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Impact of Disease Activity on Thyroid Diseases in Patients with Acromegaly: Basal Evaluation and Follow-up

Abstract

In patients with acromegaly, the exact incidence of thyroid disorders is still controversial and less is known about the impact of disease activity and successful treatment. To address this issue, we investigated 73 acromegalic patients (age 55 ± 13 yr; mean ± SD) by ultrasonography in comparison to an age-matched control group (54 ± 1 yr) in the same moderate iodine deficient area (retrospective study). These non-acromegalic volunteers (n = 199) were examined in the same clinic during a thyroid screening test. At the time of examination, 52 (71.2%) of the acromegalic patients were active, 17 (23.3%) were cured, and 4 (5.5%) were controlled with somatostatin analogues. The prevalence of goiter (normal range < 18 ml female, < 25 ml male) was significantly higher (82.2%) in the mixed group of acromegalics (active, well controlled, cured; n = 73) and in the active group (90.4%) than in the control group (n = 199, 18.1%, $p < 0.001$). Thyroid nodules were found in 63.0% of the mixed group of acromegalics and in 71.2% of patients with active disease (33.1% in controls, $p < 0.001$). ^{99m}Tc scintigraphy revealed thyroid autonomy in 9/73 (12.3%) and cold nodules in 19/73 (26.0%) patients. Thyroid cancer was diagnosed in 4 (5.5%) of acromegalic patients (3 papillary and 1 follicular carcinoma). We found a weak correlation between the disease duration and the initial thyroid volume ($r = 0.54$, $p < 0.0056$).

Thirty-seven newly diagnosed acromegalics were followed over a period of 7.3 ± 4.1 years. 5 (13.5%) of these patients remained active, 8 (21.6%) were controlled with somatostatin analogues, and 24 (64.9%) were cured. The mean age, sex distribution, disease duration, prevalence of TSH-deficiency, and initial thyroid volume (46 ± 11 ml in active, 42 ± 7 ml in controlled, and 45 ± 5 ml in cured patients) did not differ statistically between the three groups. In patients with active acromegaly, thyroid volume increased by 19.5 ± 8.1%. In contrast, thyroid volume decreased in the group of medically controlled and cured acromegalics (− 21.5 ± 7.1%; $p < 0.005$ and − 24.2 ± 5.7%; $p < 0.002$, respectively). No correlation was found between thyroid volume and TSH levels, levothyroxine and/or iodide administration neither in TSH sufficient nor in TSH insufficient patients.

In conclusion, successful treatment of patients with active acromegaly decreases thyroid volume. Cold nodules and thyroid cancer frequently occur in acromegalic patients.

Key words

Acromegaly · thyroid diseases · disease activity

Introduction

Patients with acromegaly have an increased risk of cardiovascular diseases (Colao et al., 1999; Colao et al., 2001; Herrmann et al., 2002; Herrmann et al., 2001), sleep apnea syndrome (Dostalova et al., 2001; Rosenow et al., 1996), and cancer (Orme et al., 1998). Moreover, it is well established that acromegaly is associated with an increased incidence of goiter which may be due to the

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GH excess and persistently elevated IGF-1 levels (Gasperi et al., 2002; Wuster et al., 1991; Yoshinari et al., 1992). The TSH levels and iodine deficient areas seem to be independent of the development of goiter in patients with acromegaly (Arosio et al., 1995; Cannavo et al., 2000). The exact prevalence of goiter in patients with acromegaly remains uncertain and little is known about a longer observation period of thyroid volume and the impact of activity after successful transsphenoidal surgery and treatment with somatostatin analogues. The course of thyroid volume after successful treatment of acromegaly remains controversial. Cheung et al. (Cheung and Boyages, 1997) could demonstrate a reduction in thyroid volume after one year of treatment with the somatostatin analogue octreotide in 9 patients with active acromegaly in contrast to the observations of Cannavo et al. (Cannavo et al., 2000) who reported no significant decrease of mean thyroid volume in 18 patients with acromegaly after an observation period of 2 – 7 years.

