Prevalence of thyroid diseases in patients with acromegaly: results of an Italian Multi-center Study

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ABSTRACT. Acromegaly is frequently associated with the presence of thyroid disorders, however the exact prevalence is still controversial. An Italian multicenter study was performed on 258 patients with active acromegaly (high levels of IGF-I and lack of suppression of serum GH levels below 2 µg/l after an OGTT). The control group was represented by 150 patients affected by non-functioning and PRL-secreting pituitary adenomas. Two hundred and two out of 258 acromegalic patients (78%) were affected by thyroid disorders with a significantly higher prevalence with respect to the control group (27%, *p*<0.0001). One hundred and three patients presented (39.9%) non-toxic nodular goiter, 46 (17.8%) non-toxic diffuse goiter, 37 (14.3%) toxic nodular goiter, 1 toxic diffuse goiter (0.4%), 12 (4.6%) Hashimoto's thyroiditis, 3 (1.2%) thyroid cancer. Two patients presented a co-secreting TSH pituitary adenoma. Thirty-six patients had been previously treated for various thyroid abnormalities. Among the 222 acromegalic patients never treated for thyroid disorders thyroid ultrasonography was performed on 194 subjects. Thyroid volume in patients with thyroid abnormalities was 28±17.5 ml (median 23) while it was 10.8±3.6 ml (median 10) in patients without thyroid disorders (*p*<0.0001). Thyroid volume was correlated with the estimated duration of acromegaly (r=0.7, *p*<000.1), but not with age or with serum GH, IGF-I and TSH concentrations. Thyroid volume was higher in acromegalic patients than in the above control population (23.5±16.9 ml *vs* 13.9± 12.8 ml, *p*<0.0001). In 62 acromegalic patients 101 fine-needle biopsies of thyroid nodules were performed; 7 nodules were suspicious and the patients were submitted to thyroid surgery: papillary thyroid carcinoma was found in 3 patients. In conclusion, in a large series of acromegalic patients an increased prevalence of thyroid disorders (78%), particularly non-toxic nodular goiter, has been observed. Thyroid volume, evaluated by ultrasonography, was correlated to the estimated duration of acromegaly. Finally, the prevalence of thyroid carcinoma was slightly increased than in the general population.

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INTRODUCTION

The association between acromegaly and goiter has long been recognized, but the evaluation of thyroid disorders in the presence of GH and IGF-I excess has provided conflicting results, since the prevalence of thyroid abnormalities in acromegaly ranged from 25 to 92% in different series (1-8). These discrepancies may partially be explained by differences in the assessment of thyroid volume and prevalence of goiter in geographic areas with different iodine intake (Table 1). The aims of the present multi-center study were to investigate the

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Table 1 - *Literature data regarding the prevalence of thyroid disorders in acromegaly.*

Ref.	Author	Year	No. of patients	Sex (%) of females	Prevalence (%) of thyroid disorders	Method evaluation	Correlation with activity of acromegaly	Correlation with duration of disease	Iodine status
1	Nabarro	1987	256	48	11	Palpation	N.E.	N.E.	N.E.
2	Miyakawa *et al.*	1988	17	53	82	Ultrasound	Yes (GH and IGF-I)	N.E.	N.E.
3	Wuster *et al.*	1991	80	53	71	Palpation	Yes (GH)	Yes	Deficiency
4	Arosio *et al.*	1997	68	63	76	Ultrasound	N.E.	N.E.	N.E.
5	Junik *et al.*	1997	39	46	87	Ultrasound	Yes (GH)	N.E.	Deficiency
6	Cheung *et al.*	1997	37	43	92	Ultrasound	Yes (IGF-I)	No	N.E.
7	Kasagi *et al.*	1999	48	55	87	Ultrasound	No	Yes	N.E.
8	Cannavò *et al.*	2000	28	61	78	Ultrasound	No	No	Deficiency
	Gasperi *et al.*	This study	258	57	78	Ultrasound	No	Yes	Moderate-normal

N.E.: not evaluated.

prevalence of goiter and other thyroid abnormalities in a large population of acromegalic patients residing in moderate-normal iodine intake areas and to correlate clinical and metabolic features of thyroid disorders to parameters of acromegaly.

