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Corneal endothelial cell density and morphology in patients with acromegaly

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ABSTRACT

Objective: Acromegaly has various impacts on many organs. The ophthalmologic effects of acromegaly have not yet been investigated in detail. The aim of the current study was to evaluate qualitative and quantitative changes in corneal endothelial cells and central corneal thickness (CCT) of the patients with acromegaly.
Design: In this prospective, cross-sectional study, 128 eyes of 64 patients with acromegaly (female/male = 40/24) and 208 eyes of 104 age and gender-matched healthy volunteers (female/male = 69/35) were included. Endothelial cell density (ECD), cellular area (CA), coefficient of variation (CV) in cell size, percentage of hexagonal cells, and CCT were measured in patients with acromegaly and in healthy volunteers using the noncontact specular microscopy (SP-3000P: Topcon Corporation, Tokyo, Japan).
Results: ECD and CA were lower in cases with acromegaly than in controls (ECD in acromegaly: 2615.65 cell/mm^2 and in controls: 2700.35 cell/mm^2; $p = 0.002$. CA in acromegaly: 382.30 μm^2 and in controls: 400.30 μm^2; $p = 0.02$). In the entire group with acromegaly, the time elapsed since diagnosis was positively correlated with CA and was negatively correlated with ECD ($r = +0.39$, $p = 0.001$ and $r = -0.42$, $p = 0.001$).
Conclusions: The endothelial layer of the cornea may be under risk of impairment with prolonged disease duration in acromegaly. Consistency of the corneal endothelium should be also sought during long-term follow-up of the cases with acromegaly.

1. Introduction

Acromegaly is a multisystem endocrine disorder characterized by excessive growth hormone and insulin-like growth factor-1 (IGF-1). The excess in GH and IGF-1 affects various organs and has many systemic complications. Although the majority of the systemic complications in acromegaly have been widely evaluated before, the impact of acromegaly on the ophthalmologic system is less well known.

The corneal endothelium consists of a single layer of mitochondria-rich hexagonal cells, embryologically derived from the neural crest. It is attached to the rest of the cornea through Descemet's membrane and faces the anterior chamber of the eye. Healthy corneal endothelium is essential for corneal optical transparency, serving to pump water from the stroma to the aqueous humor and keeping the corneal stroma in its usual dehydrated state of 70% water [1].

Corneal endothelium changes in number, size and shape with certain insults, including advanced age [2]. It lacks the ability to regenerate; therefore, when the corneal endothelial cells become severely damaged or the cellular density falls below a critical threshold, the barrier and pump function cannot be maintained. The resultant excessive fluid accelerates swelling of the cornea and, accordingly, increases corneal thickness. Moreover, accumulation of fluid between the basal epithelial cells results in blister-like lesions, i.e., bullae. When the bullae are ruptured, the fluid content is released onto the surface. This causes a loss of corneal transparency, leading to disturbed vision and pain, which are the major indicators of keratoplasty [3,4]. Chronic endothelial cell loss may lead to corneal decompensation and transplant failure even after corneal transplantation, a procedure with a fair prognosis for most of the low-risk cases [5–7].

GH receptors are widely distributed throughout the human body and involve many tissues and organs [8,9]. Moreover acromegaly has been associated with mitochondrial dysfunction [10]. In this regard, mitochondrial dysfunction in acromegaly may also have some impact on the endothelial layer of the cornea, which includes abundant mitochondria. There are limited data on the association between ocular diseases and acromegaly. There are a few controversial results for central corneal thickness (CCT) in cases with acromegaly [11–14]. However, corneal endothelial features in cases with acromegaly have

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not been documented, yet. In this study, we aimed to evaluate qualitative and quantitative changes in corneal endothelial cells and CCT of the patients with acromegaly.

2. Materials and methods

A total of 128 eyes of 64 consecutive patients with acromegaly (controlled n = 43, uncontrolled n = 21) and 208 eyes of 104 age-matched and gender-matched volunteers without acromegaly were included in the study. Informed consent was obtained from all patients and the volunteers participating in the study. The study protocol was approved by the Ethics Committee of Cerrahpasa Medical School, Istanbul University and the study was conducted in accordance with the tenets of the Helsinki Declaration.

Fasting blood glucose, insulin, HbA1c, height and weight were obtained for each case. Height and weight were used to calculate body mass index (BMI). Additionally, for cases with acromegaly, GH and IGF-1 levels were obtained.

In cases with clinical findings of acromegaly, failure to suppress the lowest GH level to less than 1 ng/ml during oral glucose tolerance test and high levels of IGF-1 adjusted for age and gender were used as the criteria for uncontrolled acromegaly. In cases of acromegaly where the lowest GH levels were less than 1 ng/mL during OGTT and had IGF-1 within the normal age and gender-adjusted ranges, the acromegaly was considered to be controlled [15]. History of surgery and radiotherapy, medical therapy, disease duration and the presence of any systemic disease were obtained for all patients.

All subjects underwent a complete ophthalmological examination. Exclusion criteria for the study were refractive error (in spherical equivalent) of >±2.00 diopters, history of intraocular surgery, keratorefractive surgery, scleral or corneal disease, uveitis, connective tissue disease, history of contact lens use, systemic diseases, other endocrinopathies, smoking and alcohol consumption. Corneal endothelial cell density, morphology and CCT were examined with noncontact specular microscopy (SP-3000P: Topcon corporation, Tokyo, Japan). The same examiner performed all measurements between 09:30 and 11:00 am. The procedure for specular microscopy was as follows: three images from central cornea were taken and at least 100 contiguous cells and were manually marked by the examiner for analysis by a built-in software program. The ophthalmological examination was performed as a blind test, where the ophthalmologists were not aware of the disease status of the cases.

