

Effect of Two Years of Growth Hormone and Insulin-Like Growth Factor-I Suppression on Prostate Diseases in Acromegalic Patients*

ANNAMARIA COLAO, PAOLO MARZULLO, STEFANO SPIEZIA, ASSUNTA GIACCIO, DIEGO FERONE, GAETANA CERBONE, ANTONELLA DI SARNO, AND GAETANO LOMBARDI

Department of Clinical and Molecular Endocrinology and Oncology, Federico II University of Naples (A.C., P.M., D.F., A.G., G.C., A.D.S., G.L.), and Emergency Unit, Santa Maria degli Incurabili Hospital (S.S.), 80131 Naples, Italy

ABSTRACT

The insulin-like growth factors (IGFs) have mitogenic effects on normal and tumoral prostate epithelial cells and have been suggested to be involved in prostate cancer. Moreover, chronic GH and IGF-I excess causes prostate overgrowth in patients with acromegaly. This study was designed to investigate whether the suppression of GH and IGF-I levels by surgery or pharmacotherapy could induce the regression of prostatic hyperplasia in acromegalic patients. To this end, prostate volume (PV) as well as the occurrence of prostatic diseases were studied by transrectal ultrasonography in 23 untreated acromegalic patients (with elevated GH and IGF levels). None of the patients reported symptoms due to prostatic disorders or obstruction. At study entry, prostate hyperplasia was found in half patients.

After 2 yr, GH, IGF-I, and IGFBP-3 levels were decreased, whereas prostate-specific antigen levels did not change. PV was decreased in

the 16 patients who were well controlled. Among the 6 patients with prostate hyperplasia at study entry who achieved disease control, 4 regained a normal PV at the end of the 2 yr of treatment, whereas none of the 5 patients with prostate hyperplasia at study entry and not achieving disease control normalized their PV. When patients were divided according to age, prostate volume decreased after 2 yr only in the 8 controlled patients aged below 50 yr, but not in those controlled and with age above 50 yr despite similar decrease in GH, IGF-I, and IGFBP3 levels. No clinical, transrectal ultrasonography, or cytological evidence of prostate cancer was detected during the study period. These data suggest that hyperplasia, but not cancer, is frequent in acromegalic men, and that the GH-IGF axis and age are independently associated with the development of this process. (*J Clin Endocrinol Metab* 85: 3754–3761, 2000)

IN RECENT YEARS the insulin-like growth factor (IGF) axis has been demonstrated to regulate prostate tissue, indicating a pivotal role of IGF-I and -II and IGF-binding proteins (IGFBPs) on the prostate (1, 2). Both IGF-I and IGF-II have direct mitogenic effects on several tissues, including normal and tumoral prostate epithelial cells and have been implicated in the pathogenesis of prostate cancer (2–5), but their actions still need to be clarified. GH and its effector IGF-I, mainly carried in the plasma by IGFBP-3, are physiological promoters of somatic growth, although *in vitro* and *in vivo* studies have raised the concern on whether they could also regulate hypertrophic and tumoral proliferation of various tissues, including the prostate (2–9). The expression of IGF-I and -II, IGF receptors, and IGFBPs was found in normal and tumoral prostatic tissue; *in vitro* prostate cell growth is stimulated by IGF-I and inhibited by IGFBP-3 (2, 10–12). In addition, IGF-I levels were found to be directly correlated, whereas IGFBP-3 levels inversely correlated to prostate cancer risk (4, 5).

The role played by the GH/IGF-I axis on prostate growth has also been suggested by our recent observations in acro-

megalic and GH-deficient patients. In fact, chronically elevated GH, IGF-I, and IGFBP-3 levels were shown to determine prostate overgrowth and structural changes, such as nodules, cysts, and calcifications, in a large proportion of acromegalic patients (13, 14), whereas in long-standing GH deficiency associated with hypogonadism, a decrease in prostate size was found (13, 15). Prostate hyperplasia was also found in young acromegalic patients, who were not expected to have age-dependent prostate diseases (13, 14). The evidence that prostate disorders occur in presence of hypogonadism and that prostate size decreases after 1 yr of treatment with octreotide in a small group of young patients (14), further supports the hypothesis that chronic GH/IGF-I excess causes prostate hyperplasia.

To better understand whether the control of GH and IGF-I excess by surgery and/or pharmacotherapy could reverse prostatic abnormalities in acromegaly, prostate volume as well as the occurrence of prostatic diseases were studied by transrectal ultrasonography (TRUS) in untreated patients before and 2 yr after treatment of acromegaly. The effects on the prostate were analyzed in patients achieving disease control and in those still presenting with disease activity at 2 yr.

Subjects and Methods

Patients

Twenty-three acromegalic males, aged 29–70 yr (mean \pm sem, 50.0 \pm 2.8 yr), were enrolled in this study; they were free of previous or present

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Address all correspondence and requests for reprints to: Annamaria Colao, M.D., Ph.D., Department of Clinical and Molecular Endocrinology and Oncology, University Federico II of Naples, Via S. Pansini 5, 80131 Naples, Italy. E-mail colao@unina.it.

