [17]

[c] ATP III criteria [19]

Table 3 Hypertensive vs. normotensive acromegalic patients

	Hypertensive acromegalics ($n = 15$)	Normotensive acromegalics ($n = 11$)	p
	Mean (SD)	Mean (SD)	
Age	58.1 (9)	49.6 (10.4)	0.054
Duration of disease (years)	2.5 (2.1)	6.4 (9.1)	0.281
BMI (kg/m^2)	29.7 (2.4)	31.1 (5.8)	1
BSA (m^2)	1.9 (0.1)	1.8 (0.1)	0.820
	n (%)	n (%)	p
Sex			0.228
Male	4 (26.7)	6 (54.5)	
Female	11 (73.3)	5 (45.5)	
Diabetes mellitus[a]	8 (53.3)	2 (18.2)	0.109
Low HDL cholesterol[b]	6 (40)	0	0.024
Hypertriglyceridemia[b]	7 (46.7)	2 (18.2)	0.217
Increased waist circumference[b]	10 (66.7)	6 (54.5)	0.530
Metabolic syndrome[b]	9 (60)	2 (18.2)	0.051
Active acromegaly	7 (46.7)	7 (63.6)	0.453
	Metabolic parameters		
	Mean (SD)	Mean (SD)	p
Total cholesterol (mmol/l)	4.8 (0.7)	4.5 (1.2)	0.610
HDL cholesterol (mmol/l)	1.2 (0.2)	1.2 (0.2)	0.357
Triglycerides (mmol/l)	1.6 (0.3)	1.4 (0.6)	0.330
Fasting glycemia (mmol/l)	7.0 (1.7)	5.3 (1.1)	0.005
Insulin levels (pmol/l)	102.1 (59)	106.9 (37.5)	0.384
HOMA-IR	4.7 (3.3)	3.6 (1.7)	0.540

Table 3 continued

	Hypertensive acromegalics ($n = 15$)	Normotensive acromegalics ($n = 11$)	p
	Cardiovascular parameters		
	Mean (SD)	Mean (SD)	p
Microabuminuria (mg/24 h)	25.9 (17.3)	7.3 (7.2)	0.004
Ejection fraction (%)	63.7 (4.4)	60 (3.3)	0.122
Left ventricular parietal size (mm)	14.1 (2.5)	11.4 (2.3)	0.122
Telediastolic ventricular volume (mm)	45.7 (4)	46.2 (4.9)	0.897
	n (%)	n (%)	p
Valvular fibrosis	6 (75)	4 (40)	0.188
	Adrenal morphology and function		
	Mean (SD)	Mean (SD)	p
Plasma aldosterone (nmol/l)	0.30 (0.25)	0.20 (0.14)	0.507
Plasma renin activity (ng/ml/h)	1.4 (1)	2.2 (1.1)	0.237
Plasma aldosterone/renin activity ratio	21.2 (23.2)	4.5 (3.1)	0.413
Morning cortisol levels (nmol/l)	805.6 (584.9)	471.8 (209.7)	0.198
Midnight cortisol levels (nmol/l)	640.1 (604.2)	292.4 (148.9)	0.077
Morning ACTH levels (pmol/l)	4.99 (3.65)	7.04 (3.27)	0.134
Midnight ACTH levels (pmol/l)	3.78 (3.41)	4.77 (2.77)	0.184
Free cortisol in 24-h urine (nmol/24 h)	365.8 (102.9)	337.4 (171.6)	0.683
Cortisol after Nugent's test (nmol/l)	24.2 (6.0)	23.7 (6.5)	0.843
Medial adrenal segment (right) (mm)	23.5 (6.3)	24.8 (4.7)	0.474
Lateral adrenal segment (right) (mm)	23.4 (5.2)	24.4 (6.5)	0.646
Central adrenal segment (right) (mm)	21.2 (3.1)	20.7 (2)	0.760
Medial adrenal segment (left) (mm)	24.2 (4.7)	21.6 (4.2)	0.217
Lateral adrenal segment (left) (mm)	23.3 (5)	23.9 (4.1)	0.540
Central adrenal segment (left) (mm)	23.4 (3.4)	21.8 (2.2)	0.384