The present retrospective study focused on the prevalence of goiter and nodules of acromegalic patients, the prevalence of thyroid autonomy and thyroid cancer evaluated in one single center of a moderately iodine deficient area. Thyroid volume was determined after an observation period of 7 years to evaluate the influence of cure, treatment with somatostatin analogues, and persistent activity.

Patients and Methods

Patients

Seventy-three patients (39 females, 34 males) with a mean age 55 ± 13 years (range 32 – 82) suffering from acromegaly were included in the study (Table **1**). The diagnosis of acromegaly was made on the basis of physical examination, IGF-1 and GH levels after an oral glucose load (75 g). Considering the consensus statement of criteria for cure of acromegaly, 52 patients (71.2%) had active disease (16 with octreotide [Sandostatin® 3 × 100 – 200 µg/die]; 3 with octreotide acetate [30 mg Sandostatin LAR® every 4 weeks i.m.] and 33 without medication), 17 (23.3%) patients were cured, and 4 (5.5%) patients were well controlled with somatostatin analogues: 2 with octreotide (Sandostatin® 3 × 200 µg/die); 1 with octreotide acetate (30 mg Sandostatin LAR® every 4 weeks i.m.); 1 with lanreotide (30 mg every 2 weeks i.m.). Cure was defined as IGF-1 levels within the age-adjusted normal range and nadir GH after an oral glucose load of less than 1 µg/L (Giustina et al., 2000). Patients treated with somatostatin analogues were defined as "well controlled" if they had an IGF-1 value within the age-adjusted normal range of the IGF-1 assay (25 – 39 years: 114 – 492 µg/l; 40 – 54 yr: 90 – 360 µg/l; ≥ 55 yr: 71 – 290 µg/l). At the time of the thyroid examination the mean IGF-1 level was 433 ± 337 µg/l (54 – 1500) and the mean GH level was 9.5 ± 26.9 µg/l (0.5 – 189). The duration of disease (11.9 ± 8.3 years, range 2 – 43) was assumed to be the interval between the clinical onset determined by comparison of old photographs and the time of treatment. The mean BMI was 29.0 ± 4.1 kg/m^2. All patients underwent an ultrasonography of the thyroid, and determination for free T4, T4, T3, and TSH.

Thirty-seven newly diagnosed acromegalics (Table **2**) were followed over a period of 7.3 ± 4.1 years. 5 (13.5%) of these patients remained active: 2 with octreotide (Sandostatin® 3 × 200 µg/die); 2 with octreotide acetate (30 mg Sandostatin LAR® every 4 weeks i.m.); 1 without medication. 8 (21.6%) were controlled with somatostatin analogues: 3 with octreotide (Sandostatin® 3 × 200 µg/die); 4 with octreotide acetate (30 mg Sandostatin LAR® every 4 weeks i.m.); 1 with lanreotide (30 mg every 2 weeks i.m.). 24 patients (64.9%) were cured (18 after exstirpation of the GH-producing tumor, 6 with additional radiation).

Table **1** Clinical data of 73 patients with acromegaly for basal evaluation

M/F	34/39
Age (yr)	55 ± 13
Disease duration (yr)	11.9 ± 8.3
IGF-1 (µg/l)	433 ± 337
GH (µg/l)	9.5 ± 26.9
Surgery	57 (78%)
Irradiation	19 (26%)
Active disease	52 (71%)
Cured	17 (23%)
Well controlled	4 (6%)
Gonadotropin deficiency	19 (26%)
ACTH deficiency	18 (25%)
Thyreotropin deficiency	14 (19%)
Diabetes insipidus	4 (6%)

Table **2** Clinical data of 37 newly diagnosed acromegalics for follow-up evaluation