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prostate diseases and were not receiving replacement treatment with androgen, β -adrenergic antagonists, or antiandrogen drugs. None of them had previously experienced any episode suggesting prostate, gonadal, and/or urethral disorders, such as prostatitis, orchitis, inflammation of seminal vesicles, or spontaneous or precipitated acute urinary retention. The study was performed after approval of the local ethical committee and once patients' informed consent had been obtained. The diagnosis of acromegaly was based on elevated GH levels not suppressible below 3 mU/L by oral glucose test, high IGF-I levels compared to age-matched controls, signs and symptoms of acromegaly, and radiological evidence of pituitary adenoma (16, 17). At admission, all patients were in active disease (GH, 117.9 ± 17.7 mU/L; IGF-I, 920.1 ± 60.8 μ g/L). The profiles of the patients' at their enrollment in our study is shown in Table 1. Ten patients were mild smokers; none was a heavy alcohol drinker, and all consumed a normal diet. All patients were included in a previous transversal study (13).

Study design

The study protocol included hormonal tests and subsequently TRUS. At diagnosis, serum GH was calculated as the mean of a 2-h blood sampling (0800–1000 with 30-min sampling), whereas all of the other hormone evaluations were performed in a single sample, as previously reported (18). All patients except 3 underwent surgery, followed by disease control in 9. In the remaining 14 patients, chronic treatment with lanreotide (Ipstyl, Ipsen, Italy) was started at the initial dose of 30 mg, im, every 14 days. The frequency of administration was increased to every 10–7 days in 7 patients not achieving disease control. A general clinic examination was carried out before and every 3 months during the follow-up. During treatment, the final GH level was calculated as the average value from at least 3 blood samples collected at 15-min intervals just before the next im injection of LAN (19). At this time point, circulating IGF-I, IGFBP-3, PRL, testosterone (T), dihydrotestosterone (DHT), Δ^4 -androstenedione (Δ^4), dehydroepiandrosterone sulfate (DHEA-S), prostate-specific antigen (PSA), free PSA, and prostatic alkaline phosphatase concentrations were assayed as single sampling. Data were further analyzed according to patients less than or more than (in 12 and 11) 50 yr of age. No patient received T replacement.

Hormonal assessment

Circulating GH, IGF-I, PRL, FSH, LH, T, DHT, Δ^4 , DHEA-S, PSA, free PSA, and prostatic alkaline phosphatase levels were assayed using commercially available kits. The cut-off values of 7.5 and 4 μ g/L were considered the upper limits for GH and PSA concentrations, respectively. The calculation of PSA density, expressed as the ratio of PSA levels/prostate volume (PV) was considered a risk factor for prostate cancer when it was higher than 0.15. All assessments were age adjusted. Serum GH levels were measured by immunoradiometric assay (HGH-CTK-IRMA Sorin, Saluggia, Italy). The sensitivity of the assay was 0.6 mU/L, 1 μ g/L corresponds to 3 mU/L. The intra- and interassay coefficients of variation (CVs) were 4.5% and 7.9%, respectively. Plasma IGF-I was measured by immunoradiometric assay after ethanol extraction using kits from Diagnostic Systems Laboratories, Inc. (Webster, TX). The sensitivity of the assay was 0.8 μ g/L. The intraassay CVs were 3.4%, 3.0%, and 1.5% for the low, medium, and high points on the standard curve, respectively. The interassay CVs were 8.2%, 1.5%, and 3.7% for the low, medium, and high points on the standard curve. Plasma IGFBP-3 was measured by RIA after ethanol extraction using kits from Diagnostic Systems Laboratories, Inc. The sensitivity of the assay was 0.5 μ g/L. The intraassay CVs were 3.9%, 3.2%, and 1.8% for the low, medium, and high points on the standard curve, respectively. The interassay CVs were 0.6%, 0.5%, and 1.6% for the low, medium, and high points on the standard curve.

TRUS study

Before TRUS, all 23 subjects received a preliminary enema with 200 mL sorbitol and a digital rectal exploration. TRUS was performed by means of an ATL Apogee 800 (Advanced Technology Laboratories, Bothell, WA) and a 9.0-MHz end-fire transrectal transducer with power echo color doppler module to display prostate angiographic micromaps (20). The transducer, preliminarily covered with ultrasound transmis-

sion gel (Acquasonic, Parker Laboratory, Newark, NJ) and a disposable rubber sheath, was lubricated and gradually inserted about 3 cm into the rectum, then directed toward the anterior rectal wall. The prostate examination covered the antero-posterior, transversal, and cranio-caudal diameters; the transitional zone; the morphology of boundaries; and the occurrence of calcifications and nodules. Seminal vesicles were imaged, and inflammatory events, not previously reported by the patients, were also investigated. The PV and the volume of the transitional zone were calculated by means of the standard ellipsoid formula ($0.52 \times$ antero-posterior diameter \times transversal diameter \times cranio-caudal diameter). Echo-guided prostate biopsies with power Doppler enhancement were performed if clinical or hormonal conditions required it. All scans were performed by the same investigator (S.S.), who was blind with respect to patients' responses to treatment. Prostate hyperplasia was considered for PV exceeding 30 mL according to accepted criteria for benign prostate hyperplasia (21, 22).

