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Cornea in acromegalic patients as a possible target of growth hormone action

A. Ciresi[1], M.C. Amato[1], D. Morreale[2], G. Lodato[2], A. Galluzzo[1], and C. Giordano[1]

[1]Section of Endocrinology, Department of Experimetal Oncology and Clinical Applications (DOSAC); [2]Section of Ophthalmology, Department of Clinical Neurosciences (DINEC), Palermo, Italy

ABSTRACT. ***Background:*** **GH exerts its effects on many organs and the eye also seems to be a target site, although few authors have investigated the corneal thickness in patients with acromegaly.** ***Aim:*** **To perform a detailed ophthalmological evaluation in acromegalic patients, in relation to disease activity.** ***Material and methods:*** **Twenty-eight acromegalic patients (11 males, 17 females) and 22 voluntary healthy subjects underwent complete metabolic and ophthalmological evaluation, including retinal thickness (RT), central corneal thickness (CCT), and intraocular pressure values (IOP).** ***Results:*** **Significantly greater CCT values were found in all acromegalic patients in comparison with controls (567** ***vs*** **528.5 μm;** ***p*****<0.001), without concomitant greater corrected IOP. No difference was found for RT. Analyzing these data according to disease activity, uncontrolled patients showed greater CCT values (573.5** ***vs*** **559 μm;** ***p*****=0.002) and corrected IOP (17.4** ***vs*** **16 mmHg;** ***p*****=0.001) than the controlled ones. CCT also correlated with basal and nadir GH after oral glucose load levels, IGF-I levels, and duration of active disease.** ***Conclusions:*** **Acromegaly is characterized by greater CCT values, supporting the hypothesis that GH excess may have stimulatory effects on the cornea as well as on other target organs. Higher GH levels, disease control status and duration of active disease seem to be the main causes of increased corneal thickness. We suggest a careful and detailed corneal evaluation in acromegalic patients to prevent the potential risk of increased IOP, in addition to the already-known complications.**

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INTRODUCTION

Visceromegaly is a common clinical feature of acromegaly due to the growth-promoting chronic effects of the GH on many tissues (1-3). The eye also seems to be a target site for GH action and GH may have endocrine, autocrine or paracrine roles in ocular development and growth (4), although the mechanism of this observation is still not fully understood. Very high IGF-I levels in the subretinal fluid of a patient with acromegaly have been reported (5). In recent studies, GH mRNA and GH immunoreactive proteins have been identified in the neural retina of embryonic chicks and newborn mice (6-8). The retina, therefore, is considered to be an extrapituitary site of GH gene expression during early development and is probably an autocrine or paracrine site of GH action, suggesting a role for GH in ocular development. The action of GH has been demonstrated by the ocular abnormalities that may occur in patients with pituitary GH excess or GH deficiency. In patients with primary GH insensitivity treated with GH therapy, it has been demonstrated that there is a greater average ocular dimension, including average corneal curvature, than that observed in untreated patients (9), indicating the effect of supplemental growth factor on ocular growth. Furthermore, significantly greater values of central corneal thickness (CCT) were found a few years ago in 13 patients with acromegaly compared to that of the control group (10). A less recent study suggested that the somatotropic hormone might facilitate a condition of glaucoma, showing greater GH levels after iv arginina administration in open-angle glaucoma patients than in control subjects, which supports the hypothesis that the increased plasma GH levels may interfere with the regulation of ocular pressure (11). The aim of this study was to evaluate retinal thickness (RT) and CCT values in patients with acromegaly and to determine if a true significant correlation exists between intraocular pressure (IOP) and CCT. In addition, we evaluated the impact of the variables connected to acromegaly, such as diabetes, hypertension, and disease control, on RT and CCT.

MATERIALS AND METHODS

Patients

Twenty-eight acromegalic patients (11 males and 17 females, median age 53.5) were included in the study; 3 subjects were recruited at diagnosis, before starting any medical therapy; 9 subjects were treated with first-line therapy involving long-acting somatostatin analogues (SST-A) [6 with octreotide long-acting release (LAR) 20 mg/month; 3 with lanreotide autogel 60 mg/month; duration of treatment: 10.3±3.5 months]; 16 subjects were recruited after neurosurgical therapy, among them 7 were without medical treatment (time from surgery 3.2±0.6 months), 9 were treated with SST-A (octreotide LAR 20 mg/month; duration of treatment 36.6±12.5 months). Mean duration of disease was 4.7 yr for controlled and 3.5 yr for uncontrolled acromegalics. Based on nadir GH after oral glucose load (OGTT) and age-matched IGF-I levels, patients were divided into 2 groups – with either uncontrolled (group A; 13 cases) or controlled acromegaly

Key-words: Acromegaly, corneal thickness, growth hormone, intraocular pressure.

