Elevated IGF-1 and GH Levels Are Correlated With a Thicker Iris and Wider Anterior Chamber Angle in Treatment-Naïve Acromegaly Patients

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Purpose. To compare the difference in anterior segment biometrics derived from anterior segment optical coherence tomography (AS-OCT) between treatment-naïve acromegaly patients and normal controls and evaluate the correlations between above biometrics and insulin-like growth factor 1 (IGF-1) and growth hormone (GH) levels.

Methods. Sixty eyes of 30 acromegaly patients and 60 eyes of 30 normal controls were included in this case-control study. Central corneal thickness, pupil diameter, iris thickness (IT), iris curvature (IC), anterior chamber depth (ACD), anterior chamber width, lens vault (LV), angle open distance (AOD) 500, AOD750, and trabecular iris space area (TISA) 500 and TISA750 were measured by AS-OCT. General linear regression models were constructed to evaluate the independent endocrine factors affecting iris morphology and anterior chamber angle (ACA) width.

Results. The acromegaly patients had an evenly thicker iris ($P < 0.001$), a smaller IC ($P < 0.05$), a smaller LV ($P = 0.040$) and significantly larger AOD500, AOD750, TISA500 and TISA750 ($P < 0.001$). There was a positive correlation between the serum GH level and ACD in the acromegaly patients ($P = 0.031$). Linear regression models showed the lower LV and smaller IC were independent influencing factors of the increase in the AOD500, AOD750, and TISA750 and nasal TISA500. Serum IGF-1 was an independent factor for the increase in pupil diameter ($\beta = 0.002$, $P = 0.031$) and both the average nasal ($\beta = 6.781*10^{-5}$, $P = 0.049$) and temporal ($\beta = 7.736*10^{-5}$, $P = 0.045$) IT values and for the decrease in temporal IC ($\beta < 0.001$, $P = 0.037$). GH was an independent factor for the increase in temporal AOD750 ($\beta = 0.001$, $P = 0.030$) and temporal TISA750 ($\beta = 0.002$, $P = 0.016$).

Conclusions. Patients with acromegaly have a thicker IT, smaller IC, and lower LV with a wider ACA than normal controls. Serum GH is independently correlated with the temporal ACA width, whereas serum IGF-1 is independently correlated with IT, pupil diameter, and IC.

Keywords: acromegaly, IGF-1, growth hormone, iris thickness, anterior chamber angle

Acromegaly, a chronic disease primarily caused by pituitary adenoma, is characterized by increased serum levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1),[1] which leads to numerous systemic complications. The morbidity risk associated with complications has been shown to increase significantly with the cumulative effect of serum GH and IGF-1 concentrations over time, which has been described as the GH burden and IGF-1 burden by Jayasena et al.[2] Studies have shown a significant positive correlation between the GH and IGF-1 burden and acromegalic changes in various organs, emphasizing the dual action of GH and IGF-1 concentration and disease duration.[3,4]

To date, the known ophthalmic complications of acromegaly include meibomian gland dysfunction,[5] retinitis pigmentosa,[6] retinal capillary network alternation,[7] and

extraocular muscle enlargement.[8] Our team has confirmed that increased choroid layer thickness, especially of the large vessel layer (Haller's layer), is detected in treatment-naïve nondiabetic acromegaly patients. Curiously, the degree of thickening is positively related to the serum IGF-1 level, disease duration, and IGF-1 burden.[9] Studies, in addition, have shown that patients with active acromegaly have higher central corneal thickness and corneal biomechanical values than patients with stable status,[10,11] indicating that serum GH and IGF-1 levels may be related to anterior segment structure change in acromegaly patients.

With the emergence of swept-source optical coherence tomography (SS-OCT) technology in recent years, anterior segment parameters such as anterior chamber depth (ACD), anterior chamber width (ACW), iris thickness (IT), iris curvature (IC), lens vault (LV), and lens thickness (LT) have all been shown to be useful for screening angle closure because of their close association with angle width.[12] Previous studies have shown that growth hormone may affect the aqueous humor outflow pathway by affecting the trabecular meshwork structure of the corneoscleral margin.[13] On the other hand, IT is shown to be closely related to choroidal thickness.[14] Therefore the evaluation of anterior segment structure in patients with acromegaly is helpful for exploring the correlations of GH and IGF-1 with anterior segment structure.

In recent years, human GH replacement has been widely used in adults and adolescents, whose Food and Drug Administration–approved indications have been rapidly expanded.[15,16] No clinical observations, however, have demonstrated the effects of excessive GH and IGF-1 on anterior segment anatomic parameters, which we explored on the natural disease model of acromegaly in this article to hopefully provide some indirect evidence for the safety and potential ocular complications associated with recombinant human GH and recombinant IGF-1 administration in patients with different comorbidities, such as narrow angle and glaucoma. In this study, we used spectral domain optical coherence tomography (SD-OCT) and SS-OCT to compare anterior segment parameters between treatment-naïve acromegaly patients and age- and sex-matched healthy controls. Multiple linear regression models were conducted to evaluate intercorrelations among the parameters and the independent correlations among GH, IGF-1, disease duration and anterior angle width.

Methods

Subjects

This case–control study included 30 treatment-naïve acromegaly patients (60 eyes) and 30 sex- and age-matched normal controls (60 eyes) at Peking Union Medical College Hospital from May 2021 to September 2021. All the participants agreed to join the study and signed consent forms. The healthy controls were recruited from hospital staff who underwent annual physical examinations and had normal GH and IGF-1 levels. The inclusion criteria for the acromegaly patients were as follows: (1) endocrine diagnostic criteria,[17] namely, a high level of fasting GH $\geq$ 2.5 ng/mL, lack of suppression of GH to <1 ng/mL after oral administration of 75 g glucose, and a high level of serum IGF-1 controlled for age and sex; (2) enhanced magnetic resonance imaging showing pituitary adenoma; (3) typical acromegaly clinical symptoms; and (4) pituitary growth hormone adenoma confirmed by postoperative pathology. The exclusion criteria included the following: (1) acromegaly patients treated with surgery, radiotherapy or somatostatin treatment before the first consultation; (2) patients or controls with severe lens opacities (best-corrected visual acuity [BCVA] worse than 0.3 logMAR) and other diseases known to cause anterior segment structure changes and pupillary changes, such as eye trauma, glaucoma, nanophthalmos, choroidal and retinal diseases, and optic nerve diseases, or those who underwent ophthalmological surgeries; (3) patients with a refraction error (spherical equivalent refraction) exceeding $\pm$1.50 D; (4) patients with a visual field test showing a visual field defect caused by chiasmal compression; (5) patients or controls who received exogenous glucocorticoid treatment in the previous year; (6) patients or controls who met the criteria for the diagnosis of diabetes[18] according to the American Diabetes Association; and (7) patients whose imaging examination of the anterior or posterior segment did not meet the analysis requirements after evaluation by two researchers. This study was approved by the Ethics Committee of PUMCH and adhered to the Declaration of Helsinki.