The parameters recorded from the system included endothelial cell density (ECD) (cell/mm^2), cell area (CA) (μm^2), coefficient of variation (CV), percentage of hexagonal cells (PHEX), and CCT. The CV (standard deviation divided by the mean cell area) was used as an index of the extent of variation in the cell area (polymegathism). PHEX in the analyzed area was used as an index of variation in cell shape (polymorphism).

The data was statistically analyzed with the SPSS 17.0 package program. The measurements obtained from the right and left eyes were merged for statistical analysis. The Chi-square test was used for categorical variables. Sample distribution was evaluated with the Kolmogorov–Smirnov test. Continuous variables with normal distribution were compared by using the Student's T test, presenting the results as mean and standard deviation. Continuous variables with non-normal distributions were compared by using the Mann–Whitney U test and the results were presented as median and interquartile range [IQR]. The Pearson's correlation coefficient was used for calculation of associations between variables. $p < 0.05$ was considered statistically significant.

3. Results

The mean age was 49.25 ± 11.94 years for the cases with acromegaly and was 45.86 ± 12.76 years for the control group ($p = 0.09$). Female/male distribution was not different between the two groups (40/24 in the acromegaly group and 69/35 in the control group, $p = 0.6$). The mean BMI in cases with acromegaly and the control group was 30.95 ± 6.21 and 27.35 ± 4.56 kg/m^2, respectively ($p = 0.02$). Fasting blood glucose and HbA1c levels were also higher in cases with acromegaly (fasting blood glucose in the acromegaly group: 100.24 ± 19.27 mg/dl and in the control group: 84.75 ± 7.67 mg/dl, $p < 0.001$. HbA1c in the acromegaly group: 5.83 ± 0.79 and in the control group: 5.46 ± 0.3, $p = 0.03$).

The evaluation of ocular data showed significantly lower ECD in cases with acromegaly compared to the control group ($p = 0.002$). Similarly, CA was also significantly lower in cases with acromegaly ($p = 0.002$). CCT was not different between cases with and without acromegaly ($p = 0.6$). Table 1 shows the comparison of ocular parameters between cases with acromegaly and the control group.

In the entire cohort, there was a negative but weak correlation between PHEX and HbA1c ($r = -0.23$, $p = 0.02$). PHEX was not correlated with fasting blood glucose and BMI ($p = 0.06$ and $p = 0.2$). CCT, ECD, CA and CV were not correlated with any of fasting blood glucose, HbA1c or BMI (data not shown here).

In the group with acromegaly, the median GH and IGF-1 levels were 0.9 [0.44–2.10] ng/dl and 227.25 [175.40–360.45] ng/dl, respectively. The duration between the onset of symptoms and diagnosis of acromegaly was 24.90 [12–60] months. Time elapsed since diagnosis of acromegaly was 54 [24.75–124.50] months.

When the acromegaly group was stratified by disease activity, there was no difference between cases with controlled and uncontrolled acromegaly in terms of age and gender ($p = 0.33$ and $p = 0.54$, respectively). Between controlled and uncontrolled acromegaly patients, there was no difference in mean duration of the symptoms before diagnosis and the time elapsed since diagnosis of the disease ($p = 0.96$ and $p = 0.36$). Nine patients (21%) with controlled acromegaly and 6 patients (29%) with uncontrolled acromegaly had hypopituitarism. Three patients had hypogonadism, 5 had hypothyroidism, 1 had hypocortisolism, 1 had hypothyroidism and hypogonadism, 1 had hypocortisolism and hypogonadism, and 4 had hypothyroidism and hypocortisolism. They were receiving appropriate hormone replacement therapy. GH and IGF-1 levels were higher in the uncontrolled cases than in the controlled cases ($p < 0.001$ and $p < 0.001$, respectively).

In the entire group with acromegaly, the time elapsed since diagnosis was positively correlated with CA and was negatively correlated with ECD ($r = +0.39$, $p = 0.001$ and $r = -0.42$, $p = 0.001$). When one case with outlining results was excluded the correlation of time elapsed since diagnosis with CA and ECD was still present ($r = +0.31$, $p = 0.02$ and $r = -0.31$, $p = 0.02$) (Fig. 1). In cases with acromegaly, HbA1c was correlated with CV in cell size and negatively correlated with PHEX ($r = +0.29$, $p = 0.02$ and $r = -0.29$, $p = 0.02$). Duration of symptoms before diagnosis, GH, IGF-1, BMI or fasting blood glucose was not related to any of the ophthalmologic measures in the acromegaly group (unpublished data). Medical therapy with an octreotide analogue, previous radiotherapy or surgery did not cause a significant difference in measurements of CCT, CA, CV in cell size, ECD and PHEX (unpublished data). CCT, CA, CV in cell size, ECD and PHEX were not different between the cases with controlled and uncontrolled acromegaly (Table 2).

Table 1
Ocular parameters of the cases with acromegaly and control group.

	Acromegaly (n = 64)	Control group (n = 104)	p
CCT	522.50 [498.50–540.25]	518.00 [500.50–543.75]	0.6
CA (μm^2)	382.30 [354.37–423.15]	400.30 [358.23–484.65]	***0.002***[a]
CV	34.35 [30.50–37.38]	34.75 [30.83–39.38]	0.2
ECD (cell/mm^2)	2615.65 [2363.10–2822.00]	2700.35 [2424.40–3162.43]	***0.002***[a]
PHEX (%)	57.00 [49.00–63.75]	57.00 [49.00–62.00]	0.5

CCT: Central corneal thickness, CA: Cell area, CV: Coefficient of variation, ECD: Endothelial cell density, and PHEX: Percentage of hexagonal cells.
Data was expressed as median and IQR.
[a] Statistically significant p values.