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Thyroid nodule size, not nodule presence, follows IGF-I in acromegaly

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Research Article

Keywords: acromegaly, thyroid nodule, insulin-like growth factor I, ultrasonography, thyroid neoplasms, pituitary adenoma

Posted Date: November 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11738311/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

To compare thyroid nodular disease in acromegaly with community controls and to test whether nodule size tracks insulin-like growth factor I (IGF-I) within patients.

Methods

Retrospective multicenter cohort study with community controls. We compared 216 patients with acromegaly (median follow-up, 10 years) with 240 volunteers from a thyroid screening in the same area, using Firth logistic regression adjusted for age and sex. Hybrid within–between mixed models estimated within-patient associations of IGF-I with dominant-nodule diameter (148 patients, 346 paired observations).

Results

At diagnosis, nodules were present in 79% of patients and 27% of controls (adjusted odds ratio [OR], 10.7; 95% CI, 6.0–18.9). Nodular disease was more frequent with microadenomas than macroadenomas (94% vs 74%; adjusted OR, 3.8; 95% CI, 1.2–12.3), despite lower growth hormone and similar IGF-I at diagnosis. Within patients, each doubling of IGF-I was associated with a 6.9% larger nodule diameter (95% CI, 2.2%–11.9%), robust in sensitivity analyses, whereas nodule presence was unrelated to IGF-I (OR, 0.72; 95% CI, 0.29–1.77). Thyroid carcinoma occurred in 3 patients (1.4%), all in EU-TIRADS 2 or 3 nodules.

Conclusion

Nodular disease is nearly 3 times as prevalent in acromegaly as in the community from the same area and more frequent with microadenomas, consistent with a role for the duration of untreated disease. Nodule size tracks IGF-I within each patient, whereas nodule presence does not regress. Thyroid carcinoma was rare and occurred in low-risk nodules. These findings support standard risk-stratified nodule management, with size changes interpreted in light of IGF-I control.

Introduction

Acromegaly exposes all tissues to a chronic excess of growth hormone (GH) and insulin-like growth factor I (IGF-I), and nodular thyroid disease is its most frequent structural comorbidity. A meta-analysis estimated a pooled prevalence of 59%, and its update a pooled odds ratio (OR) of 3.1 compared with controls [1, 2]. In the Italian multicenter survey, 78% of patients had a thyroid disorder [3]. The risk of thyroid carcinoma is also increased, but estimates range from an incidence rate ratio of 3.7 in a

nationwide Danish cohort to a standardized incidence ratio of 46 in a single-center series [4–6]. This spread largely reflects study design and surveillance intensity [7].

IGF-I supports thyrocyte proliferation and enhances the trophic action of thyrotropin (TSH) [8]. Accordingly, thyroid volume decreases after IGF-I normalization [9]. The link between hormone excess and nodules is less consistent. Nodular disease or nodule growth has been associated with IGF-I or disease activity in some studies [10–14], whereas thyroid volume correlated with the estimated disease duration rather than with GH or IGF-I in others [3, 9, 15]. Most studies were cross-sectional or compared 2 time points. Comparisons between patients are confounded by age, iodine intake, genetic background, and the unmeasured exposure before diagnosis. Repeated measurements within the same patient allow these stable factors to be removed by design [16]. To our knowledge, this approach has not been applied to thyroid nodules in acromegaly.

Comparisons with controls from the same geographic area are also scarce [15]. Meanwhile, the debate on thyroid surveillance remains open [17], and recent series reached opposite conclusions on dedicated ultrasound screening [6, 18, 19].

In a cohort from 2 Italian referral centers with a median follow-up of 10 years (maximum, 51 years) and a community control group from the same geographic area, we aimed (1) to compare nodule prevalence with controls, (2) to explore its determinants, including adenoma size, (3) to test whether nodule size tracks IGF-I within patients, and (4) to describe cytological and histological outcomes.

Materials and Methods

Study design and participants

This retrospective multicenter cohort study included all patients with acromegaly followed at 2 Italian referral centers, the Endocrinology Unit of the University Hospital S. Maria della Misericordia of Udine and the Endocrinology Unit of the University Hospital of Padua. Acromegaly was diagnosed according to the criteria in use at the time [20, 21]. Data were extracted from medical records into a structured database. We recorded demographics, family history of goiter and thyroid cancer, smoking, basal GH, nadir GH after an oral glucose tolerance test, IGF-I, prolactin, adenoma size, extrasellar extension, and treatments. Adenomas were classified as microadenomas (< 10 mm) or macroadenomas (≥ 10 mm). Thyroid ultrasonography, thyroid function, fine-needle aspiration (FNA) cytology, and histology were collected at diagnosis, at 12, 24, 36, 48, 60, and 72 months, and at the last visit. The study followed the STROBE statement [22].