Correspondence: C. Giordano, MD, Section of Endocrinology, Department of Oncologia Sperimentale e Applicazioni Cliniche (DOSAC), Piazza delle Cliniche 2, 90127 Palermo, Italy.

E-mail: cgiordan@unipa.it

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(group B; 15 cases). Cut-off level for controlled subjects was 1 µg/l for GH after OGTT, together with normal IGF-I for age (12). Twenty-two voluntary healthy subjects, matched for age, body mass index (BMI), and body surface area (BSA), were included as controls. Informed consent was obtained from all subjects. The Institutional Review Board at the Faculty of Medicine of the University of Palermo approved this retrospective study.

Study design

All subjects enrolled had been investigated for BMI, BSA, nadir GH after OGTT, IGF-I levels (the average value of 3 measurements assessed during the previous 6 months, expressed as IGF-I SD), lipid profile (total cholesterol, HDL, LDL, triglycerides), fasting glucose, fasting insulin. Insulin resistance (IR) had been evaluated by the homeostasis model assessment of IR Index (HOMA-IR), applying Matthews formula [fasting serum insulin (µU/ml) × fasting plasma glucose (mmol/l)/22.5] (13). All subjects underwent complete ophthalmological evaluation, including RT measurement with optical coherence tomography (OCT) (14), measurement of CCT and IOP by applanation tonometry. We excluded patients suffering any clinically relevant ocular disease and with IOP>21 mm/Hg because they were already treated with topical drug therapy.

Hormone and biochemical assays

Glycemic, lipid (HDL, LDL, and total cholesterol, triglycerides), and microalbuminuria levels were measured with standard methods. Serum GH was assessed by enzyme-linked immunosorbent assay (ELISA) (BioSource hGH-EASIA kit, Nivelles, Belgium). Sensitivity of the method was 0.07 µg/l. Inter- and intra-assay coefficients of variation (CV values) were 3.6-4.4 and 3.7-9.8% respectively, for GH levels of 6.4-21.2 and 1.9-13.1 µg/l, respectively. Serum total IGF-I was assessed by ELISA (OCTEIA IGF-1 kit, IDS Inc., Fountain Hills, AZ, USA). Sensitivity was 1.9 µg/l. Inter- and intra-assay CV values were 7-7.1 and 2.3-3.5%, respectively, for IGF-I levels of 90.7-186 and 66.7-120.9 µg/l, respectively. Normal range of total IGF-I levels (µg/l) were 150-350 (both male and female adults). Serum insulin was measured by ELISA (DRG Instruments GmbH Germany). Sensitivity of the method was 1 µUI/ml. Normal range of insulin (µUI/ml) was 5-19. Conversion factors for the International System (SI) were glucose (mg/dl *vs* mmol/l: 0.0555), insulin (µUI/ml *vs* pmol/l: 6.945), total cholesterol (mg/dl *vs* mmol/l: 0.0259), and triglycerides (mg/dl *vs* mmol/l: 0.0113).

Ocular evaluation

Quantitative assessment of RT was performed with Stratus OCT-Model 3000 (Carl Zeiss Meditec, Dublin, CA, USA), using the fast macular thickness OCT scan protocol. RT was calculated in 3 areas: fovea (central circle, with a diameter of 1 mm), pericentral area (comprised between an inner diameter of 1 mm and an outer diameter of 3 mm) and peripheral or paracentral area (inner diameter of 3 mm and outer diameter of 6 mm). Fast macular thickness scan protocol was performed in both eyes in all subjects and the same expert examiners obtained OCT scans for each eye. All subjects also underwent scanning laser polarimetry with variable corneal compensation (GDx-VCC), to a full analysis of the retinal nerve fiber layer.