Statistical analysis

Data are expressed as the mean \pm SEM. ANOVA, followed by the Newman-Keuls test, and Student's *t* test for paired data were applied where appropriate. Statistical significance was set at 5%.

Results

Hypogonadism, based on low T and DHT levels, was present in 13 (56.5%) patients. Four untreated patients had hyperprolactinemia (serum PRL ranging from 480–17220 mU/L; Table 1), and no abnormalities in DHEA-S levels were found in any patient. None of the patients had elevated PSA levels, whereas PSA density was high in 1 patient. Symptoms due to prostatic, seminal vesicle, and/or urethral disorders or obstruction were not seen in any patient. Digital rectal examination revealed no occurrence of prostatic nodules or other abnormalities. Hormone and prostate characteristics before and after treatment in the 23 patients are shown in Table 2. Prostate hyperplasia was found in 11 patients (no. 4, 8–10, 12, 13, 15, 18, 19, 22, and 23; Table 1). Similarly, an increased median lobe was observed. In fact, the transitional zone was measurable in all acromegalics, ranging from 1.3–25.8 mL (Table 2).

After 2 yr, control of acromegaly was achieved in 16 of 23 patients (Fig. 1 and Table 3). Nine patients achieved disease control by surgery alone, whereas the other 7 patients were treated with 60–90 mg/month lanreotide, im, achieving sustained GH/IGF-I suppression. Conversely, in the remaining 7 patients, GH and IGF-I levels remained slightly elevated during the follow-up despite using increasing doses of lanreotide (Table 3). In controlled patients, both T and DHT levels were significantly increased compared to basal values (Table 3), and among the 10 hypogonadal patients at study entry, 7 regained normal T and DHT levels. After 2 yr, the TRUS-measured prostate size was significantly reduced compared to the baseline in these 16 patients ($P = 0.03$; Table 3), whereas no difference was found in Δ^4 , DHEA-S, and PSA levels; PSA density; or the volume of the transitional zone (Table 3). No difference in PV decrease was found between patients controlled by surgery alone (from 38.3 ± 5.2 to 32 ± 3.7 mL) and those controlled by surgery and/or lanreotide or lanreotide alone (from 25.8 ± 3.4 to 21.6 ± 2 mL). In these 2 subgroups, similar decreases in GH (Fig. 1), IGF-I (from 884.8 ± 63.4 to 223.1 ± 41.1 and from 911.3 ± 113.8 to 236.0 ± 28.2 μ g/L, respectively), and IGFBP-3 levels (from 5.7 ± 0.6 to 3.6 ± 0.4 and from 7.4 ± 0.7 to 4.2 ± 0.6 mg/L, respectively)

TABLE 1. Hormone profile and prostate volume at study entry

Patient no.	Age (yr)	Treatment	Serum GH levels (mU/L) ^a	Plasma IGF-I levels (μg/L)	Serum PRL levels (mU/L)	Serum T levels (μg/L)	Serum DHT levels (nmol/L)	Serum PSA levels (μg/L)	Prostate vol (mL)
1	29	S	147.0	823.0	390.0	0.8	0.39	0.7	23.2
2	33	S	79.5	887.6	1390.0	4.0	0.55	1.0	23.9
3	33	S,LAN	156.0	1470.0	360.0	1.1	0.20	2.1	28.0
4	36	LAN	36.0	876.0	30.0	1.6	0.16	0.3	35.8
5	34	S,LAN	147.0	820.0	35.7	2.2	0.50	1.0	22.0
6	34 ^b	S,LAN	138.0	1600.0	17220	1.9	0.55	1.0	21.8
7	38 ^b	S,LAN	123.0	785.0	393.3	1.0	0.10	0.6	16.0
8	43	S,LAN	90.0	850.0	450.0	3.0	0.65	1.4	37.4
9	45	S,LAN	114.0	1125.0	310.0	2.0	0.21	0.7	31.0
10	46	S	23.4	1140.0	105.0	0.9	0.27	1.0	41.8
11	46	S	211.2	1254.0	480.0	1.3	0.25	1.1	27.9
12	48	S,LAN	120.0	1520.0	180.0	3.3	0.66	0.8	32.9
13	52	S,LAN	146.0	720.0	210.0	4.6	0.77	1.0	54.6
14	57	S	30.0	735.0	240.0	2.1	0.80	0.6	26.8
15	58	S	166.2	850.0	450.0	1.2	0.30	1.0	36.1
16	58	S	126.0	824.0	360.0	1.3	0.30	0.1	26.7
17	58	S	45.0	725.0	450.0	5.0	0.40	1.0	20.0
18	61	S	60.0	705.0	300.0	3.9	0.60	1.1	48.0
19	64	S,LAN	429.0	870.0	141.0	3.2	0.60	1.1	49.3
20	68	S,LAN	145.5	720.0	240.0	3.0	0.38	0.3	18.0
21	68	LAN	45.0	553.0	102.0	3.8	0.14	0.6	15.7
22	70	S,LAN	34.2	587.0	99.0	3.5	0.25	0.8	84.3
23	70	LAN	132.0	722.0	141.0	1.8	0.10	0.5	75.1
Mean ± SEM			117.9 ± 17.7	920.1 ± 60.8	1197.0 ± 747	2.4 ± 0.3	0.39 ± 0.05	0.9 ± 0.08	34.6 ± 3.7