SUBJECTS AND METHODS

Subjects

Acromegalic patients were recruited through the cooperation of 9 endocrinological centers in Italy. The iodine intake in these areas was moderate-normal, as documented by the measurement of urinary iodine secretion which ranges from 50 to 110 µg/l, as previously reported (9). Diagnosis of acromegaly was based on anamnestic, clinical and laboratory data. Active disease was defined by the presence of increased IGF-I levels (with respect to normal values according to age) and by lack of suppression of GH levels below 2 µg/l after an (75 g) OGTT (10-13). The presumptive duration of active disease was estimated by each investigator using a standardized form taking in account anamnestic, clinical and laboratory data, if available.

Two hundred and fifty-eight patients, 147 women (57%) and 111 men (43%), were enrolled in the study. Mean age (±SD) was 50±13 yr (range: 17-80 yr), with no statistical difference between genders (women: 51±12 yr, range 17-78 yr, men: 48±13 yr, range 22-80 yr; *p*=NS). Two of the patients presented a TSH co-secreting adenoma: their data were not included in the statistical analysis.

When enrolled, 88 patients (34%) had been previously treated for acromegaly, with persistence of active disease. Medical therapy had been administered in 57 patients, either alone (30 patients), in combination with surgery (17 patients), surgery plus radiotherapy (3 patients), or radiotherapy (7 patients). Twelve patients had been treated only by surgery, 7 only by radiotherapy and 11 by surgery and radiotherapy.

Eleven patients had previously been submitted to thyroid surgery, 21 patients were under treatment with L-T_4 and 4 with methimazole. Thus, 222 had never been treated for thyroid disorders.

The control group consisted of 150 patients (122 females and 28 males) with mean age of 48±15 (range: 13-85 yr) affected by either non-functioning (no.=44) or PRL-secreting pituitary adenoma (no.=106). Diagnosis had been performed by common endocrinological and imaging techniques.

Assay

Serum free T_4 (FT_4) and free T_3 (FT_3) were measured by RIA (Lisophase Kits, Lab. Bouty, Sesto San Giovanni, Italy); serum ultrasensitive TSH by an ultrasensitive IRMA (Auto-Delfia Wallac, Gaithersburg, MD, USA). Normal values were: FT_4, 8.4-23.2 pmol/l (6-18 pg/ml); FT_3, 3.8-8.4 pmol/l (2.5-5.5 pg/ml); TSH, 0.4-3.7 mU/l. Serum anti-thyroglobulin (TGAb) and anti-thyroperoxidase (TPOAb) antibodies were determined by IRMA methods with commercial kits [(Sorin Biomedica, Saluggia, Italy; normal values were respectively: <50 U/ml and <10 U/ml)]. Serum GH concentration was measured by IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, U.S.A.), with a sensitivity of 0.1 µg/l. The inter- and intra-assay coefficients of variation were 5.1-7.5% and 2.6-5.4%, respectively. Serum IGF-I was determined by RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA, U.S.A.), with a sensitivity of 0.1 µg/l. The normal ranges for serum IGF-I according to age were 182-780 µg/l at 16-24 yr, 90-492 µg/l at 25-50 yr and 71-290 µg/l over 50 yr. The inter- and intra-assay coefficients of variation were 8.8-10.8% and 5.0-9.5%, respectively. Serum PRL concentration was measured by AIA-PACK IFMA (Eurogenetic, Italy); the normal range was <25 ng/ml for women and <13 ng/ml for men.

Thyroid ultrasonography

Thyroid ultrasound evaluation was performed by well-trained physicians in each center by a real-time instrument (Esaote, Biomedica, Florence, Italy) using a 7.5 MHz linear transducer. Thyroid volume was calculated according to the formula of the ellipsoid model: width x length x thickness x 0,52 for each lobe (14, 15); all the images were re-evaluated in one center in blind manner. Goiter was defined when the thyroid volume was >13 ml for females and >18 ml in males, which are the corresponding upper normal limits (9).

Thyroid scintigraphy

Thyroid scintiscan was performed, after administration of ^{99m}technetium pertechnetate or ^{131}iodine as a tracer, using a rectilinear scanner or a γ-camera.

Fine needle aspiration

Fine needle aspiration (FNA) was advised in all subjects with nodular goiter and was performed in 62 patients with acromegaly and in 14 controls. FNA was usually advised when solid and mixed nodules where larger than 1 cm and cold at scintiscan.

Statistical analysis

Statistical analysis was performed using Statview 4.0 for Macintosh. Results were expressed as the mean±SD, median and range. The Student's unpaired *t*-test and the chi-square test (χ^2) were used when indicated. Linear regression analysis was performed to analyze the relation between thyroid volume and estimated duration of active disease, serum GH, IGF-I and TSH values.