		Active	*Well controlled*	*Cured*
Number		5	8	24
Age (yr)		51 ± 17	46 ± 14	56 ± 13
Sex (f/m)		1/4	4/4	11/13
Duration of observat. (yr)		9 ± 4	7 ± 4	7 ± 4
TSH-deficient	beginning	3 (60%)	1 (13%)	7 (29%)
	end	3 (60%)	1 (13%)	6 (25%)
Thyroid volume (ml)	beginning	46 ± 25*	42 ± 19*	45 ± 25**
	end	58 ± 28	31 ± 15	32 ± 17
TSH (mU/l)	beginning	0.30 ± 0.26[t]	0.81 ± 0.42	0.64 ± 0.54
	end	0.27 ± 0.26	0.54 ± 0.34	0.80 ± 0.59
Free T4 (pmol/l)	beginning	11 ± 4	13 ± 4	16 ± 4
	end	14 ± 1	18 ± 6	15 ± 2
T3 (nmol/l)	beginning	2.01 ± 0.25	1.94 ± 0.33	2.20 ± 0.83
	end	2.11 ± 0.15	2.48 ± 0.66	2.09 ± 0.20

[t] $p < 0.05$ active vs. well controlled; * $0 < 0.05$ beginning vs. end of observation period
** $0 < 0.001$ beginning vs. end of observation period

Control group

During a thyroid screening test in the same clinic, a group of 199 volunteers (German Survey "Papillon", Henning Berlin GmbH),

comparable for age (54 ± 5 yr, range 32 – 72) and sex distribution (111 females [56%], 88 males [44%]) served as non-acromegalic controls (BMI 25.5 ± 0.2 kg/m^2). 14% had a history of thyroid disease and received iodide and/or levothyroxine.

Hormone assays

Serum GH levels were determined by a chemiluminescence immunometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st International Standard (80/505) for Human GH. Normal range was ≤ 5 µg/l. Intra- and interassay coefficients of variation (CVs) for a low point of the standard curve were 5.4% and 7.9%, respectively. Plasma IGF-1 concentrations were measured by an immunoradiometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st International Reference Reagent 87/518. Intra- and interassay CVs for low IGF-1 concentrations were 2.4% and 5.2%, respectively. TSH (reference range 0.3 – 3.0 mU/l), free thyroxine (reference range 10 – 25 pmol/l), and triiodothyronin (reference range 1.23 – 3.08 nmol/l) were determined by sensitive chemiluminescence assay (Chiron Diagnostics, ACS 180, Fernwald, Germany). All other parameters were determined by routine methods.

Thyroid ultrasonography and thyroid scan

Thyroid high-resolution ultrasonography was performed using a 7.5 MHz B-scanner (Toshiba, Munich, Germany), by clinicians mostly not involved in the study. All goiter size and nodules were reevaluated by three investigators using the paper printouts. The reliability of the method was ascertained by comparison of all patients evaluated by all three investigators (Quadbeck et al., 2002). The volume of each thyroid lobe was calculated from the formula $l \times w \times d \times \pi/6$ where *l* is the longitudinal length, *w* the transverse diameter, and *d* is the depth of the lobe (Brunn et al., 1981). Total thyroid volume was the sum of the volumes of the two lobes. Thyroid nodularity was determined by ultrasonography following standardized criteria as previously decribed (Knudsen et al., 1999), and the classification according to thyroid nodularity has been found to be reproducible between observers (Knudsen et al., 1999). Thyroid nodules were registrated from a diameter of 5 mm. In patients with nodules > 1 cm, a thyroid scintigraphy with ^{99m}Tc-pertechnetate was performed. The thyroid scan was performed in 33 patients 20 minutes after intravenous injection of 60 MBq ^{99m}Tc-pertechnetate. Planar scan images were aquired in anterior view using a small field-of-view gamma camera equipped with an especially designed for thyroid examinations (type CX 2505 Picker, Espelkamp, Germany). In addition to the acquisition of scan images, the global thyroid uptake of ^{99m}Tc was determined by ROI technique with background correction (normal range under euthyroid conditions 0.4 – 3.0%). Sonographically-assisted fine-needle aspiration biopsy was performed in 19 patients with cold nodules > 1 cm.