Normal ranges: GH, <7.5 mU/L; IGF-I, 100–402, 90–258 μg/L for patients aged <50 and >50 y, respectively; PRL, 150–450 mU/L; testosterone, 3.5–9 μg/L; dihydrotestosterone (DHT), 0.4–1.6 nmol/L; PSA, 0–4 μg/L; prostate volume, <30 mL.

^a GH was calculated as the mean of a 2-h blood sampling.

^b These two patients were treated with cabergoline (1 mg/week) together with lanreotide throughout the study period.

TABLE 2. Hormone levels and ultrasonographic evaluation of prostate parameters in the 23 patients before and after 2 yr of treatment of acromegaly

Parameter	Baseline	2 yr after treatment	P
GH levels (mU/L)			
Range	23.4–429	0.3–111	
Mean \pm SEM	117.9 \pm 17.7	15.9 \pm 6.0	<0.0001
IGF-I levels (μ g/L)			
Range	553–1600	50–850	<0.0001
Mean \pm SEM	920.1 \pm 60.8	342.6 \pm 46.4	<0.0001
IGFBP-3 levels (mg/L)			
Range	3.2–9.2	2.1–6.5	
Mean \pm SEM	5.9 \pm 0.4	4.0 \pm 0.3	<0.0001
PRL levels (mU/L)			
Range	30–17220	0.3–1500	
Mean \pm SEM	1197.0 \pm 747	10.5 \pm 2.5	0.2
Testosterone levels (μ g/L)			
Range	0.8–5.0	0.9–10	
Mean \pm SEM	2.5 \pm 0.3	4.0 \pm 0.3	0.02
DHT levels (nmol/L)			
Range	0.10–0.80	0.11–0.95	
Mean \pm SEM	0.39 \pm 0.04	0.53 \pm 0.05	0.002
Δ^4 levels (μ g/L)			
Range	0.7–4.6	0.1–6.1	
Mean \pm SEM	2.2 \pm 0.2	2.2 \pm 0.3	0.9
DHEA-S levels (μ g/L)			
Range	15–746	20–358	
Mean \pm SEM	185.7 \pm 20.4	175.6 \pm 20.6	0.6
PSA levels (μ g/L)			
Range	0.1–2.1	0.2–4.2	
Mean \pm SEM	0.86 \pm 0.08	1.18 \pm 0.21	0.2
PSA density			
Range	0.006–0.37	0.008–0.08	
Mean \pm SEM	0.042 \pm 0.01	0.035 \pm 0.005	0.2
Prostate volume (mL)			
Range	15.7–84.3	11.7–80.5	
Mean \pm SEM	34.6 \pm 3.7	32.5 \pm 4.0	0.3
Transitional zone vol (mL)			
Range	1.3–25.8	0.9–26.7	
Mean \pm SEM	6.5 \pm 1.3	7.8 \pm 1.5	0.1

Normal ranges: GH, <7.5 mU/L; IGF-I, 100–402, 90–258 μ g/L for patients aged <50 and >50 yr, respectively; IGFBP-3, 2.1–6.5 and 2–4 mg/L, for patients aged <50 and >50 yr, respectively; PRL, 150–450 mU/L; testosterone, 3.5–9 μ g/L; dihydrotestosterone (DHT), 0.4–1.6 nmol/L; Δ^4 , 1–3.5 μ g/L; DHEA-S, 60–560 μ g/L; PSA, 0–4 μ g/L; prostate volume, <30 mL. According to a previous study (13), normal transitional zone volumes were 2.4 \pm 0.4, 3.0 \pm 0.3, and 5.8 \pm 0.6 mL for healthy controls aged <40, 40–60 and >60 yr.

were found. Among the 16 controlled, 6 patients presented with prostate hyperplasia at diagnosis, 4 had a PV of less than 30 mL at the end of the 2-yr follow-up (Fig. 1). In contrast, no change in T and DHT levels or in whole prostate (Fig. 1) and transitional zone volumes was observed in the 7 patients with uncontrolled disease during the follow-up (Table 3). In particular, hypogonadism and prostate hyperplasia, which were present in 3 and 5 patients at study entry, respectively, were not found in any of the patients.