Data are expressed as mean values ± SD

[a] ADA criteria [18]

[b] ATP III criteria [19]

had bilateral nodules, with diameter 5–16 mm. Uncontrolled acromegalics showed increased volume of all adrenal segments (medial, lateral, and central) in both glands in comparison to healthy subjects. Conversely, controlled acromegalics showed only greater central adrenal segments compared with controls (Fig. 1, Table 2). With regard to disease status, uncontrolled patients showed higher UFC/24 h levels and lower morning ACTH in comparison to control group. Mean plasma cortisol levels were slightly over normal range, although not statistically

Table 4 Acromegalic patients grouped by their adrenal function

	UFC ≤ median value ($n = 13$)	UFC > median value ($n = 13$)	p
	Mean (SD)	Mean (SD)	
Age	55.1 (11.8)	53.9 (9.1)	0.681
Duration of disease (years)	5.5 (8.5)	2.8 (2.2)	0.979
BMI (kg/m^2)	29.7 (2.8)	30.7 (5)	0.957
BSA (m^2)	1.9 (0.1)	1.9 (0.2)	0.957

Table 4 continued

	UFC ≤ median value ($n = 13$)	UFC > median value ($n = 13$)	p
	n (%)	n (%)	p
Sex			0.420
Male	6 (46.2)	4 (30.7)	
Female	7 (53.8)	9 (69.3)	
Diabetes mellitus[a]	3 (23.1)	7 (53.8)	0.226
Low HDL cholesterol[b]	1 (15.4)	4 (30.8)	0.645
Hypertriglyceridemia[b]	3 (23.1)	6 (46.2)	0.411
Increased waist circumference[b]	5 (38.5)	11 (84.6)	0.041
Metabolic syndrome[b]	3 (23.1)	8 (61.5)	0.111
Hypertension[b]	7 (53.8)	8 (61.5)	0.691
Active acromegaly	9 (69.2)	5 (38.4)	0.237
	Metabolic parameters		
	Mean (SD)	Mean (SD)	p
Total cholesterol (mmol/l)	4.5 (1)	4.9 (0.9)	0.317
HDL cholesterol (mmol/l)	1.2 (0.2)	1.2 (0.2)	0.680
Triglycerides (mmol/l)	1.4 (0.4)	1.7 (0.4)	0.218
Fasting glycemia (mmol/l)	5.8 (1.8)	6.7 (1.5)	0.058
Insulin levels (pmol/l)	98.5 (37.9)	110.1 (61.4)	0.980
HOMA-IR	3.6 (1.7)	5 (3.5)	0.626
	Cardiovascular parameters		
	Mean (SD)	Mean (SD)	p
Microabuminuria (mg/24 h)	9.8 (12)	26.2 (16.9)	0.012
Ejection fraction (%)	62.2 (4.4)	61.1 (4.1)	0.494
Left ventricular parietal size (mm)	11.4 (2.8)	13.8 (2.1)	0.025
Telediastolic ventricular volume (mm)	47.4 (4.3)	44.5 (4.2)	0.178
	n (%)	n (%)	p
Valvular fibrosis	3 (33.3)	7 (77.2)	0.153
	Adrenal morphology and function		
	Mean (SD)	Mean (SD)	p
Plasma aldosterone (nmol/l)	0.18 (0.14)	0.34 (0.25)	0.024
Plasma renin activity (ng/ml/h)	1.9 (1.1)	1.5 (1.1)	0.488
Plasma aldosterone/renin activity ratio	11.1 (19.7)	17.2 (19.3)	0.118
Morning ACTH levels (pmol/l)	5.6 (2.5)	7.04 (3.27)	0.980
Midnight ACTH levels (pmol/l)	3.5 (2.5)	4.8 (3.7)	0.555
Medial adrenal segment (right) (mm)	24.3 (5.7)	23.8 (5.7)	0.959
Lateral adrenal segment (right) (mm)	24.8 (6.9)	23.2 (4.2)	0.776
Central adrenal segment (right) (mm)	20.9 (3)	21.1 (2.4)	0.776
Medial adrenal segment (left) (mm)	22.4 (4.5)	23.7 (4.8)	0.678
Lateral adrenal segment (left) (mm)	23.5 (5.1)	23.6 (4.3)	0.979
Central adrenal segment (left) (mm)	22.4 (3.3)	23.1 (2.9)	0.697