Statistical analyses

The data, if not marked otherwise, represent the mean ± standard deviation. Differences between two groups were tested by Mann-Whitney U-test as a nonparametric procedure. Absolute differences between time points (e.g. TSH level at baseline and after the observation period) were analyzed per group using the paired Wilcoxon signed rank test. For analysis of data of the three groups (e.g. thyroid volume, Fig. **2**) we used ANOVA with posthoc testing. All tests were done two-tailed, p-values < 0.05 were considered statistically significant.

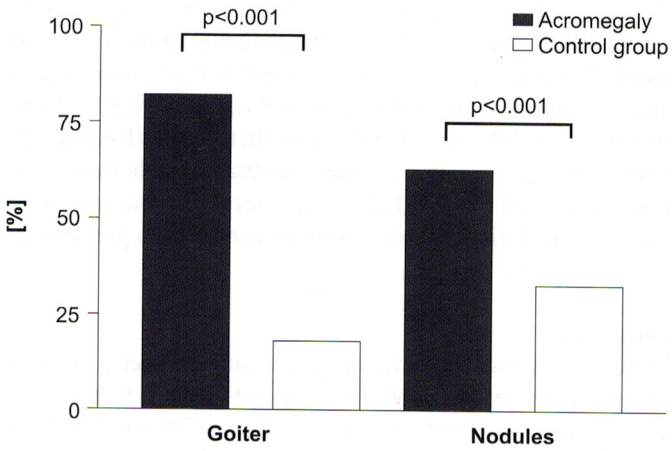

Fig. **1** Prevalence of goiter and nodules in patients with acromegaly (n = 73) and controls (n = 199).

Results

Basal evaluation

The prevalence of goiter (normal range < 18 ml female, < 25 ml male) was significantly higher (82.2%) in the mixed group of acromegalics (active, well controlled, cured; n = 73) and in the active group (90.4%) than in the control group (18.1%, p < 0.001). The mean thyroid volume of the mixed group was 40 ± 21 ml (range 11 – 115, median 33), 44 ± 22 ml in the active group (range 10 – 115, median 37), and 16 ± 10 ml (range 5 – 84, median 14) in the control group. Thyroid nodules were found in 63.0% (46/73) of the mixed group of acromegalics and in 71.2% (37/52) of patients with active disease (33.1% in controls, p < 0.001, Fig. **1**). The prevalence of nodules (71.2%) was significantly higher than in the group of acromegalics in remission (42.9%; p < 0.05). 33/46 (71.7%) had nodules > 1 cm and were evaluated by ^{99m}Tc-pertechnetate. ^{99m}Tc scintigraphy revealed thyroid autonomy in 9/73 (12.3%) and cold nodules in 19/73 (26.0%) patients. Two of the patients in whom ^{99m}Tc-pertechnetate was performed were TSH deficient and had a ^{99m}Tc-uptake of 0.3 and 0.4%. 4 patients had unifocal autonomy, 2 patients had bifocal autonomy, 2 patients had multifocal autonomy, and 1 patient had disseminated autonomy. 5/73 (6.8%) patients had functionally relevant thyroid autonomy (mean ^{99m}Tc-uptake 5.25 ± 2.1%).

Fine-needle aspiration was perfomed in all patients with cold nodules (> 1 cm). In these patients, thyroid cancer was diagnosed in 4 (5.5%) of acromegalic patients (3 papillary and 1 follicular carcinoma). All 4 patients with thyroid cancer underwent thyroidectomy and 11 patients underwent subtotal thyroid resection. One patient received radiotherapy with iodine 131 because of autonomy.