Baseline Examination

All the enrolled patients underwent a detailed ophthalmological examination. BCVA, refractive error and anterior and fundus examinations were performed. IOP was measured between 15:00 to 16:00 using a noncontact tonometer (CT-800 computerized tonometer; Topcon Corporation, Tokyo, Japan) and reported as the average of three measurements. All visual field tests were conducted with the Octopus 101 G2 program (Interzeag, Schlieren, Switzerland) after correction of refractive errors for at least two reliable results.

Central corneal thickness (CT), axial length (AL) and LT were measured with SS-OCT (IOL master 700, Carl Zeiss Meditec, Inc., Dublin, CA). The refraction examination was conducted with computer optometry. A spherical equivalent refraction was defined as spherical diopter plus 1/2 cylindrical diopter.

Image Acquisition and Analysis

SD-OCT. A specialist (Xia Zhang) examined all the patients in a standard dark room (<1 lux illumination based on a digital light meter reading) using the "anterior segment single" mode of Visante OCT (software version 3.0.1.8; Carl Zeiss Meditec, Inc., Dublin, CA) from 15:00 to 16:00. During scanning, the operator monitored the image quality and selected the images that clearly showed both scleral spurs and angle recess areas with clear and continuous anterior segment structures and no artifacts for further analysis.

Built-in software was used for image analysis. After the two independent specialists (XZ and LG) masked to the clinical data manually identified the left and right scleral spurs in the image, the algorithm automatically delineated the surfaces of the cornea, iris and lens. Then, manual correction was conducted to ensure the recognition accuracy. Scleral spurs were identified according to the criteria described by Chansangpetch et al.[19] A senior glaucoma consultant (LL) determined the location of scleral spur when they could not be identified by specialists (Fig. 1).

Three parameters were used to evaluate anterior chamber width and depth: (1) ACD, (2) ACW, and (3) LV. The

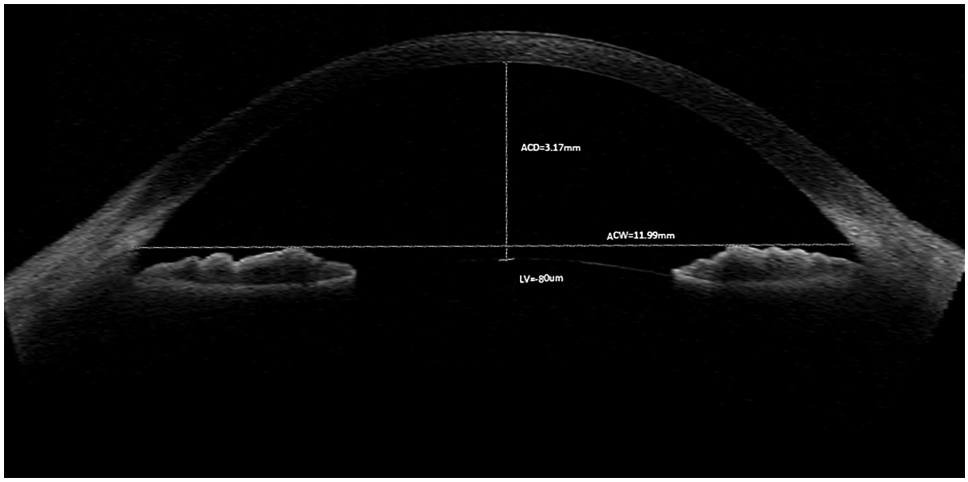

Figure 1. ACD, ACW, and LV measured by anterior segment optical coherence tomography in a standard dark room (<1 lux illumination based on a digital light meter). The specific process was as follows: the examination started after the patient closed their eyes for one minute. The specialist asked the patient to stare at the internal fixation point, manually adjusted the scanning line across the central point of the pupil, and then adjusted the nasal and temporal angles to the 180° axis. After the left and right scleral spurs were manually identified in the image, the algorithm automatically delineated the surfaces of the cornea, iris and lens. Then, manual correction was conducted to ensure the recognition accuracy.

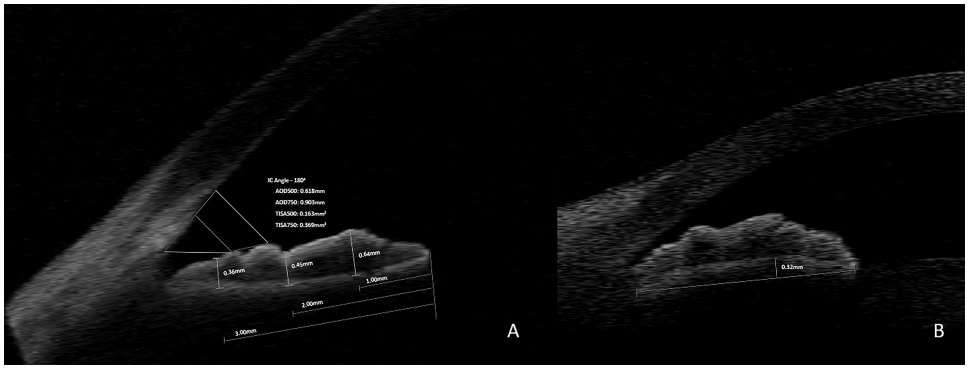

Figure 2. (A) AOD, TISA, and IT measured by anterior segment optical coherence tomography in a standard dark room. After the left and right scleral spurs were manually identified in the image, AOD500, AOD750, TISA500, and TISA750 were automatically measured by the built-in software and then manually corrected to ensure accuracy. IT100/200/300, shortest distance between the anterior and posterior surfaces of the iris measured at 100/200/300 µm from the temporal and nasal inner most tip of the pupil, respectively. Iris root thickness was measured once the iris was shorter than 300 µm. (B) IC, determined by creating a line from the most peripheral to the pupillary edge of the iris and then measuring the perpendicular distance from this line to the greatest convexity point along the posterior iris surface. The readout is positive when the iris is convex, and vice versa.