Table 1 - *Clinical, metabolic, and ocular parameters in acromegalic patients and control group.*

	Acromegalic patients (28 cases) No. (%)	Control group (22 cases) No. (%)	*p*
Gender			0.907
Males	11 (39.3)	9 (40.9)	
Females	17 (60.7)	13 (59.1)	
	Median (interquartile range)	Median (interquartile range)	
Age	53.5 (46.2-61.7)	50 (46-61.5)	0.486
BMI (kg/m^2)	29.7 (26.7-32)	29.2 (26-31.8)	0.439
BSA (m^2)	1.8 (1.8-2)	1.8 (1.7-1.9)	0.285
Systolic blood pressure (mmHg)	135 (123.7-141.2)	113 (110-120)	<0.001
Diastolic blood pressure (mmHg)	77.5 (70-90)	70 (65-70)	<0.001
	No (%)	No (%)	
Diabetes mellitus[a]	10 (38.5)	-	-
Increased waist circumference[b]	16 (61.5)	-	-
Low HDL-cholesterol[b]	6 (23.1)	-	-
Hypertension[c]	15 (57.7)	-	-
Hypertriglyceridemia[b]	9 (34.6)	-	-
Metabolic syndrome[b]	11 (42.3)	-	-
	Median (interquartile range)	Median (interquartile range)	
Right central corneal thickness (µm)	563 (560-578)	528 (514-535)	<0.001
Left central corneal thickness (µm)	569 (556-576)	531 (519-536)	<0.001
Mean central corneal thickness (µm)	567 (559-573.5)	528.5 (517-535)	<0.001
Right intraocular pressure (mmHg)	19 (18-21)	17 (16.5-18)	0.001
Left intraocular pressure (mmHg)	19 (18-20)	17 (16.5-18)	0.004
Mean intraocular pressure (mmHg)	19 (18-21)	17 (16.5-18)	0.001
Corrected mean intraocular pressure (mmHg)	17.3 (16.3-18)	17 (16.1-17.6)	0.611

Differences between continuous variables were analyzed by Mann-Whitney U-test. Differences between categorical variables were analyzed by the χ^2-test and Fisher's exact test, when appropriate. [a]ADA criteria (17), [b]ATP III criteria (19), [c]SH/ESC criteria (18). BSA: body surface area; BMI: body mass index.

Table 2 - *Metabolic parameters in acromegalic patients according to the control of disease.*

	Group A (13 cases) no. (%)	Group B (15 cases) no. (%)	*p*
Gender			0.460
Males	4 (30.7)	7 (46.6)	
Females	9 (69.3)	8 (53.4)	
Diabetes mellitus[a]	6 (46.1)	4 (26.6)	0.432
Increased waist circumference[b]	10 (76.9)	6 (40)	0.051
Low HDL-cholesterol[b]	4 (30.7)	2 (13.3)	0.372
Hypertension[c]	8 (61.5)	7 (46.6)	0.684
Hypertriglyceridemia[b]	7 (53.8)	2 (13.3)	0.041
Metabolic syndrome[b]	7 (53.8)	4 (26.6)	0.233
	Median (interquantile range)	Median (interquantile range)	
Age	50 (44-58.50)	59.5 (52.5-66)	0.076
Duration of disease (yr)	3.5 (1.1-5.7)	1 (1-2.5)	0.176
Duration of active disease (yr)	1.1 (1-1.8)	0.4 (0.3-0.5)	<0.001
Systolic blood pressure (mmHg)	140 (140-145)	125 (110-130)	<0.001
Diastolic blood pressure (mmHg)	90 (76.2-93.7)	70 (70-82.5)	0.004
BSA (m^2)	1.8 (1.7-2)	1.8 (1.8-2)	0.406
BMI (kg/m^2)	29.8 (26-32.8)	29.5 (27.7-32)	0.936
Microalbuminuria (mg/24h)	26.5 (16.2-40)	4.5 (0-12)	0.001
Total cholesterol (mmol/l)	5 (4.4-5.9)	4.5 (3.7-5.2)	0.046
HDL-cholesterol (mmol/l)	1.1 (1-1.3)	1.2 (1-1.6)	0.432
Triglycerides (mmol/l)	3.8 (3.2-4.4)	3.6 (2.3-3.8)	0.131
Fasting glycemia (mmol/l)	6.8 (5.5-7.4)	5 (4.4-7.3)	0.095
Fasting insulinemia (pmol/l)	120.8 (70.1-148.6)	86.8 (67.3-101.4)	0.085
Basal GH (µg/l)	4 (3.5-9.1)	1.2 (0.4-1.8)	<0.001
GH nadir during OGTT (µg/l)	2.6 (2.2-7.1)	0.6 (0.2-0.9)	<0.001
IGF-I (µg/l)	510.5 (357.5-654.5)	143.6 (135.5-208.2)	<0.001

