

Effect of Growth Hormone (GH) and Insulin-Like Growth Factor I on Prostate Diseases: An Ultrasonographic and Endocrine Study in Acromegaly, GH Deficiency, and Healthy Subjects

ANNAMARIA COLAO, PAOLO MARZULLO, STEFANO SPIEZIA, DIEGO FERONE,
ASSUNTA GIACCIO, GAETANA CERBONE, ROSARIO PIVONELLO,
CAROLINA DI SOMMA, 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., R.P., C.D.S., G.L.), and Emergency Unit, Incurabili Hospital Naples (S.S.), 80131 Naples Italy

ABSTRACT

The role of insulin-like growth factor I (IGF-I) in prostate development is currently under thorough investigation because it has been claimed that IGF-I is a positive predictor of prostate cancer. To assess the effect of GH and IGF-I levels on prostate pathophysiology, 46 acromegalic (30 in active disease, 10 cured from acromegaly, and 6 affected from GH deficiency) and 30 age-matched male controls, free from previous or concomitant prostate disorders, underwent pituitary, androgen, and prostate hormonal assessments and transrectal ultrasonography. Compared to control values, GH ($P < 0.0001$), IGF-I ($P < 0.0001$), and IGFBP-3 ($P < 0.001$) levels were increased, whereas testosterone ($P < 0.0001$) and dihydrotestosterone levels ($P < 0.0001$) were reduced in active acromegalic patients. Hypogonadism was present in 28 of the 46 acromegalic patients (60.8%). The anteroposterior ($P < 0.05$), and transverse ($P < 0.0001$) prostate diameters and the transitional zone volume ($P < 0.05$) were increased in acromegalic patients compared to those in controls. Prostate volume (PV) was significantly higher in untreated acromegalic patients than in

controls (41.7 ± 3.2 vs. 21.9 ± 1.4 mL; $P < 0.0001$), cured patients (23.6 ± 1.6 mL; $P < 0.0001$), and GH-deficient patients (17.5 ± 1.1 mL; $P < 0.0001$). In the patients, PV was correlated with disease duration ($r = 0.606$; $P < 0.0001$) and age ($r = 0.496$; $P < 0.0001$), whereas in controls it was correlated with age ($r = 0.476$; $P < 0.01$) and IGF-I levels ($r = -0.448$; $P < 0.05$). Benign prostate hyperplasia (PV ≥ 30 mL) was found in 58% of the acromegalics and 26.6% of the controls. When grouped by age (<40, 40–60, and >60 yr), PV was increased in elderly patients compared to younger patients ($P < 0.05$) and to controls ($P < 0.01$). The prevalence of structural abnormalities, including calcifications, nodules, cysts, and vesicle inflammation, was significantly increased in patients compared to controls (78.2% vs. 23.3%; $\chi^2 = 5.856$; $P < 0.05$). No clinical, transrectal ultrasonography, or cytological evidence of prostate cancer was detected in acromegalic or control subjects. In conclusion, chronic excess of GH and IGF-I cause prostate overgrowth and further phenomena of rearrangement, but not prostate cancer. (*J Clin Endocrinol Metab* 84: 1986–1991, 1999)

THE PHYSIOLOGICAL development and growth of the prostate have been shown to primarily depend on testosterone and its more potent 5α -reduced metabolite, dihydrotestosterone (DHT), which seem to be the leading factors in stimulating its benign and malignant disorders (1). The evidence that low testosterone levels do not exclude occult prostate carcinoma (2) and that the growth factor superfamily might regulate prostate tissue sheds new light on the role that insulin-like growth factor I and II (IGF-I and -II) and IGF-binding proteins (IGFBPs) have in the prostate (3). Both IGFs have direct mitogenic effects on several tissues, including normal and tumoral prostate epithelial cells, and their implication in prostate cancer has been suggested as well (4–6). Conversely, IGFBP-2 and IGFBP-3, the circulating carrier of IGF-I, are not unequivocally considered to be involved in prostate growth in

patients affected with prostate cancer or benign prostate hyperplasia (7–10). However, IGFBP-3 can be cleaved by the prostate-specific antigen (PSA) contained in the seminal plasma. In this way, the intraprostatic concentration of IGF-I is increased (11). Moreover, IGF-I was found to be a significant independent predictor of prostate cancer risk, whereas IGFBP-3 resulted inversely correlated to the same risk (5). The implication of IGF-I in promoting overgrowth of the prostate has been suggested by our recent observation (12) in a group of young hypogonadic acromegalic patients, in whom we did not expect to have age-dependent prostate diseases and in whom we found a high prevalence of prostate disorders. To better understand the possible regulatory role that GH and IGF-I play in prostate pathophysiology, we investigated a large cohort of acromegalic patients and control subjects and evaluated their prostate dimensions, volume, and structural impairment by means of transrectal ultrasonography (TRUS) and pituitary hormone, androgen, and prostate hormone assay. We found a significant increase in prostate disorders in acromegalic patients compared to the control population, without any evidence of prostate cancer.

