

# Elevated intraocular pressure in patients with acromegaly

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## Abstract

**Purpose** To evaluate central corneal thickness (CCT) and intraocular pressure (IOP) in a cohort of acromegalic patients, and to correlate CCT with serum levels of growth hormone (GH) and insulin-like growth factor 1 (IGF-1).

**Methods** Consecutive patients affected by acromegaly underwent a comprehensive endocrinological and ophthalmological evaluation, including serum GH and IGF-1 levels, CCT measured with ultrasonic pachymetry and IOP assessed with Goldmann applanation tonometry.

**Results** Fourteen patients with acromegaly and 28 healthy controls were included in the study. Acromegalic patients had a statistically higher median CCT (570  $\mu\text{m}$  [range 551.5–638] vs 542.7  $\mu\text{m}$  [range 461.5–610];  $p < 0.01$ ) and higher median IOP (17.2 mm Hg [range 14–21] vs 13.7 mm

Hg [range 10.5–19];  $p < 0.01$ ) than healthy controls. No statistically significant correlation was found among CCT and GH, CCT and IGF-1, IOP and GH, IOP and IGF-1 in the acromegalic group, whereas a statistically significant correlation was documented between CCT and IOP in the entire cohort (Spearman's correlation coefficient: 0.56,  $p < 0.01$ ). However, when IOP was corrected for CCT no significant difference was found between the two study groups ( $p = 0.07$ ).

**Conclusions** Our results suggest that acromegaly is associated with an increased CCT, which could lead to an overestimation of IOP readings as determined with Goldmann applanation tonometry.

**Keywords** Acromegaly · Central corneal thickness · Intraocular pressure · Glaucoma · Goldmann applanation tonometry

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## Introduction

Acromegaly is a rare condition usually caused by a growth hormone (GH)-secreting pituitary adenoma. It is characterized by excessive growth of the peripheral parts of the body and the occurrence of chronic complications which may cause impairment of quality of life and increased mortality [1–4]. Frequent ocular manifestations of acromegaly include visual field defects secondary to chiasmal compression by a pituitary adenoma, as well as proptosis, restrictive extraocular myopathy with diplopia or eyelid edema, and ptosis due to orbital soft tissue involvement [5, 6].

The presence of ocular abnormalities in children with pituitary-induced GH excess or deficiency suggests that GH plays a key role in eye development and growth during childhood [7, 8]. Moreover, patients with Laron syndrome, a primary GH receptor insensitivity, who are treated with insulin-like growth factor 1 (IGF-1) tend to have ocular

dimensions that resemble the dimensions of healthy controls; on the contrary, untreated patients tend to have smaller ocular dimensions [9].

Elevated intraocular pressure (IOP) has been previously reported in patients with acromegaly [10–12]. A study by Greco and coworkers [13] showed that, after intravenous injection of arginine, patients with primary open-angle glaucoma (POAG) exhibited higher GH levels than healthy controls, thus suggesting a possible relationship between GH secretion and POAG. Further, other reports have demonstrated higher values of central corneal thickness (CCT) in acromegalic patients than in healthy subjects [12, 14, 15].

It is now widely accepted that in a structurally normal cornea, higher CCT values may lead to an overestimation of IOP. A number of studies have therefore investigated the effect of CCT on Goldmann applanation tonometry (GAT), the gold standard technique for clinical IOP assessment [16–20]. Further, there is emerging evidence that CCT might be a useful tool for identifying patients at a greater risk of glaucoma progression and more susceptible to IOP-lowering medications [21, 22].

The aim of the present study was to evaluate CCT and IOP specifically in a cohort of consecutive acromegalic patients, and to ascertain whether there is a correlation between CCT and serum levels of GH and IGF-1.

## Materials and methods

This was an observational, case–control study carried out at the Glaucoma Service of the University of Brescia, Brescia, Italy, with patients referred to the Endocrine Service of the Spedali Civili di Brescia, Brescia, Italy. The research protocol adhered to the tenets of the Declaration of Helsinki.