As prostate size is known to increase with age, the change in PV was analyzed in the 16 patients achieving disease control and in the 7 uncontrolled patients, grouped according to age below or above 50 yr. In the 8 controlled patients

less than 50 yr of age, T and DHT levels and PV significantly decreased after 2 yr (Fig. 2). This was associated with a decrease in IGF-I levels (Fig. 2), GH (from 111.3 \pm 22.2 to 4.5 \pm 1.2 mU/L; P = 0.002), and IGFBP-3 levels (from 7.8 \pm 0.6 to 4.7 \pm 0.4 mg/L; P = 0.0002). In the 8 patients more than 50 yr of age, no significant change in T and DHT levels or PV was observed despite similar decreases in IGF-I levels (Fig. 2), GH (from 130.8 \pm 46.2 to 3.6 \pm 0.6 mU/L; P = 0.03) and IGFBP-3 (from 5.2 \pm 0.5 to 2.9 \pm 0.3 mg/L; P = 0.0001). Among the 7 uncontrolled patients, no change was found in the dimension of the whole prostate and the transitional zone in the 4 patients less than 50 yr of age (from 28.5 \pm 3.9 to 35.7 \pm 5.6 and from 4.4 \pm 1.3 to 6.4 \pm 1.7 mL) or in the remaining 3 more than 50 yr of age (from 71.3 \pm 8.8 to 67.6 \pm 11.9 and from 19.9 \pm 3.1 to 20.6 \pm 3.9 mL). However, it should be noted that elderly patients with uncontrolled disease had the greatest size of whole prostate (Figs. 1 and 3) and transitional zone at study entry.

Structural abnormalities, including calcifications, nodules, cysts, and vesicles inflammation, were found in 17 patients (73.9%): no significant changes were observed at the end of treatment. No clinical, TRUS, or cytological evidence of prostate cancer was detected during the 2-yr study period.

Discussion

In acromegaly, prolonged hypersecretion of GH and IGF-I constantly causes enlargement of most internal body organs, including thyroid, heart, liver, bone (16, 18, 23, 24), and prostate (13, 14). Our preliminary results obtained in more than 70 acromegalic men clearly demonstrated that these patients have an increased prevalence of prostate disorders compared to age-matched control subjects, mainly because of an increased size of the whole prostate and the transitional zone, together with an elevated incidence of nodules and calcifications (13, 14). It is still controversial whether IGF-I levels are directly correlated to an increased risk for prostate cancer, as some studies are in line with (4, 5), and another denies (25) this hypothesis. Among our patients, in both the previous series (13, 14) and the present one, no occurrence of prostate cancer was observed. Notably, in patients with GH deficiency, PV was decreased when compared to that in age-matched healthy controls overall when concomitant hypogonadism existed (13, 15). This finding is easily explained considering the well known evidence of direct and indirect regulatory effects of androgens on prostatic cell growth and differentiation (26, 27). On the other hand, an up-regulation of IGF-I receptor expression on prostatic epithelial cells was documented in patients with prostate hypertrophy treated with gonadotropin-releasing analogs (28). This suggested the existence of important cross-talk among androgens, growth factors, and IGFBPs at the prostatic level (29). Moreover, a decrease in intraprostatic IGF-I levels together with increased levels of IGFBP-2, -4, and -5 have been recently reported in men with benign prostate hyperplasia treated with finasteride (30). In this light, acromegalic patients can be considered as a peculiar study model, as they often present with overt hypogonadism (56.5% of the present series), but prostatic enlargement that particularly affects the median lobe is recorded in a high proportion of patients (13)