Group A: uncontrolled acromegalics; group B: controlled acromegalics. [a]ADA criteria (17), [b]ATP III criteria (19), [c]SH/ESC criteria (18). Differences between continuous variables were analyzed by Mann-Whitney U-test. Differences between categorical variables were analyzed by the χ^2-test and Fisher's exact test, when appropriate. BSA: body surface area; BMI: body mass index; OGTT: oral glucose load.

CCT was measured by the very high-frequency ultrasonic contact pachimetry Pachpen after local anesthetic instillation. The value of CCT was performed taking the average of 5 consecutive pachimetry measurements.

IOP was measured by means of the Goldmann applanation tonometry. It is known that CCT can significantly affect IOP readings obtained by different techniques of measurement. Normally hydrated, thicker corneas lead to higher IOP readings and thinner corneas to lower readings. Several studies showed a lower CCT in some cases of normal-tension glaucoma and a higher CCT in cases of ocular hypertension (15, 16). For this reason, to determine an accurate value, IOP should always correct for CCT. Various authors examining the correlation between IOP readings by applanation tonometry and CCT have reported a measurement error of 3.4±0.9 mmHg difference in IOP per 10% difference from the average CCT. In the present study, we calculated correction values for IOP readings for CCT according to Doughty's meta-analysis (15). The correction values were positive as thickness decreased and negative as thickness increased.

Statistical analysis

We used the SPSS 13 software, Windows Edition (SPSS, Chicago, IL), for all our statistical analysis. Continuous variables were without normal distribution and were described as median values and interquartile range. Rates and proportions were calculated for categorical data. Differences between continuous variables were analyzed by non-parametric tests (Mann-Whitney U-test). For categorical variables, differences were analyzed by the χ^2-test and Fisher's exact test, when appropriate. Simple univariate correlations among continuous variables were determined by Spearman's test, non-parametric equivalent for Pearson's test. $p<0.05$ was considered statistically significant.

RESULTS

Table 1 shows clinical characteristics, together with metabolic and ocular parameters. As expected, compared with controls, acromegalic patients presented a higher prevalence of metabolic syndrome features, including diabetes mellitus (17), hypertension (18), low HDL-cholesterol, increased waist circumference, and hypertriglyceridemia (19). The analysis of the ocular data showed significant greater mean CCT values in acromegalic patients in comparison with healthy subjects, with a concomitant greater mean IOP. However, when the applanation reading was corrected for the difference in the CCT, the patients with acromegaly had no greater IOP than control group. No alteration of the retinal nerve fiber layer was detected in acromegalic patients (data not shown).

When the patients were grouped according to disease status, group A showed higher total cholesterol, microalbuminuria levels and systolic and diastolic blood pressure than group B (Table 2). The analysis of the oc-

Table 3 - *Central corneal thickness and intraocular pressure values in acromegalic patients according to the control of disease.*

	Group A (13 cases)	Group B (15 cases)	*p*
	Median (interquartile range)	Median (interquartile range)	
Right central corneal thickness (μm)	578 (569-596)	560 (550-562)	<0.001
Left central corneal thickness (μm)	569 (569-596)	556 (555.2-572.2)	0.012
Mean central corneal thickness (μm)	573.5 (567-596)	559 (552.6-566.5)	0.002
Right intraocular pressure (mmHg)	20 (19-21)	17.5 (16.2-18)	<0.001
Left intraocular pressure (mmHg)	19 (19-21)	17.5 (16.2-18)	0.001
Mean intraocular pressure (mmHg)	19 (19-21)	17.5 (16.2-18)	<0.001
Corrected mean intraocular pressure (mmHg)	17.4 (17.3-18.3)	16 (14.9-16.6)	0.001

Group A: uncontrolled acromegalics; group B: controlled acromegalics. Differences between continuous variables were analyzed by Mann-Whitney U-test.

ular data according to disease activity showed that group A presented greater mean CCT values and IOP than group B (Table 3; Fig. 1, 2). When the applanation reading was corrected for the difference in the CCT, the patients with uncontrolled acromegaly confirmed greater mean IOP than patients with controlled disease (Table 3; Fig. 3).