Control group

The control group comprised volunteers without acromegaly recruited through a voluntary thyroid screening campaign, who underwent thyroid ultrasonography during the “Giornate della Tiroide” (Thyroid

Days) held in Padua, Italy, in 2024. Because controls and patients came from the same geographic area of northeastern Italy, iodine intake was considered comparable. Age, sex, presence of nodules, and diameter of the largest nodule were available. Of 278 records, 38 were exact duplicates and were removed, leaving 240 individuals. Comparisons were restricted to participants aged 18–80 years to ensure overlapping age distributions (232 controls).

Thyroid assessment

In patients and controls, ultrasonography was performed by endocrinologists with extensive experience in thyroid ultrasonography. The dominant nodule was the nodule with the largest diameter, and multinodularity was defined as 2 or more nodules. Nodules were classified according to EU-TIRADS [23]. Cytology was reported according to the Italian consensus classification (TIR 1–5) [24].

Biochemistry and disease status

IGF-I was expressed as a multiple of the age- and sex-specific upper limit of normal (×ULN) to account for assay changes over time. At each visit, disease status was classified as remission (normal IGF-I without medical therapy), biochemical control (normal IGF-I on medical therapy), or active disease (elevated IGF-I) [21].

Statistical analysis

Continuous variables are reported as median (interquartile range [IQR]) and categorical variables as number (percentage). Hormone concentrations were $\log_2$-transformed, so that estimates refer to a doubling. No continuous exposure was dichotomized. Effect estimates are given with 95% CIs. Multiplicity across univariable tests was controlled with the Benjamini–Hochberg false discovery rate (q values).

Comparison with controls. The presence of nodules at the ultrasonography performed at diagnosis was compared with controls using Firth penalized logistic regression [25], adjusted for sex and age (natural cubic spline). Standardized prevalences were obtained by g-computation, with 2000 bootstrap resamples. Effect modification by age was tested with a likelihood ratio test. Sensitivity analyses used a 1:2 match on sex and age (± 3 years) with conditional logistic regression and the last available ultrasonography of each patient with attained age. A 3-level model compared microadenomas and macroadenomas with controls.

Determinants within acromegaly. The outcome was nodular disease at any time during follow-up. Univariable associations were estimated with Firth regression. The multivariable model was specified a priori (age, sex, IGF-I at diagnosis, follow-up duration), with 42 nonevents for 4 parameters (events per variable > 10) [26]. Missing covariates were handled by multiple imputation with chained equations (50 data sets, Rubin rules) [27]. Discrimination was corrected for optimism with 500 bootstrap resamples.

The association with adenoma size was not part of the initial plan and is reported as hypothesis-generating. It was adjusted for age and sex, repeated after multiple imputation of adenoma size, and assessed for unmeasured confounding with the E-value [28].

Within-patient analysis. The $\log_2$ diameter of the dominant nodule was modeled with a linear mixed model with patient-level random intercepts and slopes for time. IGF-I ($\log_2$ ×ULN) was split into the patient mean (between-patient component) and the deviation of each visit from that mean (within-patient component) [16]. The within-patient component compares each patient with himself or herself and removes all time-invariant confounders. Models were adjusted for time since diagnosis, age at diagnosis, and sex. Estimates are expressed as percentage change in diameter per doubling of IGF-I, 100 × (2^β − 1). Sensitivity analyses used IGF-I at the previous visit, cumulative time-weighted IGF-I up to each visit, adjustment for TSH in euthyroid visits without thyroid treatment, exclusion of thyroidectomized patients, nodules of 5 mm or larger, patients with 3 or more observations, scheduled visits only, a spline for time, a fixed-effects estimator with cluster-robust SEs, a first-difference model, a cluster bootstrap (500 resamples), and leave-one-patient-out refits. Because level-1 residuals were not normally distributed (Shapiro–Wilk test), bootstrap intervals were used to confirm inference. Analogous models assessed time-varying disease activity and, with a logistic mixed model, nodule presence.

Analyses were performed with R version 4 and Python version 3. Two-sided $P < .05$ was considered significant.

Use of AI-assisted technologies

During the preparation of this manuscript, the authors used Claude Opus 5.5 (Anthropic, San Francisco, CA, USA) for language editing. The Authors reviewed and edited all output and take full responsibility for the content of the publication.

Results

Cohort characteristics

We included 216 patients (127 women [59%]; median age at diagnosis, 50 years [IQR, 38–59]). Median follow-up was 10 years (IQR, 4–18; maximum, 51), for 2470 person-years of observation (Table 1A; Online Resource 1, Fig. S1). IGF-I decreased from a median of 2.56 ×ULN (IQR, 1.78–3.56) at diagnosis to 0.74 ×ULN (IQR, 0.52–0.98) at the last visit (Online Resource 1, Fig. S2). At the last visit, IGF-I was normal in 145 of the 188 patients with an available value (77%); of the 207 patients with a recorded disease status, 69 (33%) were in remission, 93 (45%) were controlled on medical therapy, and 45 (22%) had active disease.