Received November 30, 1998. Revision received February 26, 1999.
Accepted March 8, 1999.

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

Subjects and Methods

Patients

Forty-six acromegalic males, aged 26–74 yr (mean \pm SEM, 50.5 \pm 2.2 yr) were enrolled in this study; they were free of previous or present prostate diseases and were not receiving replacement treatment with androgen, α -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 the patients' informed consents had been obtained. The diagnosis of acromegaly was based on elevated GH levels not suppressible below 1 μ g/L by oral glucose test, high IGF-I levels for age, signs and symptoms of disease, and radiological evidence of pituitary adenoma. At admission, 30 patients were in active disease (GH, 18.1 \pm 2.5 μ g/L; IGF-I, 531 \pm 34 μ g/L), whereas 16 had previously undergone surgery and/or radiotherapy and were considered to be cured on the basis of fasting GH below 2.5 μ g/L or glucose suppressed below 1 μ g/L and normal IGF-I for age (13). Ten of the 16 cured patients had normal GH and IGF-I concentrations. The remaining 6 patients were diagnosed as having severe GH deficiency (GHD) on the basis of a GH response below 3 μ g/L to a combined arginine plus GHRH stimulation test (14); 4 of them were receiving replacement therapy with L-T₄ and 2 were receiving cortisone acetate. As a control group, 30 healthy subjects were enrolled after giving their informed consents and represented the age-matched control-case subjects. The profiles of patients and controls at their enrollment in our study are shown in Table 1. The data obtained in the 76 subjects were further analyzed according to age below 40 yr, between 41–60 yr, and above 60 yr (Table 2). Data obtained at diagnosis from 10 patients less than 40 yr of age, previously reported (12), were included in the present study. Eighteen acromegalics and 11 controls were smokers; no subject in either of the 2 groups was a heavy alcohol drinker, and all consumed normal diets.

Study design

The study protocol included hormonal tests performed using commercially available kits and subsequently TRUS. Serum GH was calculated as the mean of a 2-h blood sampling (0800–1000 h, with every 30 min sampling). Circulating IGF-I, PRL, FSH, LH, testosterone, DHT, sex hormone-binding globulin, 17 β -estradiol, Δ^4 -androstenedione, dehydroepiandrosterone sulfate, PSA, free PSA, and PAP levels were assessed at least twice. The cut-off values of 2.5 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. The sensitivity of the assay was 0.2 μ g/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. The sensitivity of the assay was 0.8 μ g/L. The intraassay CVs were 3.4%, 3.0%, and 1.5% for low, medium, and high points on the standard curve, respectively. The interassay CVs were 8.2%, 1.5%, and 3.7% for low, medium, and high points on the standard curve. Plasma IGFBP-3 was measured by RIA after ethanol extraction. The sensitivity of the assay was 0.5 μ g/L. The intraassay CVs were 3.9%, 3.2%, and 1.8% for low, medium, and high points on the standard curve, respectively. The interassay CVs were 0.6%, 0.5%, and 1.6% for low, medium, and high points on the standard curve.

Transrectal ultrasonography study

Before TRUS, all 76 subjects received a preliminary enema with 200 mL Sorbitole and a digital rectal exploration. TRUS was performed by means of an ATL Apogee 800 and a 9.0-MHz end-fire transrectal transducer with Power Echo Color Doppler module to display prostate angiographic micromaps (15). The transducer, preliminarily covered with

TABLE 1. Endocrine and ultrasonographic findings in control subjects and untreated, cured non-GHD, and GHD acromegalic patients