### Participants

Consecutive patients with a confirmed clinical diagnosis of acromegaly who were under regular clinical follow-up were enrolled. The diagnosis of acromegaly relied upon evidence of failure of serum GH suppression to concentrations below 1 ng/ml after a 75-g oral glucose load together with fasting plasma IGF-1 concentrations above the normal ranges for age [23]. Patients receiving somatostatin analogue treatment were evaluated by measurement of serum random GH and IGF-1, whereas those treated with pegvisomant were evaluated by serum IGF-1 alone [24]. Acromegaly was considered well-controlled if IGF-1 values were in the reference range for the patient's age. In patients receiving somatostatin analogues, acromegaly was considered well-controlled if random GH levels were below 1.0 ng/ml [24]. Median duration of active disease was estimated on the basis of clinical history. The

duration of uncontrolled disease during medical treatment was also recorded.

The control group included healthy subjects, matched for sex and age, recruited from routine visits to the ophthalmology outpatient service. Exclusion criteria for eye conditions were: previous diagnosis of glaucoma or ocular hypertension, Snellen best-corrected visual acuity less than 0.4, corneal or other ocular conditions making applanation tonometry unreliable, signs or history of ocular diseases, and previous ocular surgeries including cataract extraction or refractive surgery. Patients were also excluded if they were using systemic or topical steroids, or other drugs that could influence IOP levels.

### Assessments

Serum GH and IGF-1 levels were collected from the patients' clinical charts: the mean of the last three measurements was used for the analysis. GH and IGF-1 were measured with Immulite 2000 (DPC, Los Angeles, CA, USA). For IGF-1, normal ranges were 136–244 ng/ml, 107–181 ng/ml and 97–159 ng/ml for patients aged 20–39 years, 40–59 years, and 60–79 years respectively.

All participants underwent a comprehensive ophthalmological evaluation that included visual acuity, anterior segment biomicroscopy, and fundus examination. After topical anesthesia with lidocaine 4 % (Alpha Intes, Casoria, Italy), CCT was measured by means of an ultrasonic pachymeter (DGH500, DGH Technology Inc., Exton, PA, USA) and, immediately afterwards, IOP was assessed with GAT (Haag–Streit, Bern, Switzerland) after a fluorescein-containing paper strip was lightly stroked at the inferior conjunctival fornix. The mean value of five CCT measurements was calculated. Two IOP readings were acquired at 10.00 AM  $\pm$  1 h; if the two readings differed by  $>2$  mmHg, a third measurement was obtained, and the mean value of the closest two readings was used. All CCT and IOP measurements were done by the same experienced ophthalmologist (IR). Both eyes of each participant were measured, but only one randomly selected eye was analyzed.

The formula suggested by Doughty and Zaman was used for the correction of IOP based on CCT values for both groups [18]. This formula assumes a correction of 2.5 mmHg per 50  $\mu$ m of CCT deviation from 535  $\mu$ m and was derived with a meta-analysis approach from hundreds of CCT datasets published in the literature over the period from 1968 through mid-1999.

### Statistics

Categorical variables were reported as absolute and relative frequency, and differences between groups were tested by means of a Chi-square test. Continuous variables, such as CCT and IOP, were described using median, minimum and

**Table 1** Characteristics of the study population

	Acromegalic patients ( <i>n</i> =14): no. (%)	Control group ( <i>n</i> =28): no. (%)	<i>P</i> -value
Men	7 (50)	12 (42.8)	0.74 <sup>†</sup>
Women	7 (50)	16 (57.1)	
	Median (range)	Median (range)	<i>P</i> -value
Age (years)	59.0 (40–71)	58.5 (46–72)	0.48*
Duration of the disease (years)	5 (1–15)	–	–
GH (ng/ml)	0.9 (0.01–22)	–	–
IGF-1 (ng/ml)	173.5 (48–513)	–	–
IOP (mm Hg)	17.2 (14–21)	13.7 (10.5–19)	<0.01*
Corrected IOP (mm Hg) <sup>‡</sup>	14.8 (11.9–20.1)	13.9 (10.3–18.6)	0.07*
CCT (μm)	570 (551.5–638)	542.7 (461.5–610)	<0.01*

IOP intraocular pressure, CCT central corneal thickness, GH growth hormone, IGF-1 insulin-like growth factor-1

<sup>†</sup> Chi-square test; \*Mann–Whitney *U* test; <sup>‡</sup> According to the formula proposed by Doughty et al. [18]

maximum values and were tested for normal distribution by means of a Shapiro–Wilk test. A Mann–Whitney *U* test was used to compare continuous variables between groups. Correlations among IOP, CCT, GH, and IGF-1 were evaluated using the Spearman's correlation coefficient. Level of significance was set at 0.05, for a bilateral test. The analyses were made using SAS software (Statistical Analysis System, version 9.4; SAS Institute Inc., Cary, NC, USA).