Nodule prevalence compared with controls

Among patients aged 18 to 80 years with ultrasonography at diagnosis, 93 of 117 (79%) had nodules, compared with 62 of 232 controls (27%) (Table 1B). After adjustment for age and sex, the OR was 10.7 (95% CI, 6.0–18.9; *P* < .001). Standardized prevalences were 77% (95% CI, 69%–85%) and 27% (95% CI, 22%–33%), a difference of 50 percentage points (95% CI, 40–59). The excess did not vary with age (*P* for interaction = .82): patients younger than 35 years already had a higher prevalence (9 of 14 [64%]) than controls aged 65 years or older (12 of 37 [32%]) (Fig. 1a). Results were similar in the matched analysis (87 patients, 169 controls; OR, 8.8; 95% CI, 4.5–17.3) and at the last ultrasonography (78%; adjusted OR, 8.8; 95% CI, 5.4–14.4). Among participants with nodules, the dominant nodule was 59% larger in patients with acromegaly (95% CI, 29%–96%; median, 13 vs 9 mm).

Determinants of nodular disease and adenoma size

During follow-up, 174 of 216 patients (81%) had nodular disease, which was multinodular in 138 (79%). Age was the only factor surviving correction for multiplicity (OR, 1.6 per decade; 95% CI, 1.2–2.1; q = .02) (Table 2). IGF-I and GH at diagnosis were not associated with nodular disease. In the multivariable model, age remained independently associated (OR, 1.5; 95% CI, 1.1–2.0), whereas IGF-I at diagnosis was not (OR per doubling, 1.1; 95% CI, 0.6–2.1). The optimism-corrected C statistic was 0.64.

Table 1
Characteristics of the patients with acromegaly and comparison with community controls *A. Patients with acromegaly (N = 216)*

Characteristic	Value	Patients with data, No.
Female sex, No. (%)	127 (59)	216
Age at diagnosis, median (IQR), y	50 (38–59)	209
BMI, median (IQR), kg/m²	27.0 (24.0–29.0)	93
Family history of goiter, No. (%)	23 (18)	127
Family history of thyroid cancer, No. (%)	4 (3)	128
Current or former smoker, No. (%)	57 (42)	137
Basal GH at diagnosis, median (IQR), μg/L	6.8 (4.0–20.0)	157
IGF-I at diagnosis, median (IQR), ×ULN	2.56 (1.78–3.56)	146
Prolactin at diagnosis, median (IQR), ×ULN	0.60 (0.34–0.96)	106
Macroadenoma, No. (%)	116 (70)	165
Adenoma maximal diameter, median (IQR), mm	14 (10–20)	100
Extrasellar extension, No. (%)	32 (33)	98
Transsphenoidal surgery, No. (%)	155 (75)	207
Radiosurgery, No. (%)	42 (21)	196
First-generation SRL, ever, No. (%)	165 (83)	199
Pasireotide, ever, No. (%)	16 (8)	199
Pegvisomant, ever, No. (%)	39 (20)	198
Cabergoline, ever, No. (%)	49 (24)	200
TSH at diagnosis, median (IQR), mU/L	1.18 (0.87–1.73)	127
Follow-up, median (IQR), y	10 (4–18)	208
Ultrasonographic follow-up, median (IQR), y	9 (3–17)	210
Time-weighted IGF-I during follow-up, median (IQR), ×ULN	1.22 (0.94–1.62)	153
B. Cross-sectional comparison with community controls (participants aged 18–80 years)		

Characteristic	Value	Patients with data, No.
IGF-I at last visit, median (IQR), ×ULN	0.74 (0.52–0.98)	188
Status at last visit: remission / controlled on therapy / active, No.	69 / 93 / 45	207
Nodular disease during follow-up, No. (%)	174 (81)	216
Multinodular disease among patients with nodules, No. (%)	138 (79)	174
B. Cross-sectional comparison with community controls (participants aged 18–80 years)		

Table 2
Determinants of nodular disease during follow-up in patients with acromegaly

Variable	Patients (events), No.	OR (95% CI)	*P*	q
Univariable analyses				
Age at diagnosis, per 10 y	209 (169)	1.6 (1.2–2.1)	< .001	.02
Female sex	216 (174)	2.0 (1.00–3.9)	.05	.20
BMI, per 5 kg/m²	93 (78)	1.4 (0.75–2.8)	.27	.52
Family history of goiter	127 (99)	0.97 (0.33–2.8)	.96	.96
Current or former smoker	137 (110)	1.2 (0.53–2.9)	.61	.77
IGF-I at diagnosis, per doubling of ×ULN	146 (120)	1.3 (0.67–2.4)	.47	.63
Basal GH at diagnosis, per doubling	157 (129)	0.85 (0.70–1.0)	.12	.30
Prolactin at diagnosis, per doubling of ×ULN	106 (87)	0.91 (0.72–1.1)	.41	.58
Microadenoma (vs macroadenoma)	165 (132)	4.7 (1.4–15.1)	.010	.10
Adenoma diameter, per 10 mm	100 (79)	0.53 (0.31–0.90)	.02	.13
Extrasellar extension	98 (76)	1.8 (0.60–5.2)	.30	.52
TSH at diagnosis, per doubling	127 (104)	0.61 (0.34–1.1)	.11	.30
Transsphenoidal surgery	207 (167)	0.86 (0.38–1.9)	.72	.85
Radiosurgery	196 (158)	1.5 (0.59–3.8)	.40	.58
First-generation SRL, ever	199 (160)	2.4 (1.0–5.4)	.04	.20