detailed definitions of each parameter have been previously described.[20,21]

The pupil diameter and IT were measured manually, and the following five parameters were used for evaluation, as shown in Figure 2A: (1) pupil diameter, namely, the length of the line connecting the inner most tip of the nasal-temporal pupil; (2) nasal iris average thickness (NIT) 100/ temporal iris average thickness (TIT)100, which is the shortest distance between the anterior and posterior surfaces of the iris measured at 100 µm from the temporal and nasal innermost tip of the pupil, respectively; (3) NIT200/TIT200; (4) NIT300/TIT300, notably, the iris root thickness was measured once the iris was shorter than 300 µm; (5) average NIT(NIT_{ave})/average TIT(TIT_{ave}), namely, average of NIT/TIT100, NIT/TIT200 and NIT/TIT300; and (6) IC, which is determined by creating a line from the most peripheral to the pupillary edge of the iris and then measuring the perpendicular distance from this line to the greatest convexity point along the posterior iris surface. The readout is positive when the iris is convex, and vice versa (Fig. 2B).

The anterior chamber angle (ACA) was evaluated by using the following four parameters: (1) angle open distance (AOD) 500; (2) AOD750; (3) trabecular iris space area (TISA) 500; and (4) TISA750. The detailed definitions of each parameter have been previously described.[20,21]

To determine the reliability of the IT and anterior chamber structure measurements, the first reader repeated this procedure for all the patients and controls once in a masked fashion at a one-month interval. The result from the first reading was used for the correlation analysis. The interobserver and intraobserver reliabilities of the data were calculated separately.

SS-OCT. IOL Master 700 (Carl Zeiss Meditec Ag) was used to evaluate the following five parameters: (1) ACD-SS;

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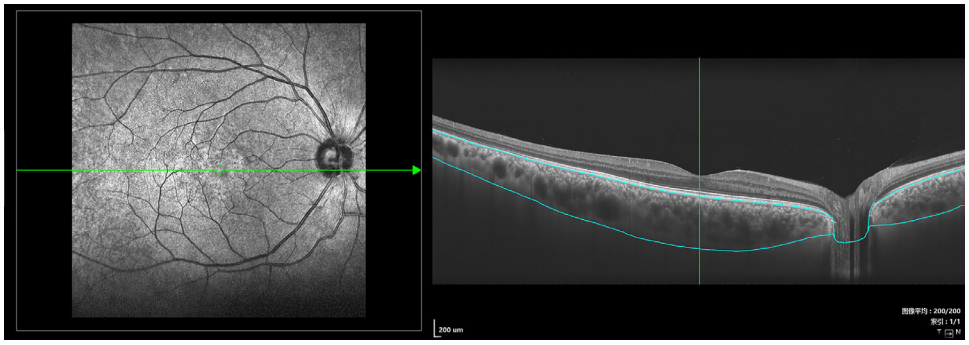

Figure 3. Choroidal thickness was obtained in enhanced-depth mode with horizontal line scans passing through the fovea in the 5 * 30° range. An automatic real-time (100 frames) averaging mode was applied to ensure good-quality images. The chorioscleral interface was automatically identified by built-in software and then adjusted by a specialist masked to clinical data. Choroidal thickness was measured automatically when the specialist adjusted the aiming line through the central fovea.

(2) white-to-white distance (WTW); (3) LT; and (4) AL. The acquisition and analysis methods were as follows: a specialist (XZ) examined all the patients and controls in the same dark room from 15:00 to 16:00. The built-in software automatically identified the positions of the anterior and posterior vertices of the cornea, the anterior and posterior vertices of the lens, the macular fovea and the corneoscleral margin. The measurer monitored the recognition during the measurement process to ensure accuracy.

Choroidal thickness was measured 30 minutes after pupil dilation (topiramate 0.5%) with SS-OCT (VG200; SVision Imaging, Ltd., Luoyang, China) by a single specialist (XZ) from 15:00 to 16:00 in a standard illuminated room. The images were obtained in enhanced-depth mode with horizontal line scans passing through the fovea in the 5 * 30° range. An automatic real-time (100 frames) averaging mode was applied to ensure good quality images. The chorioscleral interface was automatically identified by built-in software and then adjusted by a specialist (XZ) masked to the clinical data. Total choroidal thickness was defined as the vertical perpendicular distance from the outer portion of the retinal pigment epithelium to the hyperreflective line of the chorioscleral interface (Fig. 3).

GH and IGF-1 Burden

The term disease duration was defined as the time from the first emergence of clinical symptoms (according to the medical history acquired from the patients) to surgical or medical treatment. The terms GH burden and IGF-1 burden were defined as the product of disease duration and the average level of baseline serum GH or IGF-1 before surgery or any treatment. Serum GH and lGF-1 levels were routinely measured at 7:00 AM after fasting before surgery. Serum GH and IGF-1 levels were measured at least two times before surgery. The result obtained at the measuring time closest to the ophthalmology test was used in the correlation analysis. All the patients underwent 7:00 AM fasting anterior pituitary hormone examinations, including a 75-g glucose OGTT and fasting blood glucose test, two-hour postprandial blood glucose test, and serum free cortisol, ACTH, TSH, T3, T4, free T3, free T4, PRL, FSH, LH, testosterone, and estradiol tests. The lowest GH level based on a 75-g glucose OGTT before treatment was defined as the nadir GH level.

Statistics

All statistical analyses were performed using SPSS software version 26.0 (IBM, Chicago, IL, USA). Data that conformed to a normal distribution were expressed as the mean ± standard deviation, whereas data that did not conform to a normal distribution were expressed as the median (Q1, Q3). For comparison across cohorts, Student's t tests and χ^2 tests were used for the baseline demographic characteristics, whereas Student's t test (for normally distributed variables) and the independent sample Mann-Whitney U test (for nonnormally distributed variables) were applied for anterior segment parameters. Pearson correlation analysis was applied to test the relationship between anterior segment parameters and disease duration, serum GH level, serum IGF-1 level, GH burden, IGF-1 burden, and choroidal thickness, whereas the Spearman rank correlation was applied when the variables did not conform to a normal distribution. After adjusting for age and AL, linear regression models were constructed to explore the possible independent structural and endocrine risk factors for angle width. In linear regression, GH burden and IGF-1 burden were excluded due to their strong collinearity with the GH level and IGF-1 level. Interobserver reliability and intraobserver reliability are expressed as intragroup correlation coefficients. In the intercohort comparison, binocular data were included, while in the regression analysis, binocular balance was performed first, and the average of binocular measurements was then taken for regression analysis. $P < 0.05$ (bilateral) was considered statistically significant.