## Results

During the course of the study 14 consecutive patients with acromegaly and 28 age and sex-matched controls were enrolled. All participants were Caucasian. Table 1 shows the characteristics of the two cohorts.

Eleven of the 14 acromegalic patients had already been treated with neurosurgery, and all of them required further treatment (somatostatin analogues and/or pegvisomant) for the persistence of GH hypersecretion [25]. Two patients were treated with somatostatin analogues as first-line therapy. At the time of the study, 12 patients had controlled disease, whereas the remaining two patients had active acromegaly notwithstanding different treatments regimens [24]. Median duration of active disease was 5 years (range: 1–15).

The CCT and IOP values recorded in acromegalic patients were significantly greater than those documented in the controls (Table 1; *p*<0.01). However, when IOP was corrected for CCT [18], no statistically significant difference was detected between the two groups (Table 1; *p*=0.07). Moreover, no significant correlation could be documented between CCT and GH, CCT and IGF-1, IOP and GH, IOP and IGF-1 in the acromegalic group (Table 2, Fig. 1 and Fig. 2), whereas a statistically significant correlation was observed between CCT and IOP when the entire cohort was considered (Spearman's coefficient: 0.56; *p*<0.01; Table 2, Fig. 3).

## Discussion

Our results suggest that acromegaly may be associated with an increased CCT, and acromegalic patients appear to have higher IOP values than normal controls. It is well-known that CCT and other corneal parameters influence GAT readings because IOP is calculated assuming a fixed CCT of 520 μm, disregarding inter-individual variability [26]. Consequently, GAT underestimates IOP in patients with a thin cornea, and overestimates it in those with a thick cornea. A review of the literature showed corneal thickness-related deviations in GAT measurements ranging from 0.11 to 0.71 mmHg for every 10 μm change in CCT [16, 17].

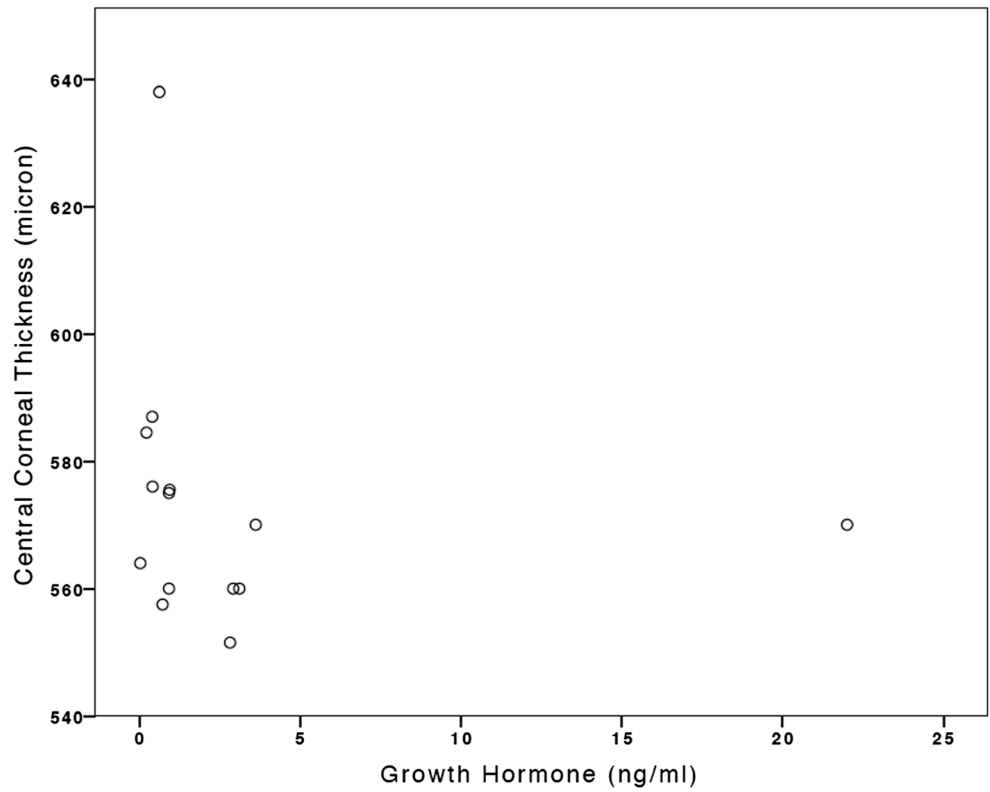
Published evidence to date has indicated that IOP is significantly increased in acromegalic patients when compared with healthy subjects [12, 14, 27]. Consequently, acromegaly has been considered a risk factor for glaucoma development [10, 11]. Polat and coworkers [15] found that acromegaly was associated with higher levels of IOP, but contrary to our results did not detect a significant difference in the CCT of patients with acromegaly compared to controls. The difference with our data may be attributed to the extreme range of CCT for