Abbreviations: OR, odds ratio; SRL, somatostatin receptor ligand; ×ULN, multiple of the upper limit of the reference range. All models used Firth-penalized logistic regression. q values are Benjamini–Hochberg false discovery rates across the 20 univariable tests. The multivariable model was specified a priori (42 nonevents for 4 variables) and fitted on 50 imputed data sets combined with Rubin rules; apparent C statistic, 0.69; optimism-corrected C statistic (500 bootstrap resamples), 0.64. The E-value for the age- and sex-adjusted OR of microadenoma was 3.3 (1.4 for the CI limit).

Variable	Patients (events), No.	OR (95% CI)	*P*	q
Pegvisomant, ever	198 (160)	1.7 (0.62–4.5)	.31	.52
Pasireotide, ever	199 (160)	0.95 (0.27–3.4)	.94	.96
Cabergoline, ever	200 (162)	0.55 (0.25–1.2)	.12	.30
Follow-up duration, per 5 y	208 (168)	0.92 (0.77–1.1)	.31	.52
Time-weighted IGF-I during follow-up, per doubling of ×ULN	153 (131)	1.0 (0.51–2.1)	.94	.96
Multivariable model (multiple imputation; 216 patients, 174 events)				
Age at diagnosis, per 10 y	—	1.5 (1.1–2.0)	.004	—
Female sex	—	1.6 (0.79–3.3)	.19	—
IGF-I at diagnosis, per doubling of ×ULN	—	1.1 (0.59–2.1)	.76	—
Follow-up duration, per 5 y	—	0.97 (0.82–1.2)	.73	—
Microadenoma vs macroadenoma: adjusted models				
Adjusted for age and sex	163	3.8 (1.2–12.3)	.03	—
Adjusted for age, sex, and follow-up duration	163	4.0 (1.2–13.0)	.02	—
Adjusted for age and sex, multiple imputation	216	4.2 (1.3–13.6)	.02	—
Adjusted for age, sex, and IGF-I at diagnosis	132	4.3 (1.1–17.3)	.04	—
Adjusted for age, sex, and GH at diagnosis	137	3.6 (0.90–14.4)	.07	—

Abbreviations: OR, odds ratio; SRL, somatostatin receptor ligand; ×ULN, multiple of the upper limit of the reference range. All models used Firth-penalized logistic regression. q values are Benjamini–Hochberg false discovery rates across the 20 univariable tests. The multivariable model was specified a priori (42 nonevents for 4 variables) and fitted on 50 imputed data sets combined with Rubin rules; apparent C statistic, 0.69; optimism-corrected C statistic (500 bootstrap resamples), 0.64. The E-value for the age- and sex-adjusted OR of microadenoma was 3.3 (1.4 for the CI limit).

Variable	Patients (events), No.	OR (95% CI)	*P*	q
Nodules at diagnosis, adjusted for age and sex	103	3.0 (0.85–10.5)	.09	—

Abbreviations: OR, odds ratio; SRL, somatostatin receptor ligand; ×ULN, multiple of the upper limit of the reference range. All models used Firth-penalized logistic regression. q values are Benjamini–Hochberg false discovery rates across the 20 univariable tests. The multivariable model was specified a priori (42 nonevents for 4 variables) and fitted on 50 imputed data sets combined with Rubin rules; apparent C statistic, 0.69; optimism-corrected C statistic (500 bootstrap resamples), 0.64. The E-value for the age- and sex-adjusted OR of microadenoma was 3.3 (1.4 for the CI limit).

Nodular disease was present in 46 of 49 patients with microadenomas (94%) and in 86 of 116 with macroadenomas (74%). The OR for microadenomas was 3.8 (95% CI, 1.2–12.3) after adjustment for age and sex and 4.2 (95% CI, 1.3–13.6) after multiple imputation. The direction was the same at diagnosis (OR, 3.0; 95% CI, 0.85–10.5). The estimate was not explained by IGF-I at diagnosis (OR, 4.3; 95% CI, 1.1–17.3) and was partly attenuated by adjustment for GH (OR, 3.6; 95% CI, 0.90–14.4). The E-value was 3.3 (1.4 for the CI limit). Compared with patients with macroadenomas, those with microadenomas were older at diagnosis (53 vs 49 years; *P* = .02) and had lower GH (5.2 vs 11.5 µg/L; *P* = .006), similar IGF-I (2.5 vs 2.8 ×ULN; *P* = .19), and lower time-weighted IGF-I after diagnosis (1.08 vs 1.32 ×ULN; *P* = .05). Compared with controls, the adjusted OR was 18.7 (95% CI, 5.8–60.9) for microadenomas and 7.3 (95% CI, 3.9–13.8) for macroadenomas (Fig. 1b).