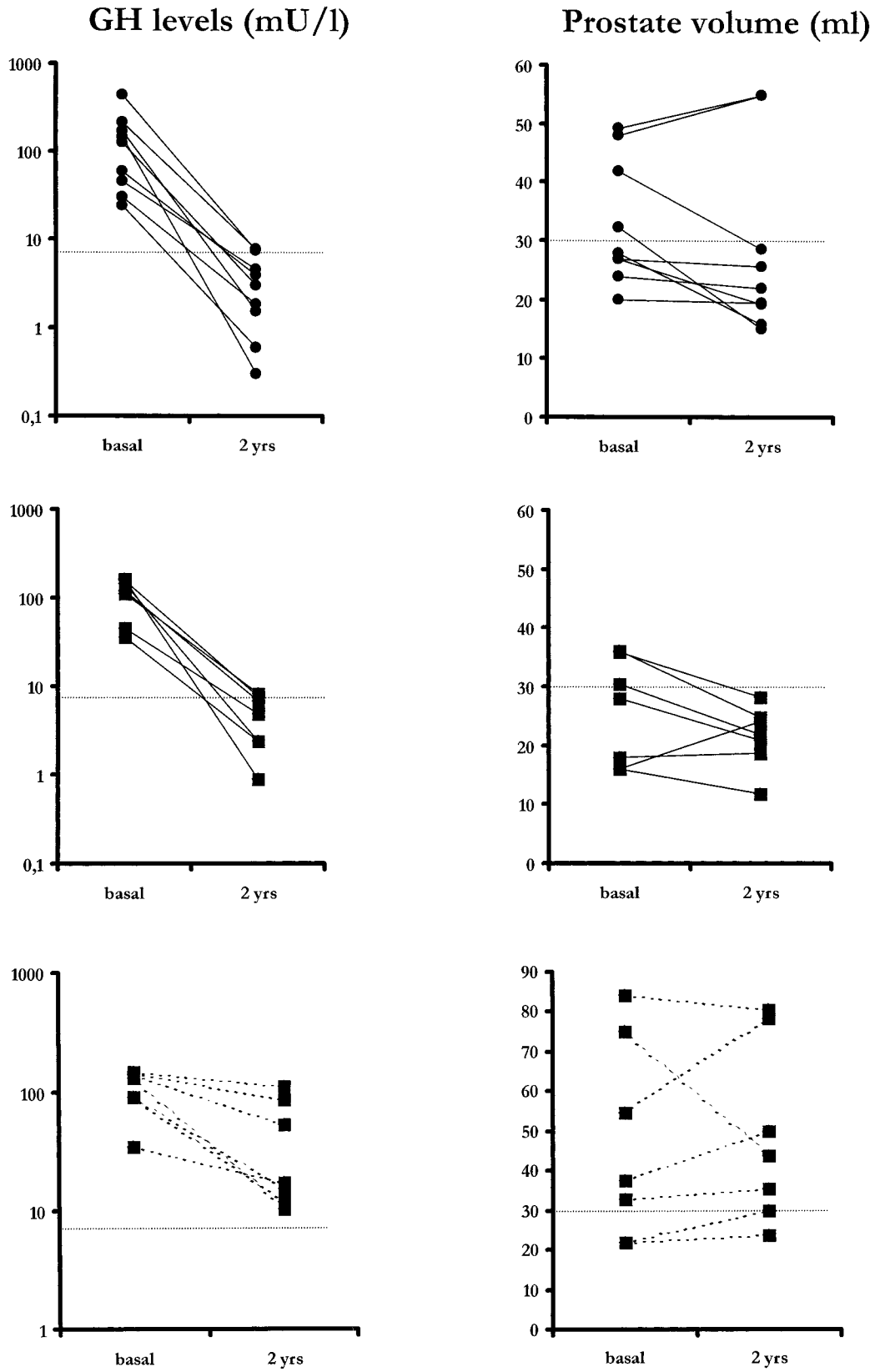
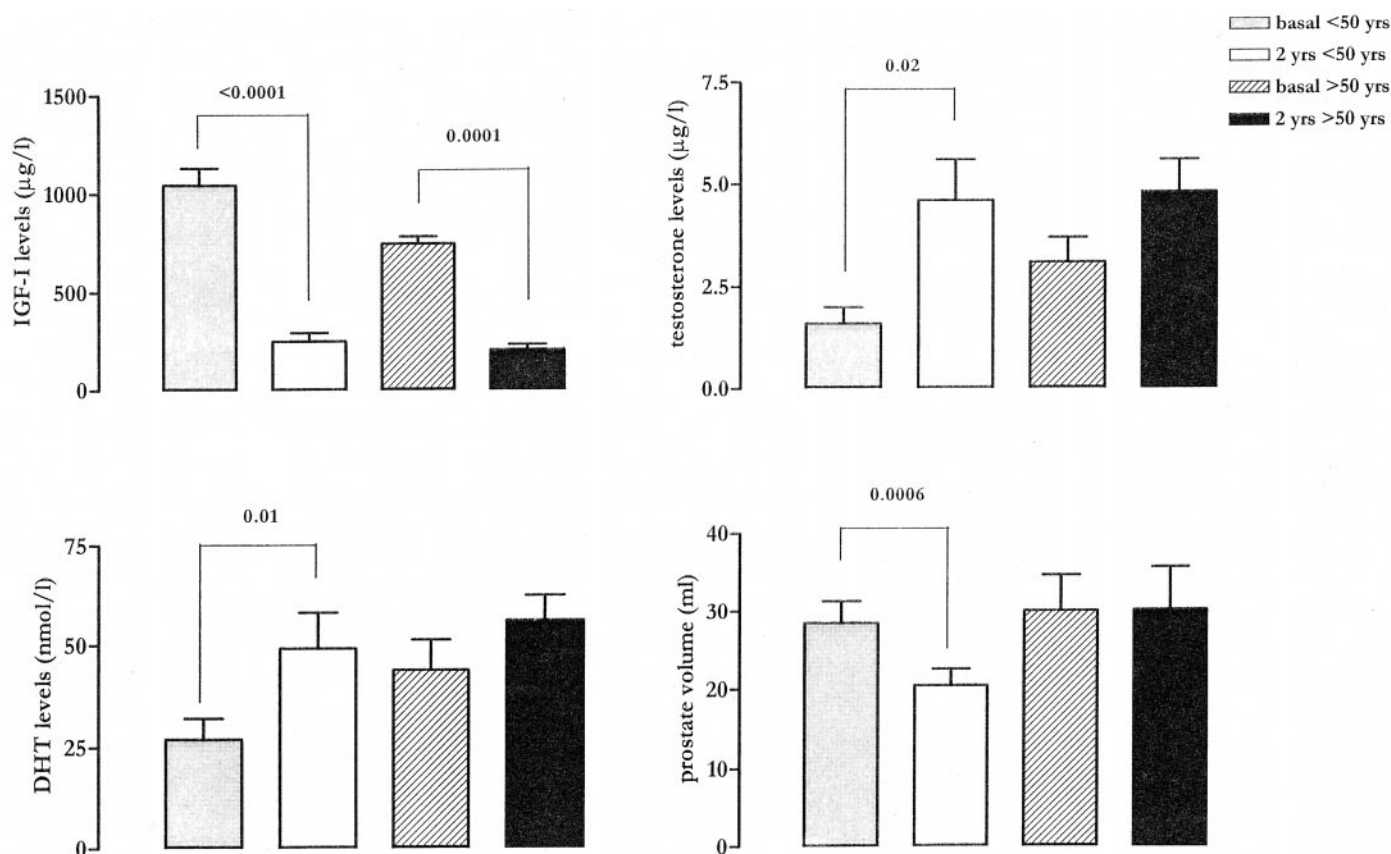