	Controls (n = 30)	Acromegalic patients		
		Untreated (n = 30)	Cured (n = 16)	
			Non-GHD (n = 10)	GHD (n = 6)
Age range (yr)	27–75	26–74	30–71	32–67
GH	1.1 \pm 0.7 ^a	18.1 \pm 2.5 ^b	2 \pm 0.2	1 \pm 0.3
IGF-I	189.9 \pm 11.4 ^a	531 \pm 34 ^b	222 \pm 31	182 \pm 46
IGFBP-3	3.53 \pm 0.2 ^a	5.39 \pm 0.4 ^b	4.18 \pm 0.5	3.1 \pm 0.4
FSH	7.1 \pm 0.4 ^c	5.9 \pm 0.7	6.2 \pm 1.1	2.5 \pm 1.1
LH	7.6 \pm 0.4 ^d	3.7 \pm 0.4	3.8 \pm 0.5	2.4 \pm 1.2
PRL	4 \pm 0.4 ^{f,c}	25.6 \pm 18	14.6 \pm 4.4	10.9 \pm 2.3
Testosterone	6.1 \pm 0.2 ^d	2.7 \pm 0.2	3.3 \pm 0.5	2.9 \pm 0.9
DHT	0.9 \pm 0.1 ^a	0.5 \pm 0.05	0.7 \pm 0.1	0.6 \pm 0.2
Estradiol	27 \pm 1	26.1 \pm 1.5	27.5 \pm 2.4	27.6 \pm 5
Δ^4	1.9 \pm 0.1	1.7 \pm 0.1	1.9 \pm 0.2	0.9 \pm 0.3
DHEA-s	216.6 \pm 16.6	209 \pm 20	192.1 \pm 29.7	191.1 \pm 32
SHBG	25.7 \pm 1.2	25.5 \pm 1.4	29.5 \pm 3	29.6 \pm 2.3
PSA	1.7 \pm 0.1	1.3 \pm 0.1	1.4 \pm 0.3	1.5 \pm 0.8
f-PSA	0.2 \pm 0.02	0.4 \pm 0.04	0.4 \pm 0.1	0.2 \pm 0.04
f-PSA/PSA ratio	0.1 \pm 0.01	0.3 \pm 0.02	0.3 \pm 0.01	0.2 \pm 0.03
PSA density	0.07 \pm 0.006	0.03 \pm 0.006	0.04 \pm 0.006	0.08 \pm 0.004
PAP	1.4 \pm 0.3	1.5 \pm 0.1	1.3 \pm 0.2	1.8 \pm 0.7
APD (mm)	27.6 \pm 0.8 ^{a,c}	33.6 \pm 1.3 ^b	27.1 \pm 1.1 ^c	23.4 \pm 1.1
TD (mm)	37.3 \pm 0.9 ^{a,f}	58.8 \pm 8.5 ^b	49 \pm 1.3 ^c	39.8 \pm 1.7
CCD (mm)	39.9 \pm 0.8	42 \pm 1.8	38.4 \pm 0.7	35.9 \pm 1.4
TZV (mL)	3.6 \pm 0.5 ^a	8.5 \pm 1.5 ^b	3.8 \pm 0.7	2.5 \pm 1.2
PV (mL)	22.1 \pm 1.4 ^a	41.7 \pm 3.2 ^b	27.3 \pm 1.6 ^c	17.5 \pm 1.1

Reference values: GH, less than 2.5 μ g/L; IGF-I, 100–502, 100–303, and 78–258 μ g/L for patients aged 20–40, 41–60, and over 60 yr, respectively; IGFBP-3, 1.7–7.6, 2.1–4.3, and 2–4 mg/L, for subjects 20–40, 41–60, and over 60 yr, respectively; FSH and LH, 5–18 mU/mL; PRL, 5–15 μ g/L; testosterone, 3.5–9 μ g/L; DHT, 0.4–1.6 nmol/L; estradiol, 20–70 μ g/L; Δ^4 , 1–3.5 μ g/L; DHEA-S, 60–560 μ g/L; SHBG, 15–43 nmol/L; PSA, 0–4 μ g/L; f-PSA, 0.05–0.25 μ g/L; fPSA/PSA ratio, less than 0.2; PSA density, less than 0.15; PAP, 0–2.6 U/L. Significance: ^a controls vs. untreated patients; ^b untreated vs. non-GHD and GHD patients; ^c controls vs. GHD patients; ^d controls vs. untreated, non-GHD, and GHD patients; ^e non-GHD vs. GHD patients. ^f controls vs. non-GHD patients. Values are the mean \pm SEM.

TABLE 2a. Endocrine and ultrasonographic findings in patients aged below 40, 40–60, and over 60 yr