Results

Demographic Characteristics

There was no significant difference in the sex ratio, age, refraction error, BCVA or IOP between the acromegaly group (30 individuals, 60 eyes) and the normal control group (30 individuals, 60 eyes) (Table 1). The average disease duration of the acromegaly patients was 6.41 ± 4.59 years; the mean visual field defect (MD) was 0.96 ± 0.42; the median serum GH level was 13.2 (7.06, 31.95) ng/mL; the average serum IGF-I level was 650.77 ± 217.85 ng/mL; the median GH burden was 84.05 (39.8, 2224.6) ng * y/mL; and the average IGF-I burden was 4458.25 ± 3655.98 ng * y/mL. All of the recruited patients were within the normal range for

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Table 1. Comparison of Demographic Data, Clinical Characteristics, and Anterior Segment Parameters Between Acromegaly Patients and Controls

	Acromegaly Group	Control Group	*P* Value
No. of eyes	60	60	>0.999
Age (y)	46.46 ± 10.83	46.46 ± 12.16	>0.999
Sex			>0.999
Male	11	11	
Female	19	19	
Best corrected visual acuity (logMar)	0 (0, 0)	0 (0, 0)	0.400*
Spherical equivalent (D)	−0.41 ± 1.41	−0.21 ± 0.95	0.417
Intraocular pressure (mm Hg)	14.81 ± 2.15	14.74 ± 3.01	0.874
Axial length (mm)	23.64 ± 0.91	23.37 ± 0.81	0.088
Central corneal thickness (mm)	533.25 ± 28.53	537.40 ± 30.78	0.158
Anterior chamber parameters (SD-OCT)			
ACD-SD (mm)	2.78 ± 0.36	2.68 ± 0.33	0.138
ACW (mm)	11.19 ± 0.54	11.31 ± 0.45	0.205
LV (µm)	125.33 ± 330.46	242.00 ± 281.54	0.041
Scotopic Pupil Diameter-SD (mm)	4.73 ± 0.83	4.99 ± 0.91	0.104
Anterior chamber parameters (SS-OCT)			
ACD-SS (mm)	3.23 ± 0.35	3.14 ± 0.34	0.179
WTW (mm)	11.78 ± 0.46	11.86 ± 0.86	0.265
LT (mm)	4.38 ± 0.52	4.26 ± 0.33	0.102
ACD-SS/AL	0.136 ± 0.0124	0.134 ± 0.012	0.350
LT/AL	0.186 ± 0.025	0.182 ± 0.018	0.380

ACD-SD, anterior chamber depth measured with SD-OCT in a darkroom.

Continuous variables conforming to a normal distribution are described as the mean ± standard deviation, and a *t* test was used for intergroup comparison.

* Continuous variables that did not conform to a normal distribution are described as the median (Q1, Q3), and the independent sample Mann-Whitney U test was used for intergroup comparisons.

Table 2. Comparison of Iris Thickness, Iris Curvature, and Pupil Diameter Between Acromegaly Patients and Controls

	Acromegaly Group	Control Group	Increased Portion	*P* Value
NIT300 (mm)	0.365 ± 0.072	0.298 ± 0.067	1.22	<0.001
NIT200 (mm)	0.500 ± 0.066	0.441 ± 0.061	1.13	<0.001
NIT100 (mm)	0.589 ± 0.079	0.525 ± 0.075	1.12	<0.001
NIT_{ave}	0.485 ± 0.041	0.421 ± 0.044	1.15	<0.001
TIT100 (mm)	0.557 ± 0.075	0.488 ± 0.083	1.14	<0.001
TIT200 (mm)	0.482 ± 0.067	0.434 ± 0.061	1.11	<0.001
TIT300 (mm)	0.372 ± 0.076	0.326 ± 0.077	1.14	0.001
TIT_{ave}	0.470 ± 0.046	0.416 ± 0.049	1.12	<0.001
NIC (mm)	0.14 (0, 0.22)	0.18 (0.13, 0.22)		0.045*
TIC (mm)	0.15(0.03, 0.21)	0.18 (0.14, 0.21)		0.046*

NIC, nasal iris curvature; TIC, temporal iris curvature.

Continuous variables conforming to a normal distribution are described as the mean ± standard deviation, and a *t* test was used for intergroup comparisons.

* Continuous variables that did not conform to a normal distribution are described as the median (Q1, Q3), and the independent sample Mann-Whitney U test was used for intergroup comparisons.

the pituitary thyroid, pituitary-adrenal, and pituitary-gonadal axes.

Anterior Segment Parameters

A significantly smaller LV was detected in the acromegaly patients ($P = 0.041$; Table 1). In addition, the IT of all measuring points in the acromegaly group were evenly thickened (1.11–1.22 times, Table 2). Among them, there was a very significant difference between the two groups in the NIT100, NIT200, NIT300, TIT100, and TIT200 points (all $P < 0.001$), and there was a significant difference between the two groups in the TIT300 points ($P = 0.001$; Table 2). The nasal and temporal IC values in the patients with acromegaly were significantly lower than those of the normal subjects (nasal, $P = 0.043$ and 0.036, respectively; Table 2). In addition, the nasal AOD500, AOD750, TISA500, and TISA750 and temporal AOD500, AOD750, TISA500 and TISA750 in the acromegaly group were significantly higher than those in the normal control group (all $P < 0.001$; Table 3).

No significant difference was detected in CT, AL, WTW, ACW, LT, scotopic pupil diameter or ACD measured by either SD-OCT or SS-OCT between the two groups (all $P > 0.05$; Table 1). We further calculated two ratios for a better description of the structure of acromegalic eyes: ACD/AL and LT/AL (ACD was measured by SS-OCT). The results showed no significant difference between the two groups (all $P > 0.05$, respectively; Table 1).

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Table 3. Comparison of AOD500, AOD750, TISA500, and TISA750 Between Acromegaly Patients and Controls

	Acromegaly Group	Control Group	*P* Value
N AOD500 (mm)	0.501 ± 0.187	0.272 ± 0.138	<0.001
N AOD750 (mm)	0.705 ± 0.264	0.541 ± 0.221	<0.001
N TISA500 (mm^2)	0.180 ± 0.066	0.125 ± 0.052	<0.001
N TISA750 (mm^2)	0.334 ± 0.124	0.242 ± 0.097	<0.001
T AOD500 (mm)	0.451 ± 0.199	0.333 ± 0.158	<0.001
T AOD750 (mm)	0.611 ± 0.243	0.454 ± 0.197	<0.001
T TISA500 (mm^2)	0.161 ± 0.073	0.117 ± 0.053	<0.001
T TISA750 (mm^2)	0.290 ± 0.120	0.213 ± 0.095	<0.001

N, nasal; T, temporal.