Nodule size tracks IGF-I within patients

The longitudinal analysis included 346 paired measurements of nodule diameter and IGF-I in 148 patients. Eighty-two patients had 2 or more measurements, spanning a median of 6 years (IQR, 2–9). Each doubling of IGF-I above the patient's own mean was associated with a 6.9% larger dominant nodule (95% CI, 2.2%–11.9%; *P* = .004) (Table 3, Fig. 2a). This corresponds to an expected reduction of 8.7% in diameter (95% CI, 2.9%–14.1%), or approximately 24% in volume, when IGF-I falls from 2.56 to 1.0 ×ULN. The estimate was stable in all sensitivity analyses (Fig. 2b and Online Resource 1, Table S1). These included IGF-I at the previous visit (8.1%; 95% CI, 2.3%–14.3%), cumulative exposure (32.3% per doubling of time-weighted IGF-I; 95% CI, 12.5%–55.5%), adjustment for TSH (6.6%; 95% CI, 1.7%–11.6%), the fixed-effects estimator (8.6%; 95% CI, 1.4%–16.2%), and the cluster bootstrap (95% CI, 0.9%–13.9%). Leave-one-patient-out estimates ranged from 5.5% to 7.9%. TSH itself was not associated with nodule size. Periods of active disease were associated with a 13.2% larger diameter within the same patient (95% CI, 1.8%–26.0%). Treatment with somatostatin receptor ligands or pegvisomant added no information beyond IGF-I. In contrast, IGF-I was not associated with the presence of nodules within patients (OR per doubling, 0.72; 95% CI, 0.29–1.77), and nodules disappeared in only 9 of 70 patients (13%). Across patients at diagnosis, nodule diameter and IGF-I were not correlated (Spearman ρ = 0.08; *P* = .47), and the change between the first and last ultrasonography was not associated with IGF-I exposure (Online Resource 1, Fig. S3).

Table 3
Within-patient and between-patient associations of IGF-I and disease activity with the diameter and presence of thyroid nodules

Term	Estimate (95% CI)	*P*
A. Diameter of the dominant nodule (148 patients, 346 observations); % change		
IGF-I, within-patient deviation, per doubling	6.9 (2.2 to 11.9)	.004
IGF-I, patient mean, per doubling	25.1 (8.6 to 44.1)	.002
Time since diagnosis, per year	1.0 (− 0.1 to 2.2)	.08
Age at diagnosis, per 10 y	8.4 (0.0 to 17.5)	.05
Female sex	14.5 (− 7.6 to 42.0)	.22
B. Diameter of the dominant nodule by disease status (135 patients, 286 observations); % change		
Active disease, within-patient deviation	13.2 (1.8 to 26.0)	.02
Proportion of visits with active disease, patient mean (0 to 1)	45.8 (9.2 to 94.7)	.01
Time since diagnosis, per year	0.1 (− 0.9 to 1.2)	.79
Age at diagnosis, per 10 y	7.1 (− 1.8 to 16.8)	.12
Female sex	32.5 (6.5 to 64.9)	.01
C. Presence of nodules (192 patients, 469 observations); OR		
IGF-I, within-patient deviation, per doubling	0.72 (0.29 to 1.77)	.47
IGF-I, patient mean, per doubling	0.70 (0.13 to 3.83)	.68

Abbreviations: OR, odds ratio. Models A and B are linear mixed models of the $\log_2$-transformed diameter with a random intercept and a random slope for time (restricted maximum likelihood); coefficients are back-transformed to percentage change in diameter, 100 × (2^β − 1). IGF-I was expressed as $\log_2$ ×ULN and decomposed into the patient mean (between-patient effect) and the deviation of each visit from that mean (within-patient effect). Active disease was compared with remission or biochemical control. Model C is a logistic mixed model with a random intercept, adjusted for time, age, and sex. Intraclass correlation of nodule diameter, 0.84; residual SD of model A, 0.34 $\log_2$ units.

Cytology, histology, and thyroid carcinoma

The highest EU-TIRADS class was 2 in 58%, 3 in 20%, 4 in 21%, and 5 in 1 patient (0.7%). Sixty-five patients (30%) underwent 98 FNA procedures. Of the 61 procedures with complete data, 15 (25%) met EU-TIRADS size criteria and 24 (39%) targeted EU-TIRADS 2 nodules (Online Resource 1, Table S2 and Fig. S4). Cytology was nondiagnostic in 17 of 83 reports (20%) and indeterminate in 7 (8%). Six patients underwent thyroidectomy. Thyroid carcinoma was diagnosed in 3 patients (1.4%; 95% CI, 0.5%–4.0%), corresponding to 127 cases per 100 000 person-years of ultrasonographic follow-up (95% CI, 26–372).