	Subjects aged below 40 yr			Subjects aged 40–60 yr			Subjects aged above 60 yr		
	Controls (n = 10)	Patients (n = 15)	P	Controls (n = 10)	Patients (n = 16)	P	Controls (n = 10)	Patients (n = 15)	P
GH	1.2 ± 0.1	11.4 ± 3.3	0.02	1 ± 0.1	15.2 ± 4.2	0.01	0.9 ± 0.06	10.1 ± 2.8	0.02
IGF-I	236 ± 26.3	528.4 ± 56.8	0.001	183.3 ± 6.9	413.6 ± 56.8	0.004	150.5 ± 10.5	312.3 ± 46.1	0.01
IGFBP-3	4.76 ± 0.37	6.63 ± 0.53	0.02	3.05 ± 0.15	4.56 ± 0.33	0.002	2.79 ± 0.16	3.3 ± 0.2	0.08
Testosterone	6.1 ± 0.2	3.1 ± 0.4	0.001	6.1 ± 0.4	2.4 ± 0.4	0.001	6.2 ± 0.3	3.1 ± 0.4	0.001
DHT	1 ± 0.1	0.6 ± 0.1	0.01	0.8 ± 0.02	0.5 ± 0.1	0.03	1 ± 0.1	0.5 ± 0.1	0.003
SHBG	33.2 ± 1.8	27.2 ± 1.8	0.03	24.5 ± 0.8	26.5 ± 1.8	0.4	35.4 ± 1.7	26.2 ± 2.3	0.009
PSA	1.9 ± 0.1	1.6 ± 0.3	0.4	1 ± 0.2	1 ± 0.1	1	2 ± 0.2	1.5 ± 0.4	0.3
f-PSA	0.2 ± 0.04	0.4 ± 0.1	0.1	0.2 ± 0.05	0.3 ± 0.1	0.5	0.2 ± 0.04	0.3 ± 0.05	0.1
f-PSA/PSA ratio	0.1 ± 0.01	0.3 ± 0.02	0.001	0.1 ± 0.03	0.3 ± 0.1	0.1	0.1 ± 0.01	0.2 ± 0.04	0.06
APD (mm)	26.3 ± 0.5	27 ± 1.1	0.6	27.6 ± 1.8	30.1 ± 0.8	0.1	28.9 ± 1.4	35.8 ± 2.4	0.04
TD (mm)	36.3 ± 0.8	48.4 ± 1.5	0.001	34.5 ± 0.7	50.6 ± 1.7	0.001	41.2 ± 2.1	51.2 ± 2.1	0.004
CCD (mm)	38.5 ± 0.9	39.8 ± 1	0.3	40.0 ± 1.3	41.6 ± 0.8	0.3	41.4 ± 2	42.6 ± 2.3	0.7
Transitional zone (mL)	1.4 ± 0.4 ^a	3.2 ± 0.8	0.09	3.0 ± 0.3	8.9 ± 2.1	0.04	5.8 ± 0.6	7.9 ± 2	0.4
Prostate volume (mL)	18.4 ± 0.6	27.6 ± 1.9	0.001	17.1 ± 0.5	34 ± 2.3	0.001	30.2 ± 2.9	44.7 ± 6.4	0.09

Values are the mean ± SEM. For reference values, see Table 1.

^a The transitional zone was measurable only in five subjects.

TABLE 2b. Ultrasonographic findings of prostate structure abnormalities

Prostate abnormalities	Age below 40 yr		Age between 41–60 yr		Age above 60 yr	
	Patients (n = 15)	Controls (n = 10)	Patients (n = 16)	Controls (n = 10)	Patients (n = 15)	Controls (n = 10)
Calcifications						
Periurethral zone	5		10	1	9	4
Peritransitional zone			2	1	4	1
Lateral lobes	5		3		1	
Seminal vesicles			1			
Cysts						
Uthricular zone	1		2		5	
Verum montanum			2		2	
Vesicles inflammation	1		2			
Adenoma			1		3	
Nodules			4		4	
Total	12	0	27	2	29	5

ultrasound transmission gel (Acquasonic, Parker Laboratories, 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 (APD), transversal (TD), and cranio-caudal (CCD) diameters; the transitional zone; the morphology of boundaries; the occurrence of calcifications and nodules; and the evaluation of seminal vesicles and of inflammatory events not previously reported by the patients. The PV and the volume of the transitional zone was calculated by means of the standard ellipsoid formula ($0.52 \times \text{APD} \times \text{TD} \times \text{CCD}$). 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 in respect to patients' disease activity. Prostate hyperplasia (PH) was considered for PV exceeding 30 mL, in line with the accepted criteria for benign prostate hyperplasia (16, 17).

Statistical analysis

Data are expressed as the mean ± SEM. ANOVA, linear correlation analysis, and χ^2 test were applied where appropriate. Statistical significance was set at 5%. Multiple regression analysis was performed by considering PV and transitional zone volume as dependent variables and the variables significantly correlated at linear correlation as independent variables.

