Objective Evaluation of Corneal Clarity in Pigment Dispersion Syndrome and Pigmentary Glaucoma

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ABSTRACT

Purpose: To compare the corneal densitometry (CD) measurements in patients with pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG).

Materials and Methods: This prospective comparative study included 22 eyes with PG, 19 eyes with PDS and 21 control individuals. After complete ophthalmological examination, all the eyes had central corneal thickness (CCT) and CD measurements by densitometry software of Pentacam HR-Scheimpflug corneal topography over a 12-mm diameter of the cornea. Chi-Square, Kolmogorov-Smirnov, analysis of variance, and Tukey's post-hoc tests were used for statistical analysis.

Results: All the eyes with PG were under prostaglandin monotherapy. The mean CCT was significantly higher in PG cases than the other groups (p=0.01). The mean CD of anterior layer at the 0-2 mm was significantly higher in PG than PDS cases and normal subjects (p=0.007). The mean CD of total layer at the 0-2 mm was significantly higher in PG cases than control subjects (p=0.03). The mean CD of anterior layer at the 2-6 mm was significantly higher in PG than PDS cases (p=0.04). There were no significant differences of CD in other zones and layers between the groups.

Conclusion: The presence of Krukenberg spindle, higher age in PG and the probable effects of glaucoma might cause corneal backscatter of light and increased CD particularly in anterior layers in central zones of cornea.

Keywords: cornea, densitometry, pigment dispersion syndrome, pigmentary glaucoma.

INTRODUCTION

Pigment dispersion syndrome (PDS) is characterized by the deposition of pigmented cells on the corneal endothelium, transillumination defects in the mid-periphery of the iris and hyperpigmentation of trabecular meshwork.[1,2] It is usually bilateral and common in male and myopic cases.[3] The source of the abnormal accumulation of the pigmented cells is the irido-zonular contact due to the posterior insertion of the iris and iris concavity. PDS can cause pigmentary glaucoma (PG), a type of secondary open-angle glaucoma, with increased intraocular pressure (IOP) and glaucomatous damage. It generally begins between 40 and 50 years of age and is caused by decreased trabecular outflow of aqueous humour due to pigment deposition of trabecular meshwork.[1,2]

Corneal densitometry (CD) is a measurement used in the objective evaluation of corneal clarity. It is positively related with corneal backscatter of light but inversely related with corneal transparency.[4-6] The Pentacam HR Scheimpflug system can analyze the corneal backscattered light and measure the CD in 3 layers (anterior, midstromal, and posterior) and 4 annular zones (0-2, 2-6, 6-10, and 10-12 mm).[7] These measurements are expressed in grayscale units (GSUs) and range from 0 (no opacification, maximum transparency) to 100 (completely opaque cornea, no transparency).

Previous studies have reported an increase in CD in disease associated with corneal deposits (such as pseudoexfoliation, subepithelial infiltrate associated with epidemic keratoconjunctivitis, monoclonal gammopathy, and Wilson's disease) as well as stromal edema due

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to endothelial cell dysfunction.[8] In addition, corneal densitometry was found to be associated with some physiologically independent factors.[4] According to this, CD measurements showed an inverse correlation with anterior chamber depth and corneal diameter, but had a positive correlation with age.

Our hypothesis was that excessive iris pigment liberation, presence of Krukenberg spindle, and probable effects of glaucoma might cause changes in corneal backscatter of light and CD in these patients. Here in this study, our purpose was to compare the CD in cases with PDS and PG and normal subjects and to discuss the possible mechanisms.

MATERIALS AND METHODS

This prospective study included 22 eyes of 22 cases with PG and 19 eyes of 19 cases with PDS who had been under control in Glaucoma department and 21 eyes of 21 control subjects who had been referred from the polyclinics of our tertiary referral eye care center between April 2018 and August 2019. All of the study procedures were conducted in accordance with the Declaration of Helsinki, and informed consents were taken from all of the participants. This study was approved by The Ethical Committee of Numune Training and Research Hospital. All patients were Turkish Caucasians.

All the eyes underwent detailed ophthalmological examination including best-corrected visual acuity (BCVA) with Snellen charts, slit-lamb examination, fundus examination by +90 D lens, IOP measurements with Goldmann applanation tonometry and gonioscopy with Goldmann three-mirror lens. Also retinal nerve fiber layer (RNFL) and optic nerve head (ONH) analysis with spectral-domain optical coherence tomography (OCT) (Spectralis Heidelberg Engineering) and visual field analysis (Humphrey Field Analyzer; SITA Standard 24-2 strategy, model 750i; Zeiss-Humphrey Instruments, Dublin, CA) were performed in all cases before CD measurements.