Fourteen of the overall 73 patients (19.2%) were TSH insufficient and 80.8% (59/73) were TSH sufficient. 21/59 of the TSH sufficient group received levothyroxine and/or iodide. Levothyroxine was administrated in 17/21 with a mean dosage of 102 ± 17 µg/

die (range 75 – 150), 1/21 received 100 µg levothyroxine + 150 µg iodide and 3/21 were treated with iodide 200 µg/die alone. The basal TSH was 0.56 ± 0.41 mU/l in the levothyroxine-treated group, 0.6 mU/l in the 3 patients treated with 100 µg levothyroxine + 150 µg iodide and 0.95 ± 0.31 mU/l in the group treated with iodide 200 µg/die alone. No correlation was found between thyroid volume and GH, IGF-1, TSH levels, levothyroxine, and/or iodide administration neither in TSH sufficient nor in TSH insufficient patients.

Follow-up

37 newly diagnosed acromegalics were followed over a period of 7.3 ± 4.1 years respectively. These patients were a subgroup of the 73 patients of the first part of the study. The mean age, sex distribution, disease duration, prevalence of TSH-deficiency, and initial thyroid volume did not differ statistically between the three groups (Table **2**). In the active group, one patient (TSH sufficient) received goiter prophylaxis with 200 µg/die iodide. In the well controlled group, two patients (TSH sufficient) received goiter prophylaxis with 50 and 100 µg levothyroxine per day (cured group: 5 patients (TSH sufficient) with levothyroxine 50 – 125 µg/die and 2 patients with 100 and 200 µg iodide/die). At baseline, the mean TSH level was significantly lower in the active group than in the well controlled group (0.30 ± 0.26 mU/l versus 0.81 ± 0.42 mU/l; $p < 0.05$). In patients with active acromegaly, thyroid volume increased by 19.5 ± 8.1 % significantly ($p = 0.03$). In contrast, thyroid volume decreased in the group of medically controlled and cured acromegalics (– 21.5 ± 7.1 %; $p < 0.005$ and – 24.2 ± 5.7 %; $p < 0.002$, respectively, Fig. **2**). The difference of the percentual change of thyroid volumes was not significant between patients in surgical remission and those in medical remission. At baseline the prevalence of goiter did not differ statistically between the three groups (active 80 %, well controlled 75 %, cured 88 %). The prevalence of goiter increased in the active group (100 %) and decreased in the well controlled (50 %) and cured group (71 %).

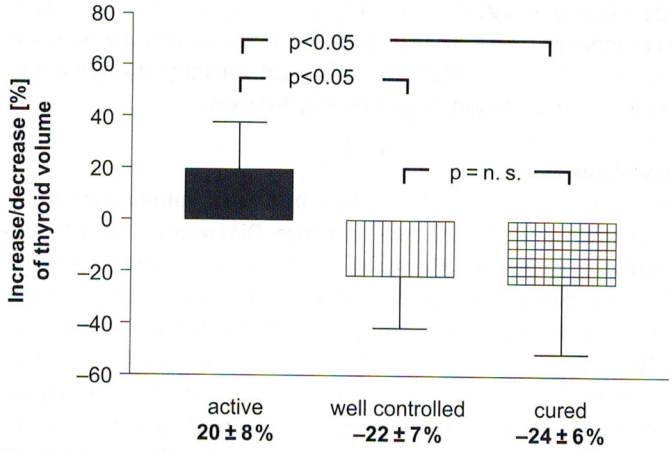

Fig. **2** Increase/decrease of thyroid volume of 37 patients with acromegaly over a period of 7.3 ± 4.1 years.