Results

Hormonal data

Hormonal profiles of patients and controls are included in Tables 1 and 2. Compared to controls, GH ($P < 0.0001$), IGF-I

($P < 0.0001$), and IGFBP-3 ($P < 0.001$) levels were increased, whereas LH ($P < 0.0001$), testosterone ($P < 0.0001$), and DHT ($P < 0.0001$) levels were reduced in active acromegalic patients (Table 1). Overt hypogonadism was present in 28 (60.8%) acromegalic patients (20 untreated and 8 cured). When grouped by age, GH, IGF-I, and IGFBP-3 were significantly increased, whereas testosterone and DHT significantly were decreased in patients compared to controls (Table 2). No difference in Δ^4 -androstenedione, dehydroepiandrosterone sulfate, 17β -estradiol, sex hormone-binding globulin, PSA, free PSA, PSA density, or the ratio between free PSA/PSA levels was found between patients and controls (Tables 1 and 2). PSA levels were elevated only in four and PSA density in three patients, respectively. Six untreated patients had hyperprolactinemia (serum PRL ranging from 16–550 $\mu\text{g/L}$).

Prostate dimensions (Tables 1 and 2)

TRUS showed an enlargement of APD, TD, and CCD in active acromegalic patients compared to controls and GHD patients. No difference was found in prostate diameters between controls and cured non-GHD patients, except for a significant increase in the transversal diameter in the latter group ($P < 0.0001$). The transitional zone was detectable in 89% of acromegalic patients and in 66% of the controls. PV

was greater in patients with active disease than in cured non-GHD ($P < 0.0001$), GHD patients ($P < 0.0001$), or controls ($P < 0.0001$; Table 1 and Fig. 1). The lowest PV values (17.5 ± 1.1 mL) and IGF-I levels (182.3 ± 47 $\mu\text{g/L}$) were detected in the six acromegalic patients with GHD (Table 1 and Fig. 1). In active patients, PV was correlated with both age ($r = 0.668$; $P < 0.0001$) and disease duration ($r = 0.626$; $P < 0.0001$), and the multiple regression model showed a greater dependence of PV on disease duration ($t = 3.297$; $P < 0.01$) than on aging ($t = 2.689$; $P < 0.05$). Conversely, no significant correlation was found in the cured patients between PV and disease duration. In the control group, PV and transitional zone volume were directly correlated with age ($r = 0.476$; $P < 0.01$ and $r = 0.763$; $P < 0.0001$, respectively) and were inversely correlated with IGF-I levels ($r = -0.448$ and $r = -0.550$, $P < 0.05$, respectively). PH was found in 24 of 30 active patients (80%), 3 of 10 cured non-GHD patients (30%), none of the GHD patients, and 8 of 30 controls (26.6%). PH prevalence was significantly associated with disease activity ($\chi^2 = 3.798$; $P < 0.05$). Grouping patients and controls by age, PH was recorded in 5 patients (10.8%) and no controls less than 40 yr of age, in 11 patients (23%) and 2 controls (6.6%) between 41–60 yr of age, and in 11 patients (23%) and 6 controls (20%) more than 60 yr of age. As expected, the highest PVs were recorded in acromegalic and control subjects above 60 yr of age, without any significant difference between them (Table 2 and Fig. 2).

Prostate features

The ultrasonographic signs of prostate abnormalities are summarized in Table 2b. No abnormality of prostate struc-

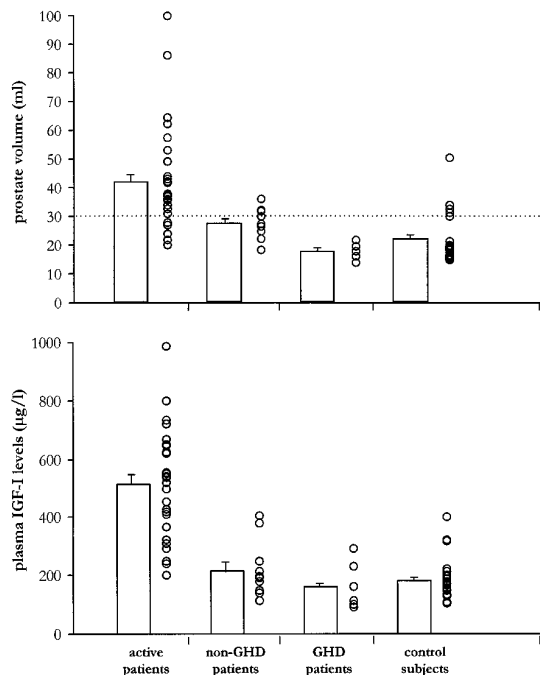


FIG. 1. PV (upper panel; analytical and mean values) and IGF-I levels (lower panel; mean values) in active, cured non-GHD, and GHD acromegalic patients and in controls. The interrupted line represents the reference limit.