The inclusion criteria of PDS were 2 of 3 classic signs: Krukenberg spindle on the corneal endothelium, transillumination defects in the mid-periphery of the iris, uniform and diffuse hyperpigmentation of trabecular meshwork. Also the presence of pigmented cells in the anterior chamber and IOP <21 mmHg without glaucomatous appearance of ONH and glaucomatous findings in OCT and visual filed examination were inclusion criteria. In addition to the criteria for PDS, the inclusion criteria of PG were high IOP (≥21 mmHg) without antiglaucomatous agents, open iridocorneal angle (≥grade 3 according to Shaffer grading system) with uniform and diffuse hyperpigmentation of trabecular meshwork, ONH changes like cup to disc ratio ≥0.3, localized or generalised neuro-retinal rim defects, peripapillary choroidal atrophy or splitter hemorrhage, glaucomatous visual field findings like nasal step, arcuate, paracentral scotomas and abnormal glaucoma hemifield test. PG cases were mild to moderate glaucoma cases (mean deviation <-12 dB) according to Hodapp-Parrish-Anderson grading system. The mean MD value was -7.57±1.93 dB (between -4.2 and -11.4) and the mean global circumpapillary RNFL thickness was 68.22±7.05 µm (59-82 µm). In 14 eyes myopic glaucomatous discs and in the remaining 8 eyes focal ischemic discs were observed. In all of them glaucoma was under control with prostaglandin monotherapy. Terminal and end-stage glaucoma (mean deviation ≥-12 dB) cases were excluded.

The exclusion criteria were the cases who had any other types of glaucoma, any corneal diseases like keratokonus, corneal opacity, dry eye or any ocular surface diseases, previous ocular surgery, trauma, uveitis or other inflammation and contact lens use. Also diabetic cases were excluded.

Central corneal thickness (CCT) and CD values were measured by densitometry software of Pentacam HR-Scheimpflug corneal topography system (Oculus GmbH, Wetzlar, Germany). All measurements were performed by the same experienced clinician between 9 am and 2 pm under standard dim-light conditions without pupil dilation. The CD values of anterior layer (anterior 120 µm), central (between anterior layer and posterior 60 µm), posterior layer (posterior 60 µm) of 4 annular concentric zones as 0-2 mm zone, 2-6 mm zone, 6-10 mm zone and 10-12 mm zone were measured. The CD values were expressed in grayscale units (GSC) as 0 for maximum transparency and 100 for total corneal opacity.

Statistical analysis was performed using SPSS v.21.0 for Windows (SPSS, Inc., Chicago, IL, USA). The normality of the data distribution was evaluated by Kolmogorov-Smirnov test. Chi-Square, one-way ANOVA and Tukey's post-hoc tests were used for statistical analysis. P values less than 0.05 were considered statistically significant.

RESULTS

The mean age of 15 male (68.2%) and 7 female (31.8%) PG cases was 44.4±6.9, the mean age of 10 male (52.6%) and 9 female (47.4%) PDS cases was 38.9±4.6 and the mean age of 11 male (52.4%) and 10 female (47.6%) control subjects was 39.1±4.9 (p=0.46, p=0.005; sex and

age respectively). PG cases were significantly older than the PDS cases and the control subjects. The mean period of glaucoma was 24.1±18.1 months in PG cases. In all eyes with PG laser peripheral iridotomy (LPI) procedure had been performed before, while it was performed in 9 eyes with PDS. The mean IOP values in PG cases, PDS cases and control subjects were 17.3±2.1 mmHg (under glaucoma treatment), 16.4±2.1 mmHg and 16.8±1.8 mmHg respectively (p=0.35). The mean CCT values in PG cases, PDS cases and control subjects were 542.9±26.7 µm, 521.7±17.5 µm and 530.9±23.4 µm respectively (p=0.01). The mean CCT was significantly higher in PG cases than the other groups (Table 1).

The CD values of the groups were summarized in table 2. The mean CD of anterior layer at the 0-2 mm was significantly higher in PG than PDS cases and normal subjects (p=0.007). The mean CD of total layer at the 0-2 mm was significantly higher in PG cases than control subjects (p=0.03). The mean CD of anterior layer at the 2-6 mm was significantly higher in PG than PDS cases (p=0.04). There were no significant differences of CD in other zones and layers between the groups.