All were women with multinodular goiter, and the highest EU-TIRADS class was 2, 3, and 2, respectively. No carcinoma arose in an EU-TIRADS 4 or 5 nodule.

Discussion

This study adds 3 findings to the knowledge of thyroid nodules in acromegaly. First, nodule size follows IGF-I within the individual patient, whereas nodule presence does not. Second, patients with microadenomas carry more nodular disease than patients with macroadenomas. Third, nodules were nearly 3 times as prevalent as in a community control group from the same area, whereas thyroid carcinoma was rare and occurred in nodules at low sonographic risk.

The within-patient association is, to our knowledge, new. Each patient served as his or her own control, which removes stable confounders such as genetic background, iodine intake, and the exposure accumulated before diagnosis [16]. The estimate was consistent across lagged and cumulative exposures, which supports temporality and a dose–response relationship. It did not depend on TSH, in keeping with experimental evidence that IGF-I acts on thyrocytes alongside TSH [8]. The same analysis explains why published studies disagree. Cross-sectional comparisons and the classification of change between 2 examinations did not detect the association in our data, as in several earlier series [3, 12], whereas studies of volume change after treatment did [9, 11]. The intraclass correlation of 0.84 indicates that most variation in nodule size lies between patients, which masks the smaller within-patient signal.

The magnitude of the effect has practical consequences. Normalization of IGF-I is expected to reduce the diameter of the dominant nodule by about 9%, which is close to the interobserver variability of ultrasonography [29]. Therefore, shrinkage should not be expected as evidence of control. Conversely, growth that meets standard criteria during biochemical control is not explained by acromegaly and should be assessed as in the general population [23, 30]. Nodule presence did not respond to IGF-I within patients, and nodules rarely disappeared. These observations fit a 2-component model: a structural burden established before diagnosis and a size component that tracks the current hormonal milieu. Other growth factors may contribute to the structural burden. Insulin resistance is common at the diagnosis of acromegaly and improves with biochemical control [31]. Insulin can stimulate thyrocyte proliferation through the insulin and IGF-I receptors, insulin resistance has been associated with thyroid nodules in the general population, and metformin modestly reduced nodule size in insulin-resistant patients [32, 33]. Glucose metabolism was not recorded in our database, so this hypothesis could not be tested. Because the structural burden appears to accumulate before treatment, our findings also add the thyroid to the arguments for early diagnosis and prompt biochemical control emphasized by recent consensus recommendations [31].

The excess of nodular disease in microadenomas is counterintuitive and was not part of our initial plan. Microadenomas were associated with older age and lower GH at diagnosis, similar IGF-I, and lower IGF-I exposure after diagnosis. A greater post-diagnostic exposure therefore cannot explain the finding. We hypothesize that the milder clinical and biochemical phenotype of microadenomas delays diagnosis and

prolongs the exposure to GH excess before treatment. This interpretation is consistent with the inverse relationship between tumor size, age, and GH in the Liège Acromegaly Survey [34], with longer diagnostic delays reported for smaller somatotroph tumors [35], and with the association between thyroid volume and estimated disease duration [3, 9, 15]. A longer diagnostic delay has also been linked to cancer in acromegaly [36]. Partial attenuation after adjustment for GH supports a role of disease severity. Our database did not record symptom onset, so the hypothesis requires testing in cohorts with documented diagnostic delay. The E-value of 3.3 indicates that only a strong unmeasured confounder could fully explain the association.

The prevalence of nodules in our patients agrees with meta-analytic estimates [1, 2], and the adjusted OR of 10.7 over controls is larger than in most case-control studies [1, 2]. The community control group was recruited from the same area and was likely enriched for people concerned about their thyroid, which would bias our estimate toward the null. Its prevalence of 27% is lower than that reported with high-frequency probes in general populations [37], which suggests differences in the selected population. Importantly, the excess was already evident in young patients. The prevalence in patients younger than 35 years exceeded that of controls older than 65 years, which suggests that acromegaly anticipates thyroid nodular aging by decades.

Thyroid carcinoma occurred in 1.4% of our patients. This proportion is similar to that of the Italian multicenter and Spanish studies [3, 38] and lower than in many tertiary series [6, 18, 39], although one prospective series found no carcinoma [40]. Nationwide cohorts confirm an increased relative risk of thyroid cancer [4, 5, 41], although the Swedish registry recorded only 3 thyroid cancers in 1296 patients [42]. The variation across designs points to surveillance intensity and selection [7, 43]. In our cohort, all carcinomas arose in EU-TIRADS 2 or 3 nodules within multinodular goiters and were diagnosed at thyroidectomy, and three-quarters of FNAs did not meet EU-TIRADS criteria. Because patients with acromegaly routinely undergo thyroid ultrasonography at diagnosis and during follow-up, they are also exposed to the overdiagnosis of small papillary carcinomas of limited clinical relevance, which accounts for much of the recent increase in thyroid cancer incidence [43, 44]. Together with the size findings, these data support standard risk-stratified management of nodules in acromegaly rather than intensified acromegaly-specific screening, in line with recent proposals [18, 19].