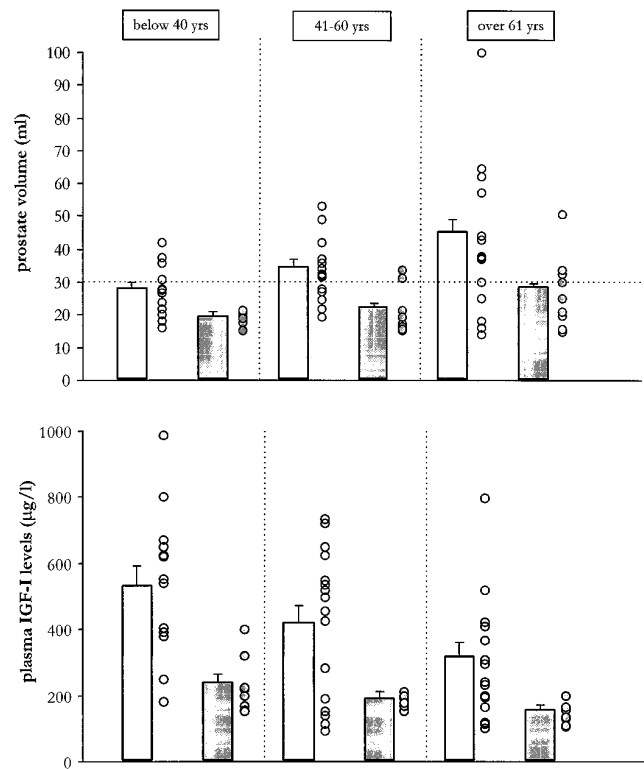


FIG. 2. PV (upper panel; analytical and mean values) and IGF-I (lower panel; mean values) levels in control subjects and acromegalic patients grouped for age (<40, 40–60, and >60 yr). The interrupted line represents the reference limit.

ture was detected in 10 of 46 patients (21.7%) or in 23 of 30 controls (76.6%). Calcifications were detected in 28 acromegalic patients (60.8%) and 7 controls (23.3%): in the periurethral zone in 13 patients and 5 controls, within the lobes in 3 patients, and in the zone immediately close to the transitional zone (peritransitional) in 3 patients and 2 controls. Concomitant periurethral/lobar calcifications were observed in 5 patients and periurethral/peritransitional calcifications were found in 4 patients. Utricular cysts were found in 8 patients (17.4%), and in 2 cases were multiple, whereas cysts of the verum montanum were found in 4 other patients (8.7%). Echoic signs suggesting a condition of vesicles inflammation, including structural impairment and/or calcifications, were observed in 4 patients (8.7%). Clear-cut nodules were detected in 6 patients (13%); in 2 of them, 2 distinct nodules were detected. After echo-guided needle aspiration, cytological examination was performed; it revealed nodular fibroadenomatous hyperplasia in all cases. In addition, sextant biopsies of the transitional zone were performed in 3 other patients due to elevation of PSA levels and/or PSA density. In none of the patients or controls was prostate cancer found. The prevalence of prostate abnormalities was significantly associated with acromegaly ($\chi^2 = 5.856$; $P < 0.05$).

Discussion

The current study was conceived to evaluate whether chronic exposure to high GH and IGF-I levels could con-

tribute to prostate enlargement or cancer in acromegaly. The results clearly demonstrated that acromegalic patients have an increased prevalence of prostate disorders compared to age-matched control subjects, mainly because of increased transitional zone volume and PV and elevated incidence of nodules and calcifications. Conversely, no occurrence of prostate cancer was observed among our patients. Notably, in the few patients with GH deficiency, PV was not increased and was even decreased compared to values in age-matched healthy controls.

In the normal human, the endocrinology of prostate development depends mainly on the stimulatory effect of testosterone and its 5 α -reduced metabolite DHT throughout developmental and aging stages; castration or pharmacological androgen deprivation notoriously cause impairment of prostate growth (1). Nevertheless, androgens are supposed to act as indirect factors, whereas cell to cell or stromal-epithelial interactions might regulate the definitive development of the prostate (1, 18, 19). A growing body of evidence is accumulating that IGFs may be involved in prostate cell proliferation (3), 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 about whether they could also regulate hypertrophic and tumoral proliferation of various tissues, including the prostate (3–6, 20–23). In fact, the expression of IGF-I and -II, IGF receptors, and IGFBPs has been found in normal and tumoral prostatic tissue; *in vitro* prostate cell growth is stimulated by IGF-I and inhibited by IGFBP-3 (3, 8, 24, 25). Although GH and IGF-I excess has been reported as being associated with an increased risk of developing cancer in acromegaly (13, 26, 27), the increased growth effect on body organs and bones predominates. In the 46 patients enrolled in this study, a more than 3-fold prevalence of TRUS-documented prostate disorders was observed compared to that in age-matched control subjects together with a significant increase in PV in patients below 60 yr of age. Although abnormality of the prostate structure was detected in 23% of controls, in acromegalic patients calcifications were detected in 60.8%; cysts, vesicle impairment, and/or benign nodules were found in 17.5% of patients, accounting for a total prevalence of prostate abnormalities in 78.3% of patients. The evidence that acromegalic patients either cured or with GHD had normal or even decreased PVs further supports the role of the GH/IGF-I axis in the pathophysiology of prostate growth. The presence of prostate structural abnormalities in five of the six GH-deficient patients is not surprising, as they might have developed during the period of active disease. However, the risk of developing PH increases with aging in both our control and acromegalic populations; as a matter of fact, a significant correlation between PV and age was found in both patients and controls. Furthermore, a significant correlation was found between the thickening of the transitional zone (detected in 89% of the acromegalics and in 20% of the controls) and age. In the untreated patient group, PV was significantly correlated to age and disease duration, and disease duration was the strongest predictor of PH. By contrast, in the control group, PV was significantly correlated with age