FIG. 1. Serum GH profile (*left*) and PV measured by TRUS (*right*) before and after 2 yr of follow-up in the nine patients controlled by surgery (*top*), in the seven patients controlled by lanreotide (*middle*), and in the seven uncontrolled patients (*bottom*).

TABLE 3. Hormone levels and ultrasonographic evaluation of prostate parameters before and after 2 yr of treatment of acromegaly in the 23 patients grouped in line to the response to treatment

Parameter	Patients well controlled (n = 16)			Patients not controlled (n = 7)		
	Basal	Treatment	P	Basal	Treatment	P
Age (yr)	49.9 ± 3.3	/		50.1 ± 5.7	/	
GH (mU/L)	121.2 ± 24.9	4.2 ± 0.6	<0.0001	110.7 ± 15.6	43.8 ± 15.3	0.002
IGF-I (μg/L)	896.4 ± 63.4	223.1 ± 59.0	<0.0001	974.1 ± 154.8	602.9 ± 77.6	0.04
IGFBP-3 (mg/L)	6.4 ± 0.5	3.9 ± 0.4	<0.0001	4.6 ± 0.6	4.4 ± 0.5	0.6
PRL (mU/L)	555.0 ± 237	282.0 ± 75	0.1	2664.0 ± 2340	260.0 ± 184	0.3
Testosterone (μg/L)	2.3 ± 0.3	4.7 ± 0.6	0.02	2.9 ± 0.4	2.5 ± 0.4	0.5
DHT (nmol/L)	0.35 ± 0.05	0.52 ± 0.05	0.003	0.49 ± 0.09	0.55 ± 0.01	0.3
Δ ⁴ (μg/L)	2.0 ± 0.3	2.0 ± 0.3	0.9	2.7 ± 0.5	2.8 ± 0.7	0.8
DHEA-S levels (μg/L)	191.3 ± 24.1	154.7 ± 18.3	0.6	172.7 ± 40.9	223.3 ± 51.6	0.2
PSA (μg/L)	0.8 ± 0.1	1.1 ± 0.3	0.3	0.92 ± 0.1	1.34 ± 0.4	0.4
PSA density	0.05 ± 0.02	0.04 ± 0.006	0.5	0.02 ± 0.005	0.03 ± 0.009	0.4
Prostate vol (mL)	29.3 ± 2.6	25.4 ± 3.1	0.03	46.9 ± 9.5	48.8 ± 8.6	0.8
Transitional zone vol (mL)	4.6 ± 0.8	5.8 ± 1.5	0.2	11.0 ± 3.4	12.5 ± 3.3	0.1

Normal ranges: GH, <7.5 mU/L; IGF-I, 100–402, 90–258 μg/L for patients aged <50 and >50 yr, respectively; IGFBP-3, 2.1–6.5 and 2–4 mg/L for patients aged <50 and >50 yr, respectively; PRL, 150–450 mU/L; testosterone, 3.5–9 μg/L; dihydrotestosterone (DHT), 0.4–1.6 nmol/L; Δ⁴, 1–3.5 μg/L; DHEA-S, 60–560 μg/L; PSA, 0–4 μg/L; PSA density, <0.15; prostate volume, <30 mL. According to a previous study (13), normal transitional zone volumes were 2.4 ± 0.4, 3.0 ± 0.3, and 5.8 ± 0.6 mL for healthy controls aged <40, 40–60, and >60 yr.

**FIG. 2.** Circulating levels of IGF-I (top left), T (top right), and DHT (bottom left) and PV (bottom right) before and after treatment in the 16 well controlled patients grouped according to age: less than 50 yr (top) and more than 50 yr (bottom).

and in 47.8% of those included in the current study. Therefore, although adequate levels of androgens are necessary in early developmental stages, IGF-I and GH are also required for prostate gland development (31), and in the acromegalic male prostate, overgrowth seems to rely on chronic GH and IGF-I excess.