**Table 2** Spearman's correlation coefficients for tested variables

Correlation	Group	<i>N</i>	Spearman $\rho$	<i>P</i> -value
CCT - IOP	Entire cohort	42	0.56	<0.01
	Acromegalic patients	14	0.07	0.8
	Healthy subjects	28	0.44	0.01
CCT - GH	Acromegalic patients	14	-0.43	0.14
CCT - IGF-1	Acromegalic patients	14	0.23	0.42
IOP - GH	Acromegalic patients	14	0.08	0.78
IOP - IGF-1	Acromegalic patients	14	0.21	0.47

CCT central corneal thickness, IOP intraocular pressure, GH growth hormone, IGF-1 insulin-like growth factor 1

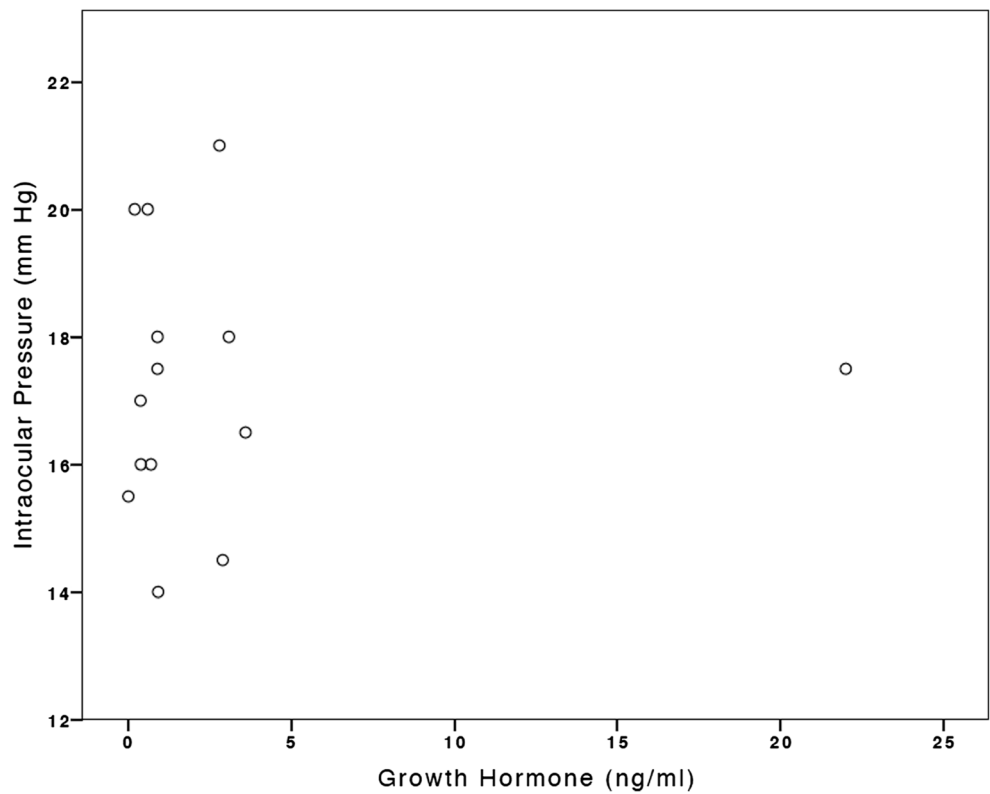
**Fig. 1** Scatter-plot of central corneal thickness vs. growth hormone serum levels for acromegalic patients