RESULTS

In the whole group of acromegalic patients thyroid abnormalities were found in 202 out of 258 patients (78%), including non-toxic nodular goiter (NNG) in 103 patients, non-toxic diffuse goiter (NDG) in 46, toxic nodular goiter (TNG) in 37 patients with one or more hot nodules shown by thyroid scintigraphy, toxic diffuse goiter (TDG) in 1, Hashimoto's thyroiditis (HT) in 12, and differentiated thyroid cancer (DTC) in 3. In the control group thyroid abnormalities were found in 41 out of 150 patients (27%), including NNG in 20 patients, NDG in 6, TNG in 2, TDG in 1, HT in 11, and DTC in 1. The prevalence of thyroid disorders in acromegaly was statistically significant with respect to the control group ($p<0.0001$, $\chi^2=100.1$). Similarly the prevalence of NNG, NDG and TNG was significantly higher in acromegalic patients than in the control group but not in HT, TDG and thyroid carcinoma (Fig. 1). The prevalence of thyroid abnormalities in acromegalic patients did not differ in women (119/147: 81%) and men (85/111: 77%). Mean age was higher in patients with than in those without thyroid disorders (51±12 yr, range 22-80 yr *vs* 45±13 yr, range: 17-76 yr; $p<0.01$). The prevalence of thyroid abnormalities in controls was borderline significantly greater in women vs men (38/122 or 31% *vs* 3/28 or 11%, $\chi^2=3.8$ $p=0.05$). There was no difference found between age of controls with and without thyroid disorders.

In the subset of 222 acromegalic patients never treated for thyroid disorders ultrasound data were available in 194 patients. Thyroid volume was 23.5±16.9 ml (median 21 ml, range 4-137 ml), with no differences between 108 women (22.9±16.8 ml, median 19 ml, range 4-103 ml) and 86 men (24.2±17.1 ml, median 21 ml, range 6-137 ml). In the 143 patients with thyroid abnormalities the volume was 28±17.5 ml (median 23 ml, range 4-137 ml), while in the 51 patients without thyroid abnormalities it was 10.8±3.6 ml (median 10 ml, range 5-18 ml; $p<0.0001$). Thyroid volume was correlated with the estimated duration of acromegaly (r=0.7, $p<0.0001$) (Fig. 2) but not with the age of patients (r=0.2). Serum GH levels were 25.3±29.1 ng/ml (range 0.8-185 ng/ml) and IGF-I 752±349 ng/ml (range 328-1999 ng/ml), with no correlation between either parameter and thyroid volume. In control subjects the thyroid volume was 13.9±12.8 ml (median 9 ml, range 4-87 ml), significantly smaller ($p<0.0001$) than that of acromegalic patients. In the 41 patients with thyroid disorders the mean volume was 24.3±20 ml (median 20 ml, range 4-87 ml), while in the 109 patients without thyroid disorders

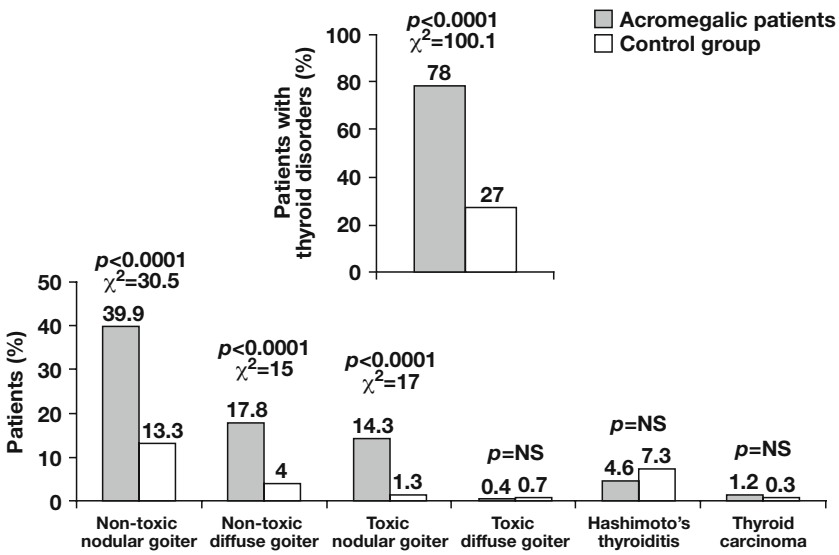

Fig. 1 - *Prevalence of thyroid diseases in 258 acromegalic patients and in the control group (106 PRL-secreting pituitary adenomas and 44 non-functioning pituitary adenomas).*