The pivotal role played by the chronic excess of GH and

IGF-I in prostate overgrowth was also indicated by the significant decrease in PV obtained after 2 yr of treatment of the primary disease by surgery and/or lanreotide in the 16 patients who achieved successful GH/IGF-I suppression. As further support, in the 7 patients presenting with mild disease activity during the 2-yr follow-up, the levels of T and DHT and both the volume of the whole prostate and that of

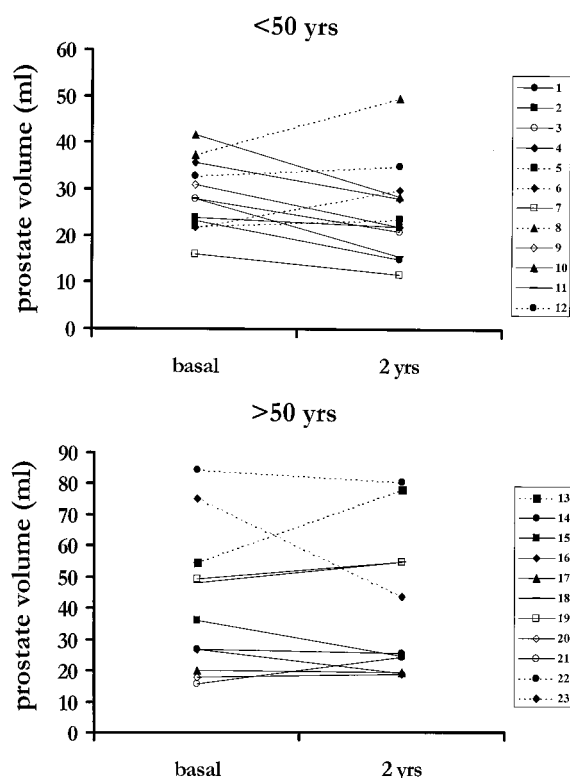


FIG. 3. PV before and after treatment in patients grouped according to age: less than 50 yr (*top*) and more than 50 yr (*bottom*). Patients are numbered according to Table 1. *Continued lines and closed symbols*, patients controlled after surgery; *continued lines and open symbols*, patients controlled after lanreotide treatment; *interrupted lines*, uncontrolled patients.

the transitional zone were unchanged. In the current series, the prevalence of cysts and micro- and macrocalcifications occurred in as many as 73.9% of the cases, confirming a previous report (13), and no significant changes in structural abnormalities of the prostate were found after 2 yr of treatment, at partial variance with a previous report (14). It should be mentioned, however, that our first study included only patients less than 40 yr of age. The age of the patients plays a relevant role when prostate dimensions and structure are investigated, as in humans prostate enlargement starts approximately at the age of 40 yr and rises from 23% to 88% by the ninth decade (26, 32). It is thus arguable that in elderly acromegalic patients prostate enlargement is due to both GH/IGF-I excess and the physiological age-related changes. On this basis, it is hard to expect a decrease in prostate dimension after suppression of GH/IGF-I levels in elderly patients. In fact, after 2 yr of treatment a significant decrease in prostate size was only found in well controlled patients less than 50 yr of age, not in those more than 50 yr, despite similar decreases in GH, IGF-I, and IGFBP-3 levels. In these controlled patients, a reduction in prostate volume was observed despite the significant increase in both T and DHT levels, confirming previous data obtained in another cohort of younger patients (14). In the small group of patients not achieving satisfactory disease control during the study period, however, no increase in prostate size was observed, and it should be noted that all 3 elderly patients in this group had

very high prostate volumes at study entry. Together, these findings suggest that the possibility of documenting changes in prostate size and structure during a 2-yr period in subjects over 50 yr of age is unlikely.

With regard to the detection of somatostatin receptors, primarily subtypes 1 and 2, in stromal cells of benign and malignant prostate (33–35), it is arguable that the chronic lanreotide administration could regulate the paracrine-autocrine pathways of the GH/IGF/IGFBP system within the gland. Lanreotide treatment can induce a decrease in prostate dimension by displaying a direct antiproliferative effect (36), by indirectly suppressing circulating levels of GH/IGF-I, or both. It should be mentioned that octreotide, another somatostatin analog, was used together with complete androgen blockade in patients with prostate carcinoma with beneficial results (37). Lanreotide treatment could also prevent prostate enlargement by inducing apoptosis of the mesenchymal tissue and by modifying the hemodynamic conditions of the local blood circulation (38). As the reduction in PV was also observed in patients achieving disease control by surgery alone, the possibility that GH and IGF-I suppression itself had a direct shrinking effect on the prostate is highly likely. Finally, in none of the patients were PSA levels, digital rectal exploration, or TRUS able to detect the occurrence of prostatic cancer in young/adult and elderly patients.

In conclusion, the prostate is a primary target tissue of GH and IGF-I. Chronic suppression of GH and IGF-I levels by surgery or lanreotide treatment induced a significant decrease in PV in the acromegalic patients achieving disease control, mostly in those less than 50 yr of age and thus not affected by age-dependent prostate hyperplasia. The inhibitory effect of GH and IGF-I suppression on prostate size was documented despite a significant increase in androgen levels. These data indicate that the GH/IGF-I axis plays a role in the development of prostate overgrowth in acromegaly; that it plays a similar role in nonacromegalic subjects cannot be ruled out.

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