and inversely with IGF-I levels; age was the strongest predictor of PH.

The epidemiological peculiarity of our findings, however, cannot add further to reports of positive association between IGF-I levels and prostate cancer risk in normal men (5, 6, 28), which, far from being fully understood, ultimately suggest a predictor role for IGF-I levels in developing prostate cancer. Similar observations have been confirmed in females affected with breast cancer (29). In our series, despite chronic exposure to high IGF-I and IGFBP-3 concentrations, none of the patients was diagnosed as having prostate cancer. Therefore, it remains arguable whether IGF-I itself in the normal man could be a direct mitogen for tumoral proliferation. The possibility that IGF-I could be produced by the tumor itself or be implicated in a cause-effect phenomenon cannot be ruled out (3–5, 30). The evidence that a higher cancer risk is associated with lower IGFBP-3 levels, when adjusted to total IGF-I (5, 6), supports the possible modulatory role of free IGF-I bioavailability on prostate tissue.

It is intriguing that in acromegalic males, prostate diameters increased with aging, even with low androgen levels. Testosterone and DHT levels were significantly reduced in acromegalic patients, and 61% of them were clearly hypogonadic. Although adequate levels of androgens are necessary in early developmental stages, in the acromegalic male, prostate overgrowth seems to rely also on chronic GH and IGF-I excess, probably through the maintenance of proper cellular interactions.

In conclusion, the results of the present study show that chronically elevated GH, IGF-I, and IGFBP-3 levels determine prostate overgrowth and further phenomena of rearrangement, such as the increased prevalence of nodular lesions, calcifications, and cystic areas, but not cancer. However, as occult prostate cancer was found in 14% of men with low testosterone levels (2), the possibility of occult prostate cancer in patients not subjected to biopsy cannot be ruled out. It remains to be elucidated whether IGF-I itself might be implicated in the development of prostate cancer as a marker or, rather, whether the activities of different IGFBPs could regulate prostate cell proliferation.

References

1. Cuhna GR, Donjacour AA, Cooke PS, et al. 1987 The endocrinology and developmental biology of the prostate. *Endocr Rev*. 8:338–362.
2. Morgentaler A, Bruning III CO, DeWolf WC. 1996 Occult prostate cancer in men with low serum testosterone levels. *JAMA*. 276:1904–1906.
3. Cohen P. 1998 Serum insulin-like growth factor-I levels and prostate cancer risk—interpreting the evidence. *J Natl Cancer Inst*. 90:876–879.
4. Daughaday WH. 1990 The possible autocrine/paracrine and endocrine roles of insulin-like growth factors of human tumors. *Endocrinology*. 127:1–4.
5. Chan JM, Stampfer MJ, Giovannucci E, et al. 1998 Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. *Science*. 279:563–566.
6. Wolk A, Mantzoros CS, Andersson SO, et al. 1998 Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. *J Natl Cancer Inst*. 90:911–915.
7. Rajaram S, Baylink DJ, Moan S. 1997 Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and function. *Endocr Rev*. 18:801–831.
8. Cohen P, Peehl DM, Stamey TA, Wilson KF, Clemmons DR, Rosenfeld RG. 1993 Elevated levels of insulin-like growth factor-binding protein-2 in the serum of prostate cancer patients. *J Clin Endocrinol Metab*. 76:1031–1035.
9. Kanety H, Madjar Y, Dagan Y, et al. 1998 Serum insulin-like growth factor-binding protein-2 (IGFBP-2) is increased and IGFBP-3 is decreased in patients with prostate cancer: correlation with serum prostate-specific antigen. *J Clin Endocrinol Metab*. 77:229–233.
10. Ho PG, Baxter R. 1997 Insulin-like growth factor binding protein-2 in patients