it was 10±4.6 ml (median 9 ml, range 4-18 ml; $p<0.0001$).
Serum thyroid hormones levels in 222 acromegalic patients untreated for thyroid disorders were 11.5±5 pg/ml (range 5-60 pg/ml) for FT_4 and 3.4±1.4 pg/ml (range 1.2-15 pg/ml) for FT_3. Serum TSH averaged 1.1±1 mU/l (range 0-9 mU/l); no correlation was found with the estimated duration of acromegaly (FT_4: r=0.2; FT_3: r=0.2; TSH: r=0.02). TSH was not correlated with thyroid volume as well. TGAb and TPOAb were positive in 21 and 23% of patients, respectively. Serum thyroid hormones levels in 150 control subjects were 10.3±3 pg/ml (range 2-20.1 pg/ml) for FT_4 and 3.2±0.8 pg/ml (range 1.7-6.6 pg/ml) for FT_3. Serum TSH averaged 1.3±1 mU/l (range 0-9mU/l). TGAb and TPO Ab were positive in 26 and 21% of controls, respectively.
In 62 patients 101 FNA of thyroid cold nodules were performed: 56 were benign nodules, 30 cysts, 7 suspicious nodules (belonging to 7 different patients), while the procedures were not diagnostic in 8 cases. Of the 7 suspicious samples, 2 showed microfollicular architecture, 2 contained Hurthle cells, 2 had cellular abnormalities and one was suggestive for thyroid carcinoma. Estimated duration of disease in these 7 patients was highly variable, ranging from 48 to 300 months. All the patients with a suspicious nodule underwent thyroid surgery. In 3 patients diagnosis of papillary thyroid carcinoma (PTC) was confirmed (estimated duration of disease was 48, 120 and 300 months), while in 4 micromacrofollicular goiter was diagnosed. Thus, 3 out of 93 nodules with diagnostic results (3.2%) were found to be PTC. In the control group 21 FNA were performed in 14 patients: in 1 case there was a suspicion of PTC that was confirmed at surgery, while in the remaining 20, 12 were benign, 4 cysts and 4 not diagnostic.

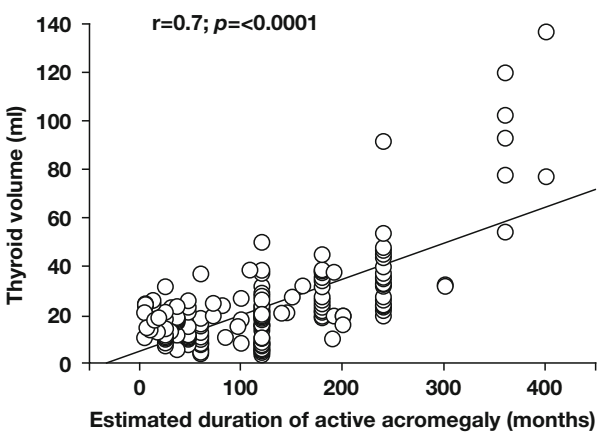

Fig. 2 - *Correlation between thyroid volume and estimated duration of disease in a large group of acromegalic patients studied in 9 centers throughout Italy.*

DISCUSSION

The occurrence of goiter in acromegaly has long been recognized (1-3). Differences in the reported prevalence (ranging from 25 to 92%) may be related to variations in the definition and assessment of thyroid disorders (1-8). The apparent increased prevalence recently observed can be attributed to the use of highly sensitive thyroid ultrasonography. Cheung and Boyages (6) detected thyroid enlargement by ultrasound in 92% of 37 acromegalic patients, with higher prevalence of nodular disease in acromegaly of long duration. They also reported that patients adequately treated for acromegaly (normal serum IGF-I levels) tended to have smaller thyroid glands than those with active acromegaly, suggesting that goiter may partially be reversible with the control of GH/IGF-I excess (6). Our study in a large population of active acromegalic patients confirms the high prevalence (78%) of various thyroid disorders, much higher than in a control population consisting of patients affected by non-secreting and PRL-secreting adenoma. This difference was of particular relevance considering that: 1) in the control group the female/male ratio was higher than in acromegalic patients; and 2) the prevalence of thyroid disorders is usually much higher in females.
Goiter was by far the most frequent disorder, being present with its different expression (non-toxic *vs* toxic) in 91% of acromegalic patients with thyroid abnormalities. The observed prevalence was significantly higher than that found in the control population consisting of patients affected by PRL-secreting and non-functioning pituitary adenomas (27%). In our study, patients with thyroid disorders tended to be older, confirming what was observed in a recent survey carried out in a Southern Italian village located in a iodine-deficient area which had never been submitted to a iodine prophylaxis program. The study demonstrated that the prevalence of goiter progressively increased with age, being 16% in children and 60% in adults (9). In our acromegalic patients no influence of gender could be demonstrated in the development of thyroid disorders, at variance with the observation of a higher prevalence of goiter in women, at least in iodine-sufficient areas (16).
The mechanisms underlying the development of goiter are not completely understood. It is well