Continuous variables conforming to a normal distribution are described as the mean ± standard deviation, and a *t* test was used for intergroup comparisons.

Correlations Between the Anterior Segment Parameters and Endocrine Parameters

We further explored the correlation between the anterior segment parameters and disease duration, serum GH level, serum IGF-1 level, GH burden and IGF-1 burden of the acromegaly patients. After binocular balance, no significant correlation was detected between CT, AL, LT, LV, ACW, WTW, IOP and endocrine parameters (Supplementary Table S1). However, ACD measured with SS-OCT ($r = 0.394$, $P = 0.031$) and ACD measured with SD-OCT ($r = 0.370$, $P = 0.044$) were significantly correlated with the serum GH level (Supplementary Table S1).

In the acromegaly patients, the pupil diameter was significantly correlated with the IGF-1 level ($r = 0.413$, $P = 0.023$), GH burden ($r = 0.366$, $P = 0.047$) and IGF-1 burden ($r = 0.503$, $P = 0.005$) (Fig. 4A, Supplementary Table S2). The serum IGF-1 level was also significantly correlated with the NIT_{ave} ($r = 0.362$, $P = 0.049$); and TIT_{ave} ($r = 0.369$, $P = 0.045$; Fig. 4A, Supplementary Table S2); the NIT_{ave} and TIT_{ave} were also correlated with the subfoveal choroid thickness ($r = 0.441$, $P = 0.015$ and $r = 0.381$, $P = 0.038$, respectively). The IC, however, was not correlated with any endocrine parameters (Fig. 4A, Supplementary Table S2).

The serum GH level was significantly positively correlated with the nasal AOD500 (r = 0.488, P = 0.006), nasal AOD750 ($r = 0.513$, $P = 0.004$), and nasal TISA750 ($r = 0.494$, $P = 0.006$) and was correlated with the nasal TISA500 ($r = 0.463$, $P = 0.010$), temporal AOD750 ($r = 0.406$, $P = 0.026$), temporal TISA500 ($r = 0.415$, $P = 0.022$), and temporal TISA750 ($r = 0.427$, $P = 0.018$). The serum IGF-1 level was positively correlated with the nasal AOD750 ($r = 0.382$, $P = 0.037$), nasal TISA750 ($r = 0.366$, $P = 0.047$), temporal AOD500 ($r = 0.370$, $P = 0.044$), temporal AOD750 ($r = 0.378$, $P = 0.039$), and temporal TISA750 ($r = 0.381$, $P = 0.038$) (Fig. 4B, Supplementary Table S3).

Linear Regression

The predictors of angle width (AOD500, AOD750) were analyzed in the acromegaly patients via multiple linear regression models (Table 4). After controlling for age and AL, the independent factors associated with a narrower angle, ranked by their contribution to the variation in angle width, were a more curved iris (standardized regression coefficient [SRC] = −0.530 and −0.547 for AOD500 and AOD750, respectively; $P < 0.001$) and a larger LV (SRC = −0.434 and −0.536 for AOD500 and AOD750, respectively; $P = 0.012$ and 0.004) for the nasal side. For the temporal angle width, the associated factors were a more curved iris (SRC = −0.614 and −0.667 for AOD500 and AOD750, respectively; $P < 0.001$) and a larger LV (SRC = 0.380 for AOD750, $P = 0.001$).

We developed another linear regression model to further validate the independent endocrine risk factors associated with the angle width in the acromegaly patients. After controlling for age and AL, a higher serum GH level was an independent risk factor for enhanced TAOD750 ($\beta = 0.002$, $P = 0.028$) and TTISA750 ($\beta = 0.001$, $P = 0.030$, Table 5).

Moreover, after controlling for age and AL, IGF-1 was an independent factor of increased pupil diameter ($\beta = 0.002$, $P = 0.031$; Table 5), thicker iris of both the nasal ($\beta = 6.781*10^{-5}$; $P = 0.049$) and temporal side ($\beta = 7.736*10^{-5}$, $P = 0.045$; Table 5) and smaller curvature of the temporal iris ($\beta < 0.001$, $P = 0.037$; Table 6).