Data are expressed as mean values ± SD

[a] ADA criteria [18]

[b] ATP III criteria [19]

different from control group. Comparing uncontrolled to controlled patients, uncontrolled subjects showed higher UFC/24 h, aldosterone levels, and aldosterone/renin activity ratio. However, cortisol after low-dose dexamethasone suppression test was in the normal range (Table 2). No difference was found in any adrenal parameter regarding disease activity and between normotensive and hypertensive acromegalic patients (Table 3). Plasma and urinary normetanephrines and metanephrines were not significantly different in all groups.

Grouping patients according to UFC/24 h levels, no difference was found in acromegalic patients regarding adrenal size (Table 4).

Discussion

The aim of this study was to investigate adrenal morphology and function in acromegalic patients in relation to disease activity. Recently, Scaroni et al. described a prevalence of 28% of adrenal lesions in acromegalics (10% unilateral masses and 19% hyperplasia), without correlation between adrenal lesions and GH, IGF-1, or any other major endocrine alterations [13].

Our study confirmed higher prevalence (30.7%) of adrenal alterations in acromegalic patients in comparison to healthy subjects. In particular, uncontrolled acromegalics showed greater adrenal size for all segments evaluated, supporting the hypothesis that GH excess may have stimulatory effects on adrenal gland size as well as on other organs. This is further confirmed by the observation that controlled patients showed only greater central adrenal segments. Interestingly, only disease status seems to influence adrenal morphology, as no correlation was found with duration of the disease.

Concerning adrenal function, cortisol levels were not significantly different among the groups. However, all acromegalics showed lower morning ACTH in comparison with healthy subjects and uncontrolled patients had also higher UFC/24 h values. These findings suggest functional alterations of adrenal glands; however, normal cortisol values after low-dose dexamethasone suppression test indicate a preserved regulation of the hypothalamic–pituitary–adrenal axis. The rare coexistence of acromegaly and adrenal pheochromocytoma has been also described [12, 20]; therefore, it has been suggested that acromegalic patients with hypertension should always be screened for pheochromocytoma [21]. Our data do not support this hypothesis as no difference was found in plasma and urinary metanephrine between acromegalics and healthy subjects. In addition, hypertensive and normotensive patients did not show significant difference in all adrenal parameters, suggesting that hypertensive status in these