known that IGF-I potentiates the TSH-induced thyroid cellular growth in different cells systems *in vitro*, such as FRTL-5 cells (17) or human normal thyroid cells (18). In addition, the mitotic response of the thyroid gland to TSH is lost in rats after hypophysectomy, but can at least partially be restored by the administration of pituitary extracts (19). On the other hand, the crucial role of TSH is demonstrated by the inability of GH treatment to induce any change in thyroid volume in GH and TSH-deficient patients (20).

It has recently been demonstrated that TSH can induce the expression of IGF-I mRNA in porcine thyroid follicles (21). Moreover, TSH induces a decrease in serum concentrations of different IGF-I binding proteins (22), thus probably raising the availability of free IGF-I (23). Then, it would appear that both TSH and IGF-I might be part of a complex network of signals contributing to modulate and control thyroid cell growth and function (24).

At variance with some of the data from the literature (2, 6), but in accordance with others (5), data regarding thyroid volume (estimated by ultrasound) did not correlate with either serum GH or IGF-I levels. These parameters, however, reflect the metabolic situation at the time of sampling, but do not reflect the disease history of the patient. Thus, it is not surprising that, while no correlation was found between these parameters and thyroid volume, a positive correlation was demonstrated between thyroid volume and the estimated duration of disease. At variance with Cheung and Boyages (6) and Miyakawa *et al*. (2), we did not find any correlation between thyroid volume and TSH, making it unlikely that long-standing thyroid hyperstimulation might result in thyroid autonomy, as suggested by Cheung and Boyages. Our patients affected by toxic goiter were not older nor had a longer duration of acromegaly. Mutations in the TSH receptor or in the Gs protein (Gsp)-α subunit have recently been detected, leading to constitutive activation of the TSH receptor-dependent adenylate cyclase cascade, at least in a subset of toxic thyroid adenomas and hyperfunctioning goiter nodules (25, 26). About 40% of acromegalic patients are bearing Gsp positive pituitary adenomas (27); it would be of interest to investigate the distribution of Gsp-mutation among pituitary adenomas and thyroid nodules, and it seems reasonable to postulate their involvement in the genesis of functional autonomy.

Positive thyroid autoantibody tests were found in approximately 20% of our series of acromegalic patients. This figure is similar to what reported in the adult population of iodine-deficient areas. Six percent of acromegalic patients and 11% of controls (mainly females) had biochemical, clinical and echographic signs of HT. Like in iodine-deficient areas (9, 28, 29), also in acromegaly an increased presentation of thyroid antigens to the immune system may be a key factor in the activation of humoral and cell-mediated immune reactions.

Three of 145 acromegalic patients with thyroid nodules had thyroid cancer (2%). This figure is in agreement with the expected prevalence of thyroid cancer in nodule-bearing non-acromegalic patients (30) and similar to that found in control subjects, but is somewhat higher if we consider the limited proportion (43%) submitted to fine-needle thyroid biopsy. On the other hand, the association between acromegaly and neoplasia of various organs has widely been recognized (31-34) and many experimental data lend support to a possible tumorigenic action of GH/IGF-I on thyroid cells: IGF-I receptors were found to be present in neoplastic human thyroid tissues (35).

In conclusion, this multi-center study carried out in a large series of acromegalic patients confirmed the increased prevalence of thyroid disorders, particularly in non-toxic goiter. Thyroid volume, as evaluated by ultrasound, is not correlated to circulating levels of GH and/or IGF-I, but shows a good correlation with estimated duration of disease. Attention should be paid in the diagnosis and follow-up of thyroid abnormalities in acromegalic patients, particularly concerning thyroid nodules for the probability to find a thyroid carcinoma.

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