To our knowledge, this is one of the largest European series with thyroid ultrasonography in acromegaly and the first with serial ultrasonography paired with IGF-I measurements over up to 19 years. Larger European cohorts were cross-sectional surveys or cancer registries without serial ultrasonography [3, 5, 34, 42]. Other strengths include a control group from the same area and a statistical approach that addresses confounding, missing data, and small numbers of events.

The study has limitations. It was retrospective, and missing data were frequent, particularly for patients diagnosed in earlier decades. We used multiple imputation under a missing-at-random assumption and report the number of patients in each analysis. The control group had limited information (age, sex, and nodules), with no data on thyroid function or thyroid autoimmunity, and its composition may differ from

that of the general population. Patients were examined at 2 centers over several decades, whereas controls were examined during a single screening campaign in 2024. Differences in ultrasonographic technique cannot be excluded, but older equipment would, if anything, have reduced nodule detection in patients, and within-patient estimates are unaffected by stable differences between centers. Nodules were measured as the diameter of the dominant nodule rather than volume, and the dominant nodule may change between examinations. IGF-I assays changed over time; expressing IGF-I as ×ULN reduces but does not eliminate this heterogeneity. The within-patient design controls stable confounders but not time-varying factors such as iodine intake or levothyroxine therapy, although adjustment for TSH did not change the estimate. Histological details of the carcinomas were not available, and the small number of cancers precludes the analysis of predictors.

In conclusion, nodular disease is nearly 3 times as prevalent in acromegaly as in the community from the same area, and it is more frequent with microadenomas, consistent with a role for the duration of untreated disease. The size of nodules tracks IGF-I within each patient, whereas their presence does not regress. Thyroid carcinoma was rare and occurred in low-risk nodules. These findings support standard risk-stratified management of thyroid nodules in acromegaly, with size changes interpreted in light of IGF-I control.

Declarations

Competing interests:

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethics approval:

In accordance with the Declaration of Helsinki, this study was approved by the local Ethics Committee (PITACORA, protocol number AOP3318, Ethics Committee registration 5938-AO-24).

Consent to participate:

All patients provided informed consent.

Consent to publish:

Not applicable.

Funding:

This research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author Contribution

J.M. and L.M.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. J.M.: Project administration. G.V., A.S.S., A.B., M.C., F.G., and C.C. : Data curation. F.C. and C.M.: Resources, review & editing. F.V.: Supervision. All authors critically reviewed the manuscript and approved the final version.

Acknowledgments:

none.

Data Availability

The datasets generated and analyzed during the current study are not publicly available due to ethical and privacy restrictions but are available with restricted access from the corresponding author on reasonable request, subject to approval by the participating institutions. The R code used for the statistical analyses is available from the corresponding author on request.