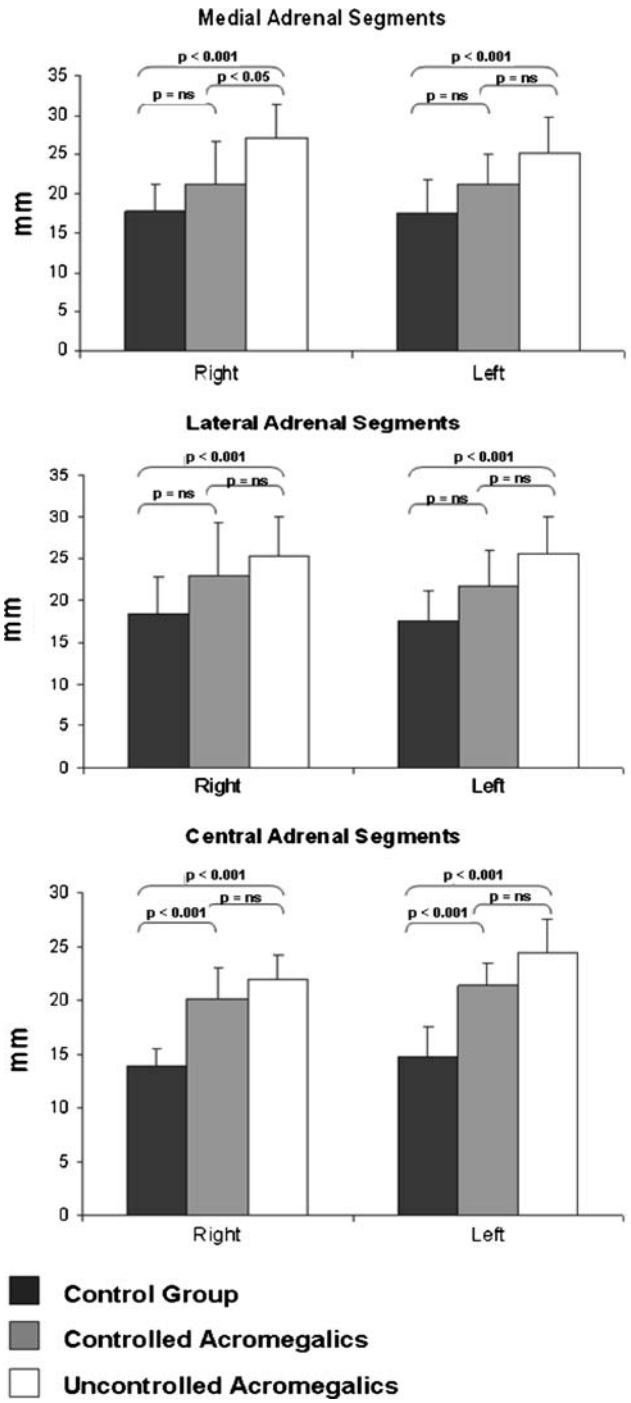

Fig. 1 Adrenal size in control subjects, controlled, and uncontrolled acromegalic patients. Increased volume of all adrenal segments (medial, lateral, and central) in both glands of uncontrolled acromegalics (*white bars*) in comparison to healthy subjects (*black bars*). Central adrenal segments are increased in controlled acromegalics (*gray bars*) compared with controls

patients is multifactorial. The finding of higher microalbuminuria/24 h levels and left ventricular parietal size in acromegalics with UFC values above the median is

consistent with the increased waist circumference found in these patients.

In conclusion, adrenal glands seem to represent another target of GH-axis in acromegaly, as already demonstrated for other organs and tissues. A morphological and functional evaluation of adrenal glands is advisable in acromegalics at onset and then periodically, in particular in relation to control of disease activity. A prospective study on a larger cohort of patients, with homogeneous medical treatment and longer follow-up, may help to individuate more defined indications for proper clinical management of such a complex disease.