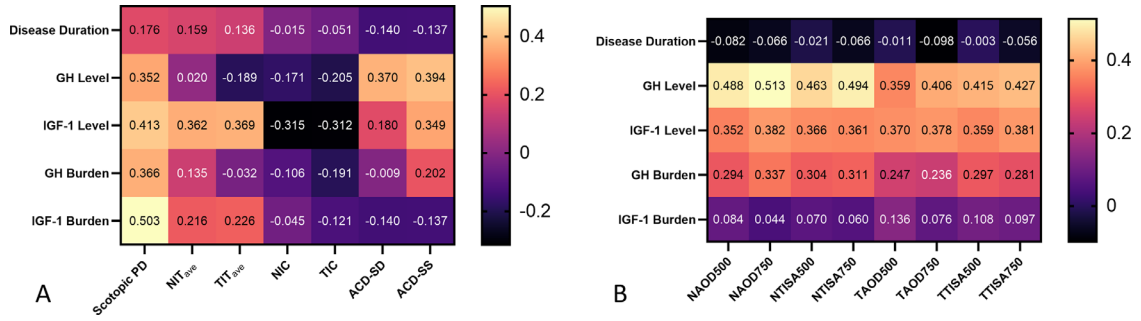

Figure 4. (A) Correlation between disease duration, GH level, IGF-1 level, GH burden, IGF-1 burden and pupil diameter (PD), IT, IC and ACD of acromegaly patients: NIT_{ave}, nasal average iris thickness; NIC, nasal iris curvature; TIC, temporal iris curvature. The scotopic pupil diameter was significantly correlated with the IGF-1 level ($r = 0.413$, $P = 0.023$) and GH burden ($r = 0.366$, $P = 0.047$) and was very significantly correlated with the IGF-1 burden ($r = 0.503$, $P = 0.005$,); NIT_{ave} was significantly correlated with the IGF-1 level ($r = 0.362$, $P = 0.049$), and TIT_{ave} was significantly correlated with the IGF-1 level ($r = 0.369$, $P = 0.045$). (B) Correlation between disease duration, GH level, IGF-1 level, GH burden, IGF-1 burden, and AOD500, AOD750, TISA500, TISA750 in acromegaly patients. N, nasal; T, temporal. The serum GH level was positively correlated with NAOD500 ($r = 0.488$, $P = 0.006$), NAOD750 ($r = 0.513$, $P = 0.004$), NTISA500 ($r = 0.463$, $P = 0.010$), NTISA750 ($r = 0.494$, $P = 0.006$), TAOD750 ($r = 0.406$, $P = 0.026$), TTISA500 ($r = 0.415$, $P = 0.022$), and TTISA750 ($r = 0.427$, $P = 0.018$). The level of serum IGF-1 was significantly correlated with NAOD750 ($r = 0.382$, $P = 0.037$), NTISA750 ($r = 0.366$, $P = 0.047$), TAOD500 ($r = 0.370$, $P = 0.044$), TAOD750 ($r = 0.370$, $P = 0.044$), and TTISA750 ($r = 0.378$, $P = 0.039$). The number in the square represents the correlation coefficient *R*. For the normally distributed variables, Pearson correlation was used for testing; Spearman rank correlation was used to test the variables that did not conform to a normal distribution.

Table 4. Anterior Segment Parameters Associated With AOD500 and AOD750 Measured in Acromegaly Patients

	B	*P* Value	95% CI	SRC
NAOD500				
PD	0.007	0.789	−0.044 to 0.057	0.028
ACW	−0.42	0.376	−0.054 to 0.137	0.116
LV	**−0.235**	**0.012**	**−0.413 to −0.057**	**−0.434**
IC	**−0.660**	<0.001	**−0.939 to −0.382**	**−0.530**
IT	−0.598	0.217	−1.572 to 0.377	−0.140
AL	0.005	0.859	0.016 to 0.053	0.026
AGE	−0.003	0.172	0.004 to −0.007	−0.179
NAOD750				
PD	−0.005	0.890	−0.079 to 0.069	−0.015
ACW	0.078	0.261	−0.062 to 0.217	0.154
LV	**−0.406**	0.004	**−0.666 to 0.145**	**−0.536**
IC	**−0.953**	<0.001	**−1.360 to −0.546**	**−0.547**
IT	−0.905	0.201	−2.330 to 0.519	−0.152
AL	−0.031	0.460	−0.116 to 0.054	−0.114
AGE	−0.002	0.269	−0.000 to 0.003	−0.150
TAOD750				
PD	−0.013	0.718	−0.086 to 0.060	−0.043
ACW	−0.002	0.984	−0.139 to 0.134	−0.005
LV	**−0.262**	0.001	**−0.412 to −0.112**	**0.380**
IC	**−1.095**	<0.001	**−1.452 to −0.738**	**−0.667**
IT	−0.050	0.932	−1.248 to 1.148	−0.010
AL	0.036	0.374	−0.046 to 0.117	0.144
AGE	−0.002	0.399	−0.008 to 0.003	−0.124
TAOD500				
PD	−0.012	0.693	−0.075 to 0.051	−0.049
ACW	0.009	0.872	−0.108 to 0.129	0.024
LV	−0.080	0.435	−0.289 to 0.129	−0.140
IC	**−0.835**	<0.001	**−1.198 to −0.473**	**−0.614**
IT	−0.218	0.665	−1.250 to 0.813	−0.054
AL	0.047	0.178	−0.023 to 0.117	0.185
AGE	−0.002	0.348	−0.007 to 0.003	−0.144

B, regression coefficient; CI, confidence interval; PD, pupil diameter; AGE, age of the patients.

Multiple linear regression models were constructed controlling for the AL and age. ACD was excluded because of its strong collinearity with LV. In the NAOD500 and NAOD750 models, NIT_{ave} and NIC were included, while in the TAOD500 and TOAD750 models, TIT_{ave} and TIC were included. The VIF of all variables was <5. The residuals conformed to a normal distribution. Bold *P* values denote statistical significance at the $P < 0.05$ level.

Table 5. Endocrine Parameters Associated With AOD500 and AOD750 in Acromegaly Patients

	B	*P* Value	95% CI	SRC
NAOD500				
DD	0.004	0.577	−0.010 to 0.017	0.098
IGF−1	0.000	0.449	0.000 to 0.000	0.145
GH	0.001	0.277	−0.001 to 0.003	0.203
AL	**0.073**	**0.017**	**0.014 to 0.131**	**0.376**
AGE	**−0.006**	**0.013**	**−0.011 to −0.001**	**−0.415**
NAOD750				
DD	−0.001	0.923	−0.019 to 0.017	−0.016
IGF−1	0.000	0.342	0.000 to 0.001	0.171
GH	0.001	0.229	−0.001 to 0.004	0.212
AL	0.080	0.064	−0.005 to 0.165	0.295
AGE	**−0.009**	**0.016**	**−0.016 to −0.002**	**−0.414**
NTISA500				
DD	$9.793*10^{-5}$	0.965	−0.005 to 0.004	−0.007
IGF−1	$4.223*10^{-5}$	0.410	0.000 to 0.000	0.149
GH	0.000	0.229	0.000 to 0.001	0.213
AL	**0.026**	**0.023**	**−0.004 to 0.000**	**0.373**
AGE	**−0.002**	**0.040**	**−0.004 to 0.047**	**−0.351**
NTISA750				
DD	$-2.025*10^{-5}$	0.996	−0.008 to 0.008	−0.001
IGF−1	$7.495*10^{-5}$	0.433	0.000 to 0.000	0.142
GH	$7.495*10^{-5}$	0.228	0.000 to 0.002	0.214
AL	**0.045**	**0.026**	**0.004 to 0.085**	**0.349**
AGE	**−0.004**	**0.032**	**−0.007 to −0.001**	**−0.382**
TAOD500				
DD	0.002	0.810	−0.012 to 0.015	0.041
IGF−1	0.000	0.426	0.000 to 0.000	0.147
GH	0.001	0.252	−0.001 to 0.003	0.206
AL	**0.083**	**0.015**	**0.017 to 0.149**	**0.407**
AGE	−0.005	0.070	−0.010 to 0.000	−0.331
TAOD750				
DD	0.000	0.953	−0.017 to 0.016	0.045
IGF−1	0.000	0.422	0.000 to 0.001	0.143
GH	**0.002**	**0.028**	**0.000 to 0.004**	**0.330**
AL	**0.094**	**0.016**	**0.019 to 0.169**	**0.382**
AGE	**−0.006**	**0.042**	**−0.012 to 0.000**	**−0.322**
TTISA500				
DD	0.000	0.994	−0.006 to 0.005	−0.013
IGF−1	$5.339*10^{-5}$	0.385	0.000 to 0.000	0.173
GH	0.000	0.341	0.000 to 0.001	0.184
AL	**0.029**	**0.029**	**0.003 to 0.055**	**0.389**
AGE	−0.001	0.186	−0.004 to 0.001	−0.240
TTISA750				
DD	−0.001	0.903	−0.009 to 0.008	−0.021
IGF-1	$9.123*10^{-5}$	0.348	0.000 to 0.000	0.38
GH	**0.001**	**0.030**	**0.000 to 0.002**	**0.345**
AL	**0.061**	**0.003**	**0.023 to 0.100**	**0.496**
AGE	−0.003	0.138	−0.006 to 0.001	−0.259