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Figures

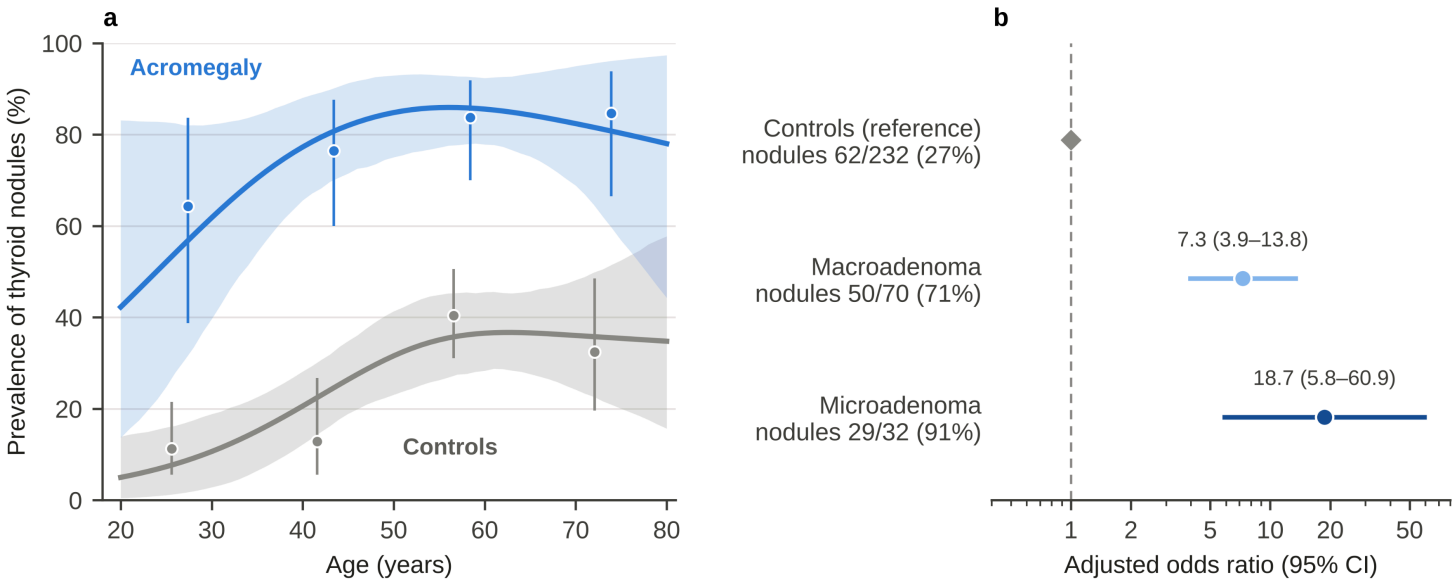

Figure 1

Prevalence of thyroid nodules in acromegaly and in community controls from the same area. (a) Age-specific prevalence estimated by logistic regression with a group-by-age interaction (natural cubic spline for age; sex standardized to the pooled proportion of women). Shaded areas indicate 95% bootstrap CIs (1000 resamples); points and bars indicate observed prevalence with Wilson 95% CIs in the age bands 18–34, 35–49, 50–64, and 65–80 years. Age is the age at diagnosis for patients and at screening for controls. (b) ORs for nodules in patients with macroadenomas and microadenomas compared with controls, adjusted for age and sex (Firth-penalized logistic regression)

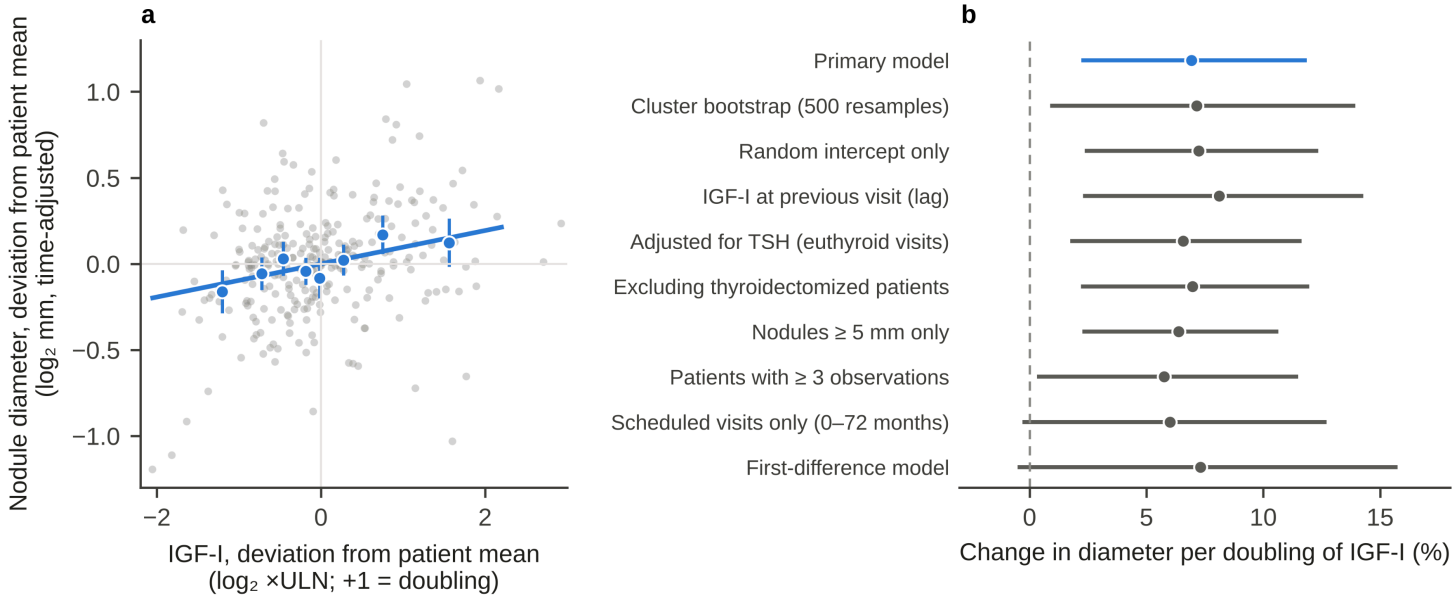

Figure 2

Nodule size tracks IGF-I within patients. (a) Deviation of the $\log_2$ diameter of the dominant nodule from the patient's own mean (adjusted for time) plotted against the deviation of $\log_2$ IGF-I (×ULN) from the patient's own mean, in the 82 patients with 2 or more paired observations. Gray dots are single observations; blue points and bars are means and 95% CIs within octiles of IGF-I deviation; the line is the within-patient slope of the hybrid mixed model. (b) Within-patient estimate (percentage change in diameter per doubling of IGF-I) in the primary model and in sensitivity analyses (Online Resource 1, Table S1)

Supplementary Files

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