After analyzing CCT values separately into 2 groups of acromegalics, we found that no controlled patients had normal CCT and a strong significant difference was found between CCT of controlled patients and the control group, with median value respectively of 559 (552.6-566.5) and 528.5 (517-535.2) μm ($p<0.001$). The same data, as expected, was detected between uncontrolled patients and the control group, with CCT median value of 573.5 (567-596) and 528.5 (517-535.2) μm ($p<0.001$).

The analysis of corneal thickness values with univariate correlation showed a significant correlation with basal and nadir GH after OGTT levels, systolic and diastolic blood pressure. No correlation was found with age of patients and duration of total disease in both groups of acromegalic patients. In addition, we analyzed the data according to duration of "active disease", evaluated as the estimated time to achieve disease control from diagnosis. A significant difference between uncontrolled and controlled patients (Table 2) and a correlation between this parameter and CCT in all acromegalic patients (Table 4) were found. When patients were grouped according to blood pressure, no significant difference was found in corneal and tonometry values between hypertensive and normotensive patients (data not shown).

DISCUSSION

It is an accepted fact that the normal CCT value in human corneas based on reported worldwide literature values is about 536±0.31 μm, with the evidence of a slight chronological increase in CCT values of 0.006 μm/dec-

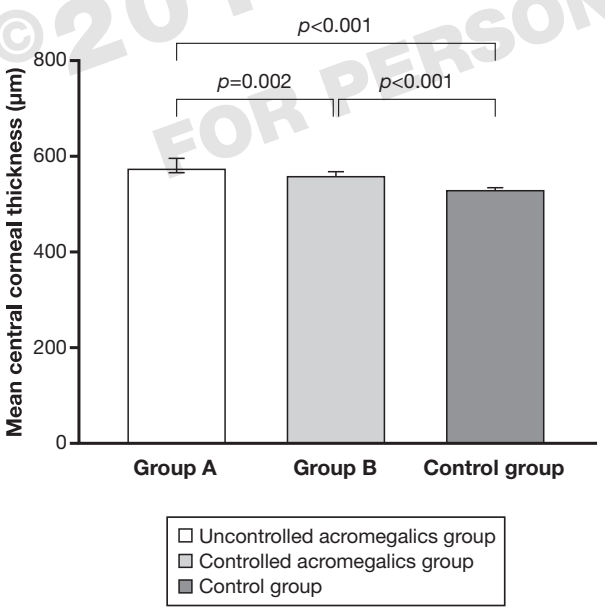

Fig. 1 - *Mean central thickness values (μm) in control group, uncontrolled, and controlled acromegalic patients.*

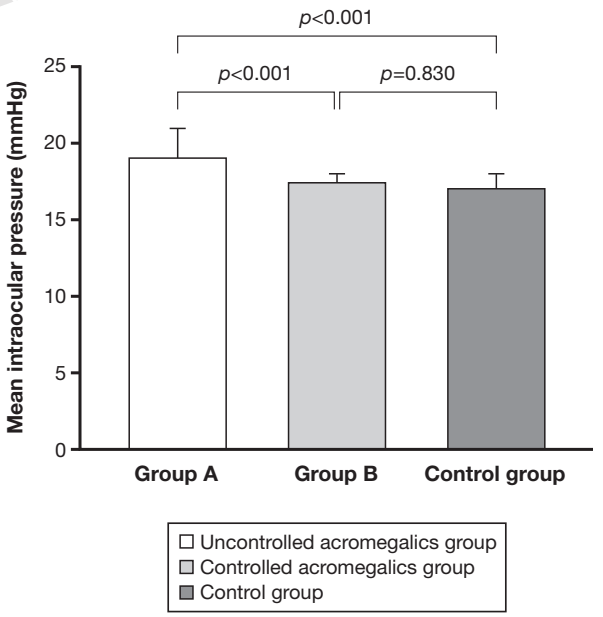

Fig. 2 - *Mean intraocular pressure (mmHg) in control group, uncontrolled, and controlled acromegalic patients.*

Table 4 - *Analysis of mean central corneal thickness (CCT) values with univariate correlation in all acromegalic patients.*