B, regression coefficient; CI, confidence interval; DD, disease duration; AGE, age of the patients.

Multiple linear regression models were constructed controlling for the AL and age; VIF of all variables <5; the residual conforms to the normal distribution. Bold *P* values denote statistical significance at the $P < 0.05$ level.

Reliability Analysis

The scleral spur and sclerochoroidal junction can be visualized and clearly defined in all eyes, and no images were excluded because of an inability to delineate the border of the iris and choroid. The intraobserver and interobserver intraclass correlation coefficients of the IT ranged from 0.944 to 0.976 and 0.881 to 0.985, respectively (Supplementary Table S4). The intraobserver and interobserver intraclass correlation coefficients of the IC ranged from 0.935 to 0.941 and 0.869 to 0.873, respectively (Supplementary Table S4). The intraobserver and interobserver intraclass correlation coefficients of the angle width (AOD and TISA) ranged from 0.892 to 0.948 and 0.812 to 0.946, respectively (Supplementary Table S4). The results showed good agreement for IT, IC, and ACA measurements within and between observers.

Discussion

In the present study, we validated that scotopic pupil diameter in the acromegaly patients showed significant positive correlations with the IGF-1 level, GH burden and IGF-1 burden, with no difference from the healthy controls. The linear regression model showed that a high serum IGF-1 level was independently correlated with larger pupil sizes in dark rooms. These results indicated that endocrine hormones, especially IGF-1, may affect pupil size in acromegaly patients and possibly share a cumulative effect. Pupil size is jointly controlled by two interconnected yet distinct pathways: the parasympathetic contraction pathway

Investigative Ophthalmology & Visual Science

Table 6. Endocrine Parameters Associated With Pupil Diameter, Iris Thickness, Iris Curvature, and ACD in Acromegaly Patients

	B	*P* Value	95% CI	SRC
Scotopic pupil diameter				
DD	0.020	0.816	−0.090 to 0.131	0.043
IGF−1	**0.002**	**0.031**	**0.000 to 0.004**	**0.394**
GH	0.007	0.846	−0.008 to 0.021	0.168
AL	0.262	0.315	−0.265 to 0.778	0.200
AGE	0.008	0.726	−0.036 to 0.051	0.073
NIT_{ave}				
DD	0.002	0.663	−0.002 to 0.005	0.081
IGF−1	**$6.781*10^{-5}$**	**0.049**	**0.000 to 0.000**	**0.362**
GH	$-8.008*10^{-5}$	0.851	−0.001 to 0.000	−0.039
AL	−0.004	0.669	−0.022 to 0.015	−0.085
AGE	−0.001	0.152	−0.003 to 0.000	0.152
TITave				
DD	0.000	0.633	−0.004 to 0.005	0.088
IGF−1	**$7.736*10^{-5}$**	**0.045**	**0.000 to 0.000**	**0.369**
GH	0.000	0.261	−0.002 to 0.002	−0.228
AL	−0.002	0.833	−0.023 to 0.019	−0.030
AGE	$-4.122*10^{-6}$	0.996	−0.002 to 0.002	−0.001
NIC				
DD	0.003	0.664	−0.10 to 0.016	0.092
IGF−1	0.000	0.309	0.000 to 0.000	−0.234
GH	0.000	0.725	−0.002 to 0.001	−0.078
AL	−0.031	0.288	−0.091 to 0.028	−0.208
AGE	0.002	0.398	−0.003 to 0.007	0.173
TIC				
DD	0.001	0.607	−0.012 to 0.013	0.095
IGF−1	**0.000**	**0.037**	**0.000 to 0.000**	**−0.383**
GH	0.000	0.617	−0.002 to 0.001	−0.102
AL	−0.041	0.185	−0.103 to 0.021	−0.264
AGE	0.002	0.500	−0.003 to 0.007	0.140
ACD-SD				
DD	−0.14	0.235	−0.039 to 0.010	−0.187
IGF-1	0.01	0.068	0.000 to 0.001	0.315
GH	−0.01	0.615	−0.004 to 0.002	−0.082
AL	**−0.153**	**0.012**	**0.036 to 0.269**	**0.383**
AGE	**−0.013**	**0.012**	**−0.022 to 0.003**	**−0.404**

B, regression coefficient; CI, confidence interval; DD, disease duration; AGE, age of the patients.

Multiple linear regression models were constructed controlling for the AL and AGE; VIF of all variables <5; the residual conforms to the normal distribution. Bold *P* values denote statistical significance at the $P < 0.05$ level.

and the sympathetic dilation pathway.[22] Herein, the levels of GH and IGF-1 may impact the pupil size through sympathetic innervation. The sympathetic-mediated vasoconstrictive response was found to increase in active acromegaly patients in a study conducted by Maison et al.[23] Furthermore, Chemla et al.[24] found decreased sympathetic and increased parasympathetic modulation of the cardiovascular system in acromegaly patients in the remission stage with normalized serum IGF-1 levels.