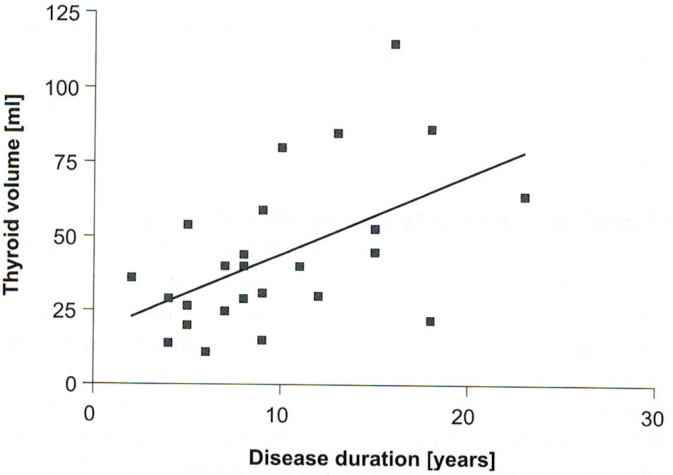

Fig. **3** Bivariate lineary regression analysis of relationship between thyroid volume and disease duration of patients with newly diagnosed acromegaly ($n = 37$; $r = 0.537$, $p = 0.0056$).

We found a weak correlation between the disease duration and the initial thyroid volume ($r = 0.54$, $p < 0.0056$, Fig. **3**). At baseline, the prevalence of nodules was higher in the group who remained active (4/5 [80.0 %]) than in the cured (17/24 [70.8 %]) and well controlled groups, respectively (5/8 [62.5 %]). Interestingly, in most of the patients, the size of nodules in the 3 groups remained stable (active 3/4 [75.0 %]; cured 13/17 [76.5 %]; well controlled 4/5 [80.0 %]). No correlation was found between the course of the thyroid volume and GH, IGF-1, TSH levels, levothyroxine, and/or iodide administration in either TSH sufficient or in TSH insufficient patients.

Discussion

In the present study, we examined the impact of disease activity after a mean observation period of 7 years on thyroid volume and we have evaluated respectively the prevalence of goiter and nodules in patients with acromegaly in one single center of a moderately iodine-deficient area.

According to previous studies (Cheung and Boyages, 1997; Gasperi et al., 2002; Wuster et al., 1991; Yoshinari et al., 1992), which reported a high prevalence of goiter between 67 – 92 %, we diagnosed thyroid enlargement in 82 % of a mixed group of acromegalics (cured, well controlled, active) and in 90 % in patients with active acromegaly. The duration of disease activity seems to be the most important factor of thyroid enlargement (Cannavo et al., 2000; von Werder, 2002) similar to the observation that the development of cardiomegaly correlates with the disease duration (Lombardi et al., 1997). In addition to the major production and secretion of hepatic IGF-1 due to GH excess in active acromegaly, IGF-1 is produced locally by fibroblasts in the thyroid gland under the control of GH and is an important factor for promoting thyroid growth and differentiation (Bechtner et al., 1996; Westermark et al., 1983). This could be demonstrated in FRTL-5 rat thyroid cells *in vitro* (Saji et al., 1987; Takahashi et al., 1990). Whereas some studies noted a direct relationship between IGF-1, GH levels, and goiter (Cheung and Boyages, 1997; Junik et al., 1997; Miyakawa et al., 1988; Wuster et al., 1991), we did not find a positive correlation between thyroid volume and serum IGF-1 or GH levels, similar to the other observations (Cannavo et al., 2000; Kasagi et al., 1999). One single IGF-1 value reveals less the impact of disease activity than multiple IGF-1 values over a lon-

ger period. Therefore, disease duration correlates better with thyroid volume than IGF-1 levels.

Moreover, we demonstrated that goiter development is independently of TSH and iodine deficiency and independent of age and weight in contrast to the positive correlation of thyroid size with age and weight in non-acromegalic subjects (Hegedus et al., 1983). The role of TSH in the pathogenesis of goiter in patients with acromegaly is more complicated, considering the fact that low or suppressed TSH levels may be due to autonomy or may be due to TSH deficiency. Moreover, secretion of TSH in patients with acromegaly can be affected by an increased hypothalamic somatostatin production (Williams et al., 1988) or by treatment with somatostatin analogues (Arosio et al., 1995; von Werder, 2002). In addition, GH may have a direct stimulatory effect on the thyroid secretion of T4 and conversion of T4 in T3 via increased IGF-1 levels, despite suppressed TSH secretion (Bechtner et al., 1996). Furthermore, IGF-1 levels correlated inversely with TSH responsiveness to TRH and positively with serum levels of free T4 (Yoshinari et al., 1992).