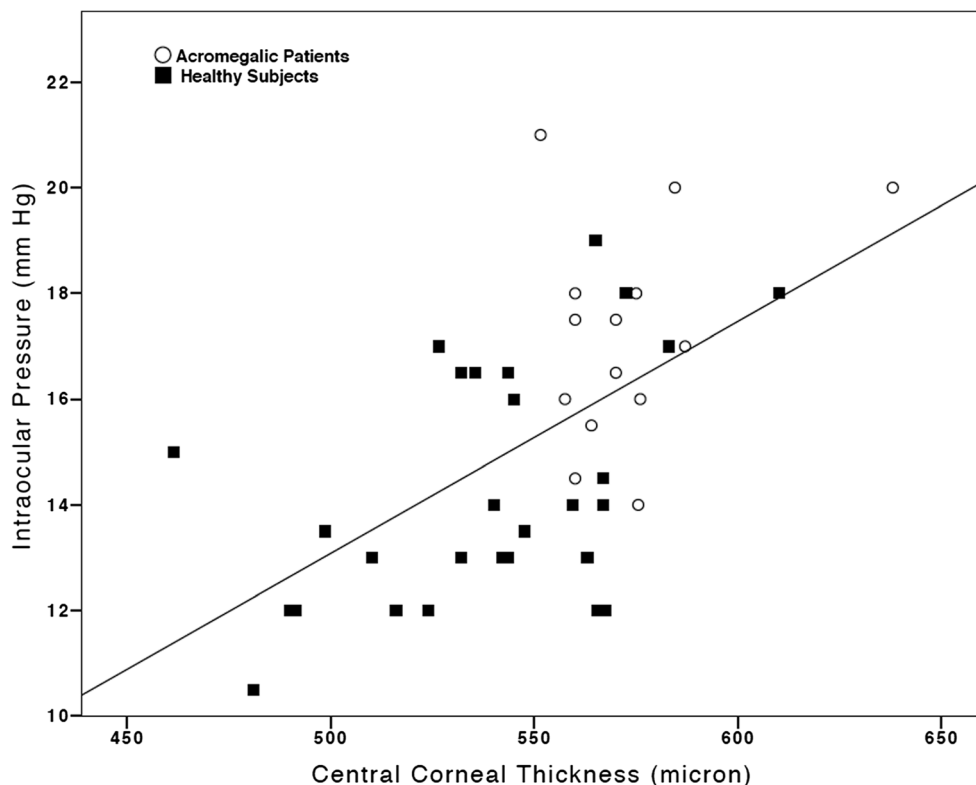
normal eyes reported in that study (right eye CCT range: 274–643  $\mu\text{m}$ , left eye CCT range: 267–643  $\mu\text{m}$ ). In a recent study

using the Ocular Response Analyzer, Ozkok et al. [28] reported that patients with acromegaly had significantly different

**Fig. 2** Scatter-plot of intraocular pressure vs. growth hormone serum levels for acromegalic patients



**Fig. 3** Scatter-plot of central corneal thickness vs. intraocular pressure for the entire cohort of the study



corneal biomechanical properties compared to age- and sex-matched controls. Specifically, the authors found that acromegalic patients had higher corneal hysteresis and corneal resistance factor compared to controls. Although Goldmann-equivalent readings were higher in the patient group, neither CCT nor CCT-compensated IOP readings were significantly different between the two groups. Consequently, in this cohort, the apparent differences in Goldmann-equivalent readings could be attributed to acromegaly-induced corneal biomechanical changes. On the other hand, our data suggest that the higher GAT readings observed in patients with acromegaly are due to an increased CCT and do not represent an actual