- with prostate carcinoma and benign prostatic hyperplasia. *Clin Endocrinol (Oxf)*. 46:333–342.
11. **Cohen P, Graves HCB, Peehl DM, Kamarei M, Giudice LC, Rosenfeld RG.** 1992 Prostate-specific antigen (PSA) is an insulin-growth factor binding protein-3 protease found in seminal plasma. *J Clin Endocrinol Metab*. 75:1046–1053.
 12. **Colao A, Marzullo P, Ferone D, et al.** 1998 Prostate hyperplasia: an unknown feature of acromegaly. *J Clin Endocrinol Metab*. 83:775–779.
 13. **Colao A, Lombardi G.** 1998 GH and PRL excess. *Lancet*. 352:1455–1461.
 14. **Shalet SM, Togood AA, Rahim A, Brennan BMD.** 1998 The diagnosis of growth hormone deficiency in children and adults. *Endocr Rev*. 19:203–223.
 15. **Rubin JM, Bude RO, Carson PL, Bree RL, Adler RS.** 1994 Power Doppler US: a potentially useful alternative to mean frequency-based color Doppler US. *Radiology*. 190:853–856.
 16. **Collins GN, Raab GM, Hehir M, King B, Garraway WM.** 1995 Reproducibility and observer variability of transrectal ultrasound measurements of prostatic volume. *Ultrasound Med Biol*. 21:1101–1105.
 17. **Berry SJ, Coffey DS, Walsh PC, et al.** 1984 The development of human benign prostatic hyperplasia with age. *J Urol*. 132:474–479.
 18. **McNeal JE.** 1988 Normal histology of the prostate. *Am J Surg Pathol*. 12:619–633.
 19. **Byrne RL, Leung H, Neal DE.** 1996 Peptide growth factors in the prostate as mediators of stromal epithelial interactions. *Br J Urol*. 77:627–633.
 20. **Reiter E, Kecha O, Hennuy B, et al.** 1995 Growth hormone directly affects the function of the different lobes of the rat prostate. *Endocrinology*. 136:3338–3345.
 21. **Kimura G, Kasuya J, Giannini S, et al.** 1996 Insulin-like growth factor (IGF) system components in human prostatic cancer cell lines: LNCaP, DU145 and PC-3 cells. *Int J Urol*. 3:39–46.
 22. **Russel PJ, Bennett S, Stricker P.** 1998 Growth factor involvement in progression of prostate cancer. *Clin Chem*. 44:705–723.
 23. **Grimberg A, Rajah R, Zhao H, Cohen P.** 1998 The prostatic IGF system: new levels of complexity. In: Takano K, Hizuka N, Takahashi SI, eds. *Molecular mechanisms to regulate the activities of insulin-like growth factors*. Amsterdam: Elsevier; 205–215.
 24. **Monti S, Di Silverio F, Lanzara S, et al.** 1998 Insulin-like growth factor-I and -II in human benign prostatic hyperplasia: relationship with binding proteins 2 and 3 and androgens. *Steroids*. 63:362–366.
 25. **Rajah R, Valetinis B, Cohen P.** 1997 Insulin-like growth factor (IGF)-binding protein-3 induces apoptosis and mediates the effects of transforming growth factor β 1 on programmed cell death through a p53- and IGF-independent mechanism. *J Biol Chem*. 272:12181–12188.
 26. **Orme SM, McNally RJQ, Cartwright RA, Belcheta PE for the United Kingdom Acromegaly Study Group.** 1998 Mortality and cancer incidence in acromegaly: a retrospective cohort study. *J Clin Endocrinol Metab*. 83:2730–2734.
 27. **Popovic V, Damjanovic S, Micic D, et al.** 1998 Increased incidence of neoplasia in patients with pituitary adenomas. *Clin Endocrinol (Oxf)*. 49:441–445.
 28. **Mantzoros CS, Tzonou A, Signorello LB, Stampfer M, Trichopoulos D, Adami HO.** 1997 Insulin-like growth factor-I in relation to prostate cancer and benign prostatic hyperplasia. *Br J Cancer*. 77:1115–1118.
 29. **Hankinson SE, Willett WC, Colditz GA, et al.** 1998 Circulating concentrations of Insulin-like growth factor-I and risk of breast cancer. *Lancet*. 351:1393–1396.
 30. **Boudon C, Rodier G, Lechevallier E, Mottet N, Barenton B, Sultan C.** 1996 Secretion of insulin-like growth factors and their binding proteins by human normal and hyperplastic prostatic cells in primary culture. *J Clin Endocrinol Metab* 81:612–617.