The diagnosis of nodular goiter was made in 63% of all acromegalics and the prevalence being nearly two-fold higher than in the control group of the same moderate iodine deficient area, consistent with previous observations showing an incidence of 39–63% in patients with acromegaly (Cheung and Boyages, 1997; Miyakawa et al., 1988; Wuster et al., 1991). In non-acromegalic patients, iodine deficiency is the major cause of the pathogenesis of nodules and appears to favour the event of novel mutations in growth-regulatory genes (Derwahl et al., 1999; Kopp et al., 1994). While thyroid autonomy was diagnosed in 12.3%, similar to previous reports of a frequency of 12.5% (Wuster et al., 1991), the prevalence of cold nodules was relatively high (26%). This may be due to the longer disease duration of 12 years in our patients with acromegaly in contrast to mean disease duration of 8 years reported in a previous study with a lower prevalence of cold nodules (Kasagi et al., 1999). These results suggest that long-term stimulation by GH and IGF-1 of thyroid follicular cells might be responsible for subsequent formation of nodules in acromegalic patients.

In 37 newly diagnosed acromegalics, followed over a period of 7 years, we have seen a significant increase of thyroid volume in patients with active acromegaly, whereas thyroid volume decreased in well controlled or cured patients. These observations are consistent with the results of Cheung et al. (Cheung and Boyages, 1997) who demonstrated a reduction in thyroid volume after one year treatment with the somatostatin analogue octreotide in 9 patients with active acromegaly. The fact that nodule size was unaffected after cure or treatment with somatostatin analogues indicates that reduction of GH or IGF-1 in serum have little effect on diffuse nodular goiter but successfully reduce normal parenchymal tissue. Considering the fact that somatostatin receptors are present in thyroid tissue (Ain and Taylor, 1994), and that proliferation of FRTL-5 cells can be inhibited by octreotide (Medina et al., 1999), it is conceivable that thyroid reduction is directly influenced by somatostatin analogues.

Nevertheless, a limitation of the present study is the retrospective character of the evaluation whenever the data were analyzed from a representative number of patients (n = 73) from one single center. Since the original description by Pierre Marie in 1886, acromegaly has been known to be associated with increased morbidity and mortality mostly due to cardiovascular, respiratory, and metabolic diseases (Bengtsson et al., 1989; Bengtsson et al., 1988; Grunstein et al., 1991; Lombardi et al., 1996; Rosenow et al., 1996). Epidemiology studies have provided increasingly debated evidence that acromegaly may enhance the neoplastic risk, particularly of colon (Ezzat et al., 1991; Ron et al., 1991), breast (Jenkins and Besser, 2001; Orme et al., 1998), and prostate (Colao et al., 2003; Colao et al., 2000; Grimberg and Cohen, 1999). Consistent with previous studies, we found a prevalence of thyroid cancer in 5.5% of patients with acromegaly (Balkany and Cushing, 1995; Gasperi et al., 2002; Popovic et al., 1998). The observation of a higher specific binding of IGF-1 by neoplastic thyroid cells than by non-neoplastic cells (Yashiro et al., 1989) may be a predisposing factor for nodular formation and thyroid neoplasms.

In conclusion, successful treatment of patients with active acromegaly decreases thyroid volume. Considering the fact of a high prevalence of nodules (cold 26.0%; warm 12.3%) and thyroid cancer (5.5%), a careful thyroid examination should complete the work-up of patients with acromegaly.

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