References

1. A. Colao, P. Marzullo, C. Di Somma, G. Lombardi, Growth hormone and the heart. Clin. Endocrinol. (Oxf) **54**, 137–154 (2001)
2. A.J. Sober, P. Gorden, J. Roth, T.W. AvRuskin, Visceromegaly in acromegaly. Evidence that clinical hepatomegaly or splenomegaly (but not sialomegaly) are manifestations of a second disease. Arch. Intern. Med. **134**(3), 415–417 (1974)
3. M. Gasperi, E. Martino, L. Manetti, M. Arosio, S. Porretti, G. Faglia, S. Mariotti, A.M. Colao, G. Lombardi, R. Baldelli, F. Camanni, A. Liuzzi, Acromegaly Study Group of the Italian Society of Endocrinology, Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multi-center study. J. Endocrinol. Invest. **25**(3), 240–245 (2002)
4. M.D. Coyne, Effect of growth hormone and corticotrophin on steroidogenesis in cultured rat adrenocortical cells. Horm. Res. **19**(3), 185–190 (1984)
5. C. Fottner, D. Engelhardt, M.M. Weber, Regulation of steroidogenesis by insulin-like growth factors (IGFs) in adult human adrenocortical cells: IGF-I and, more potently, IGF-II preferentially enhance androgen biosynthesis through interaction with the IGF-I receptor and IGF-binding proteins. J. Endocrinol. **158**(3), 409–417 (1998)
6. P. Michl, D. Engelhardt, R. Oberneder, M.M. Weber, Growth hormone has no direct effect on human adrenal steroid and insulin-like growth factor-binding protein secretion. Endocr. Res. **25**(3–4), 281–293 (1999)
7. P.E. Cryer, Plasma norepinephrine and epinephrine in acromegaly. J. Clin. Endocrinol. Metab. **41**, 542–545 (1975)
8. G. Deray, P. Chanson, G. Maistre, A. Warnet, J. Eurin, C. Barthelemy, F. Masson, F. Martinez, J. Lubetzki, J.C. Legrand, Atrial natriuretic factor in patients with acromegaly. Eur. J. Clin. Pharmacol. **38**, 409–413 (1990)
9. C.M. Ritchie, B. Sheridan, R. Fraser, D.R. Hadden, A.L. Kennedy, J. Riddell, A.B. Atkinson, Studies on the pathogenesis of hypertension in Cushing's disease and acromegaly. Q. J. Med. **76**, 855–867 (1990)
10. G.R. Van Loon, Abnormal plasma catecholamine response in acromegalics. J. Clin. Endocrinol. Metab. **48**, 784–789 (1979)
11. J.A. McKnight, D.R. McCance, D.R. Hadden, L. Kennedy, G. Robert, B. Sheridan, A.B. Atkinson, Basal and saline-stimulated levels of plasma atrial natriuretic factor in acromegaly. Clin. Endocrinol. (Oxf) **31**, 431–438 (1989)
12. J. Baughan, C. de Gara, D. Morrish, A rare association between acromegaly and pheochromocytoma. Am. J. Surg. **182**(2), 185–187 (2001)
13. C. Scaroni, R. Selice, S. Benedini, E. De Menis, M. Arosio, C. Ronchi, M. Gasperi, L. Manetti, G. Arnaldi, B. Polenta, M. Boscaro, N. Albiger, E. Martino, F. Mantero, Adrenal morpho-functional alterations in patients with acromegaly. J. Endocrinol. Invest. **31**(7), 602–606 (2008)
14. A. Giustina, A. Barkan, F.F. Casanueva, F. Cavagnini, L. Frohman, K. Ho, J. Veldhuis, J. Wass, K. Von Werder, S. Melmed, Criteria for cure of acromegaly: a consensus statement. J. Clin. Endocrinol. Metab. **85**(2), 526–529 (2000)
15. D.R. Matthews, J.P. Hosker, A.S. Rudenski, B.A. Naylor, D.F. Treacher, R.C. Turner, Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia **28**, 412–419 (1985)
16. D.J. Sahn, A. Demaria, J. Kisslo, A. Weyman, The Committee on M-Mode Standardization of the American Society of Echocardiography: recommendations regarding quantitation in M-Mode echocardiography: results of a survey study of echocardiography measurements. Circulation **58**, 1072–1083 (1978)
17. European Society of Hypertension-European Society of Cardiology Guidelines Committee, 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J. Hypertens. **21**(6), 1011–1053 (2003)
18. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care **20**, 1183–1197 (1997)
19. Third Report of the National Cholesterol Education Panel (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel or ATP III). NIH Publication No. 01-3305, May 2001
20. G.G. Sleilati, K.T. Kovacs, M. Honasoge, Acromegaly and pheochromocytoma: report of a rare coexistence. Endocr. Pract. **8**(1), 54–60 (2002)
21. R.J. Anderson, E.G. Lufkin, G.W. Sizemore, J.A. Carney, S.G. Sheps, Y.E. Silliman, Acromegaly pituitary adenoma with phaeochromocytoma: a variant of multiple endocrine neoplasia. Clin. Endocrinol. (Oxf) **14**(6), 605–612 (1981)