	Basal GH	GH nadir during OGTT	IGF-I	Age	Duration of disease	Duration of active disease	Systolic blood pressure	Diastolic blood pressure
	Rho (*p*)	Rho (*p*)	Rho (*p*)	Rho (*p*)	Rho (*p*)	Rho (*p*)	Rho (*p*)	Rho (*p*)
Mean CCT (µm)	0.529 (0.020)	0.570 (0.011)	0.356 (0.134)	0.104 (0.522)	0.165 (0.500)	0.569 0.011	0.726 (<0.001)	0.721 (<0.001)

OGTT: oral glucose load.

ade approximately and a statistically significant correlation between CCT and IOP (15). Very few studies have investigated the abnormalities in CCT in patients with chronic diseases. Only the ocular diseases associated with collagen disorders or endothelian-based corneal dystrophies have proved likely to result in decreases or increases, respectively, of CCT (15). Conversely, very few authors have investigated the CCT in patients with pituitary adenomas. In a less recent study, corneal thickness was evaluated in patients with pituitary adenomas, showing significantly greater values in patients with acromegaly with concomitant greater intraocular tension measured by applanation, than that found in the control group (10). However, no correlation between these data and the parameters of acromegalic disease was detected by the authors. In our study, we confirm the finding of altered CCT in acromegalic patients, with corneal thickness values greater than in healthy subjects. We also identified a strong linear correlation of corneal thickness with GH levels, blood pressure values, and duration of active disease. Acromegalic patients with longer active and uncontrolled disease showed greater CCT values, supporting the hypothesis that GH excess may have stimulatory effects on the cornea as well as on other target organs. Systolic and diastolic blood pressure levels are also correlated with corneal thickness, probably due to higher blood pressure levels found in uncontrolled patients. Nevertheless, the analysis of these data according to blood pressure status, showed no significant difference in corneal and tonometry values between hypertensive and normotensive patients, most likely due to the anti-hypertensive therapy administered to hypertensive patients. The initial finding of greater IOP in acromegalic patients with respect to healthy subjects was not confirmed when the applanation reading was corrected for CCT values, while greater IOP in uncontrolled acromegalics compared with controlled patients was confirmed, suggesting that the main role of GH and IGF-I is to increase corneal thickness and stressing the importance of disease control. Conversely, IOP was within the normal range in all patients and no alteration of retinal fibers was found by OCT and GDx-VCC, so that the presence of real glaucoma could be excluded (20).

In conclusion, our data demonstrated that the exposure to high levels of GH, duration of active disease, and control status, regardless of patient age, seem to be the main causes of increased corneal thickness. With this in mind, we suggest a careful corneal evaluation in acromegalic patients, with IOP measurements during the follow-up, to prevent the potential risk of increased IOP, in addition to the already-known complications.

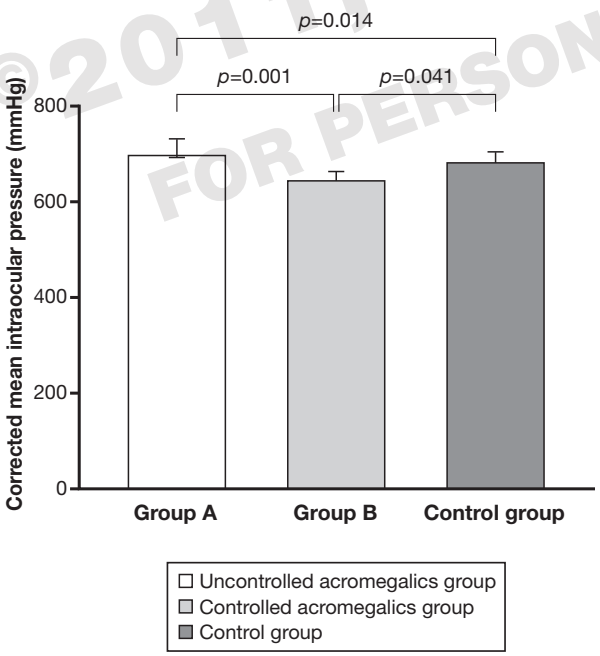

Fig. 3 - *Mean corrected intraocular pressure (mmHg) in control group, uncontrolled, and controlled acromegalic patients.*

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Declaration of interest and funding

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