Because of the irregularity of the front surface, IT can be affected by its furrows and crypts.[25] In the present study, IT was measured at six points on the nasal and temporal sides and found to be evenly thickened in the acromegaly patients, consistent with the hypothesis that the thickening is attributed to systemic diseases or hormones. Further analysis showed that the average nasal and temporal IT values of the acromegaly patients were significantly correlated with the serum IGF-1 level, indicating the possibility that of all the endocrine factors, IGF-1 affects IT with no significant cumulative effect. The iris is a dynamic and layered structure, a permeable sponge-like structure that allows the free passage of fluid between the iris stroma and aqueous solution.[26] Similar to the choroid, the iris stroma is composed of highly vascularized connective tissue containing melanocytes, melanin granules and pigment cells. A previous study estimated that iris vessels comprise up to 10% of iris volume in vivo. Hence, changes in iris volume and thickness might be correlated with changes in iris blood volume.[27] The increased sympathetic innervation in acromegaly patients leads to decreased iris venous outflow, which in turn expands the intravascular space and results in a thicker iris. On the other hand, an increased serum IGF-1 level has been demonstrated in animal models to regulate the expression of vascular endothelial growth factor (VEGF).[28,29] The high VEGF levels in the aqueous humor and vitreous have been confirmed to be correlated with an increase in IT.[30] Previous studies have validated that insulin-like growth factor binding protein-1 mRNA can be detected in rat irises.[31] Insulin-like growth factor binding protein-1 may act as a target of IGF-1 and VEGF in the aqueous humor and is worth further study. In addition, iris stroma is rich in fibroblasts, melanocytes, and melanin particles. IGF-1 can significantly promote the proliferation of fibroblasts[32] and melanocytes and the formation of melanin particles[33] to increase the IT of acromegaly patients. Our study has revealed a significant correlation between the IT and the foveal choroidal thickness in acromegaly patients. The choroid and iris are continua of each other and share a similar structure, with the IGF system expressed on both.[31,34] The correlation between choroidal thickness and IT has been confirmed in healthy individuals.[14] Therefore IGF-1 may increase the iris and choroidal thickness in patients with acromegaly through a similar mechanism.

No difference was detected in the CT, AL, LT, ACW, WTW, LT/AL, or ACD/AL between the acromegaly patients and normal controls, and no correlations were detected between the above anterior segment parameters and disease duration, serum IGF-1 level, serum GH level, IGF-1 burden, or GH burden in the acromegaly patients. Past studies demonstrated conflict results toward central corneal thickness of acromegaly patients as Ozkok et al.,[35] Kan et al.,[36] and Sen et al.[10] measured central CT with an ultrasound pachymeter and reported no significant difference, whereas Altinkaynak et al.[11] documented a significantly thicker cornea in acromegaly patients than in healthy controls with a Placido disk topographer. Our study adopted SS-OCT to measure central corneal thickness, and our results supported the former two studies. As an adult-onset systemic disease, acromegaly has little effect on the AL, LT, ACW, and WTW, which has been demonstrated to be more correlated with genetics and development. A case report showed that the body height of adolescent patients with cerebral gigantism was higher than that of normal people, as were the corneal diameter and binocular AL,[37] indicating that excessive GH and IGF-1 secretion might have an impact on eye structures during development but has little impact on individuals in adulthood. This hypothesis is also consistent with the conclusion that the AL and height of normal people are significantly correlated.[38] Additionally, no significant difference was detected in IOP. Varies methods, such as Goldmann applanation tonometer and ORA, have been adopted to measure the IOP of acromegaly patients, although conflicting results have been reported.[10,35,36] Because it may be influenced by multiple factors, such as corneal biomechanical properties, systemic hormones, and the aquaous outflow pathway, the IOP of acromegaly patients should be further discussed in future studies.

Investigative Ophthalmology & Visual Science

In the present study, we found that the ACA width of the acromegaly patients was significantly larger than that of the normal controls, with temporal AOD750 and TISA750 independently positively correlated with the serum GH level. Positive correlations were also detected between the ACD and serum GH level, although there was no significant difference in the ACD between the two groups. These results highlighted the possible impact of an excessive GH level on anterior segment structures. The underlying mechanisms and the impact of GH on adolescents are worth further investigation. This conclusion is inconsistent with that of Kilic et al.[5], who detected the iris corneal angle of acromegaly patients using a Scheimpflug camera and observed that it was significantly narrower than that of normal controls. These conflicts may be explained by the use of different methods and procedures to measure ACA and the possible selection bias introduced due to the lack of a comparison of the refraction error and axial length in the study by Kilic et al.[5] In the present study, only subjects with a refraction error between −1.50 D and 1.50 D spherical equivalent refraction were included to minimize the effects of refraction error on ACD and ACA.[39] No significant differences in the AL and refraction error were observed between the two groups. In the regression model, the effect of AL was controlled to ensure less of an effect on the results. Ethnic differences may also contribute to the inconsistency.

The ACA width affects the pathway of aqueous outflow, which is closely related to the onset of angle closure glaucoma. At present, the mainstream mechanism of anterior segment optical coherence tomography–detected angle closure mainly includes the following four points: pupil block, plateau iris, thickening of peripheral collarette, and increased height of the LV.[40] The acromegaly patients had an evenly thickened iris with a similar degree of thickening (1.12–1.22 times) at 1 mm, 2 mm, and 3 mm from the pupil edge. Paradoxically, the temporal AOD500, bilateral AOD750, bilateral TISA500 and bilateral TISA750 were significantly larger than those in the normal controls. Therefore we further measured the IC and LV and found a less curved iris and smaller LV in the acromegaly patients. We developed a linear regression model and recognized a less curved iris and larger ACD to be independently correlated with the AOD and TISA, which is consistent with previous studies on Chinese people showing that the LV is an independent factor affecting the ACA width, whose influence outweighs those of the IT and IC.[10]

In conclusion, the scotopic pupil size, IT, and ACA width increased in acromegaly patients, whereas the IC and LV decreased. Therefore we can roughly outline the basic characteristics of the anterior chamber structure in acromegaly patients: a relatively thickened and flat iris, a relatively backward lens, and the resulting relatively widened angle. A higher serum IGF-1 level was independently correlated with a larger pupil in dark rooms, a thicker iris, and a smaller temporal IC. The serum GH level was independently positively correlated with the temporal AOD750 and TISA750 and positively correlated with the ACD. The impact of excessive GH and IGF-1 on ocular structures should be noted, because GH and IGF-1 replacement therapy is increasingly widely used in clinical situations, including for patients with dwarfism and hypophysis, especially when the patients are not only adults but also juveniles. There are still some limitations in this study. First, we used SD-OCT when measuring IT; therefore the iris volume was not included. Second, the sample size was relatively small, and possible differences in the individuals participating in our study might be magnified. Larger cohorts should be included in further studies. Last but not least, we lacked a description of the position of the ciliary body; thus ultrasound biomicroscopy is a better tool to be adopted in the future to describe the position and structural characteristics of the iris and ciliary body and further clarify the reasons for the widening ACA of acromegaly patients.

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