IOP elevation. This is supported by the fact that when IOP was corrected for CCT according to the formula proposed by Doughty and Zaman [18], no significant IOP difference could be detected between acromegalic and healthy subjects. Our results corroborate findings by Bramsen et al. [12]. The authors investigated GAT readings and CTT measurements obtained with optical pachymetry in patients with pituitary tumors with ( $n=13$ ) and without acromegaly ( $n=14$ ). They found that both CCT and GAT readings were higher in acromegalic patients, but the CCT-corrected IOP readings were similar in the two groups. Although not explicitly stated by Bramsen et al. [12], it seems that they used the correction

**Table 3** Summary of previous studies about CCT and IOP in patients affected by acromegaly in comparison with controls

	Patients affected by acromegaly			Controls		
	<i>N</i>	CCT (mean ± SD, μm)	IOP (mean ± SD, mm Hg)	<i>N</i>	CCT (mean ± SD, μm)	IOP (mean ± SD, mm Hg)
Bramsen et al. (1980) [12]	13 patients	561±35	16.9±2.3	14 subjects	526±30	14.7±2.4
Ciresi et al. (2011) [14]	28 patients	567 (559–573.5)*	19 (18–21)*	22 subjects	528.5 (517–535)*	17 (16.5–18)*
Polat et al. (2013) [15]	30 patients	529.2 (471–630) ‡	16 (11–19) ‡	21 subjects	537 (487–643) ‡	13 (9–20) ‡
Ozkok et al. (2014) [28]	46 right eye	545.4±29.2	17.1±4.2†	42 right eye	555.1±28.4	15.1±3.0†
	46 left eye	545.8±31.6	17.3±4.2†	42 left eye	557.5±27.1	14.7±3.1†

CCT central corneal thickness, IOP intraocular pressure, \*median of the mean (interquartile range); ‡: median of the mean (range) †: Ocular Response Analyzer Goldmann correlated intraocular pressure

algorithm suggested by Ehlers et al. [16]. This algorithm assumes a different correction factor depending on the level of GAT reading and CCT value. On the other hand, we assumed a correction of 2.5 mmHg per 50  $\mu\text{m}$  of CCT deviation from 535  $\mu\text{m}$  as suggested by Doughty and Zaman [18]. In their study, Bramsen et al. found that the mean CCT-corrected IOP in pituitary tumor patients with and without acromegaly was  $14.1 \pm 2.3$  and  $14.2 \pm 2.4$  mmHg respectively. These results closely match our data: the median CCT-corrected IOP of acromegalic patients and controls was 14.8 (range: 11.9–20.1) and 13.9 (range: 10.3–18.6) mmHg respectively.

It is not entirely understood why acromegalic patients have thicker corneas than healthy subjects. Visceromegaly is a common clinical feature of acromegaly attributed to the growth-promoting chronic effect of the GH on many organs. The eye seems to be a target site for GH action, and GH may have endocrine, autocrine or paracrine roles in ocular development and growth. Thus, it is conceivable that corneal tissue is a target for GH action. It is noteworthy that Ciresi and coworkers [14] observed a strong linear correlation between CCT and GH levels in a group of 28 patients with acromegaly. Our study did not find a statistically significant correlation between CCT and GH plasma levels. This lack of correlation may be due to the small sample size and the inevitable data scatter. The relationship between CCT and GH requires further research in a larger cohort of patients with acromegaly. Confounding factors may include previous treatments (radiotherapy, medical, or surgical therapies) and lack of documented GH and IGF-1 plasma levels at diagnosis.

In common with previous reports, a limitation of the present study is the small sample size due to the rarity of the disease (Table 3). A potential bias of our study is related to the fact that most our patients were on treatment with somatostatin analogues which may have impacted ocular tissues regardless of control of GH hypersecretion, as already demonstrated for other clinical investigations [29–31]. Further controlled studies are needed to better delineate the impact of GH upon ocular tissues.

In conclusion, our data suggest that acromegaly is associated with increased CCT that could lead to an overestimation of IOP readings as determined by GAT and possibly future glaucoma development risk. Therefore, CCT evaluation should be considered an important component of the ophthalmic assessment in acromegalic patients.

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**Conflict of interest** None.

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