DISCUSSION

Decreased CD is related with decreased corneal backscatter of light and also corneal transparency. There can be corneal

Table 1: *The demographics of the participants.*

	PG (n=22)	PDS (n=19)	Control (n=21)	P value
Gender (m/f)	15/7	10/9	11/10	0.46
Age (mean±SD)	44.4±6.9	38.9±4.6	39.1±4.9	**0.005**
IOP (mmHg)	17.3±2.1	16.4±2.1	16.8±1.8	0.35
CCT (µm)	542.9±26.7	521.7±17.5	530.9±23.4	**0.01**

PG: Pigmentary glaucoma, **PDS:** Pigment dispersion syndrome, Statistically significant P values were shown in bold manner.

Table 2: *The mean corneal density values of the participants.*

	0-2 anterior	0-2 center	0-2 posterior	0-2 total
PG	22.6* (**p=0.007**)	10.9	8.4	14.1** (**p=0.03**).
PDS	18.8	11.1	8.6	13.1
Control	18.8	11.2	8.7	12.7
	2-6 anterior	2-6 center	2-6 posterior	2-6 total
PG	20.4*** (**p=0.04**)	10.5	7.8	12.7
PDS	16.8	10.2	8.1	11.7
Control	17.2	10.3	8.1	11.8
	6-10 anterior	6-10 center	6-10 posterior	6-10 total
PG	19.2	11.2	9.5	13.2
PDS	17.6	11.5	9.7	12.9
Control	17.9	11.6	9.4	12.8
	10-12 anterior	10-12 center	10-12 posterior	10-12 total
PG	27.9	16.9	12.4	19.1
PDS	31.6	17.4	13.5	21.1
Control	27.7	16.5	12.2	19.1
	Total anterior	Total center	Total posterior	Total total
PG	21.2	11.7	9.1	14.2
PDS	20.3	11.9	9.5	14.3
Control	18.6	11.9	9.3	13.8

PG: Pigmentary glaucoma, **PDS:** Pigment dispersion syndrome
Statistically significant P values were shown in bold manner.
*significantly higher in PG than PDS and control group (one way ANOVA, Tukey's post hoc test)
**significantly higher in PG than control group (one way ANOVA, Tukey's post hoc test)
***significantly higher in PG than PDS group (one way ANOVA, Tukey's post hoc test)

back-scattering of light even in the absence of corneal edema in slit lamb examination so measurement of CD might be an indicator for mild corneal edema. Here in this study, we examined the cases with PG and PDS and compared the CD values of them with normal subjects.

Age, gender, refractive status and some corneal parameters might affect corneal transparency and accordingly CD values. Cankaya et al. investigated 588 healthy cases between 6 and 76 years-old in their study and observed a significant positive correlation between age and increased CD.[4] They stated that increased CD was related with increased age as conclusion. But they didn't observe any significant correlations between CCT, corneal volume, corneal power and refractive status of the eye with CD values. Inversely Pekel et al. did not find a significant association between CD and age in healthy subjects.[6] In our study, PG cases were significantly older than the PDS cases and the control subjects so this might have caused significantly higher CD values in PG cases in anterior layers at the 0-2 mm and 2-6 mm and total layer at the 0-2 mm zones.

PDS and PG cases have shown to have some alterations in the anterior segments of their eyes.[9] Flatter keratometry of approximately 2 diopters was found in PG and PDS cases compared with age-matched myopic controls.[9] Yip et al. found similar results and stated that flatter curvature of the posterior corneal surface of the eye should have been related to pigment loss in PDS and PG.[10] Also alterations of anterior segment in PDS and PG like flatter corneal curvature might affect CD values in spite of the absence of a previous study about this subject and this point was one of our hypotheses in our study.

Murrell et al. tried to answer whether pigment deposition might have cause some alterations in endothelial layer in their study but observed insignificant difference in the central corneal endothelial cell density and CCT between PDS cases and normal subjects.[11] But the relationship between the health of corneal endothelial layer and CD have been demonstrated. Tekin et al. investigated the correlations between CD and corneal endothelial cell density, average cell area, coefficient of variation (CV) of the cell area, maximum cell area, minimum cell area, and percentage of hexagonal cells (HEX) were measured by a specular microscope.[7] Inversely and moderately correlations between CD and HEX, but positively and moderately correlations between CD and CV were found in their study and it was concluded that CD might be used as an indicator of the health of cornea. In spite of insignificant effect of PDS and PG on endothelial layer according to study by Murrell et al.,[11] this point was also one of our hypotheses in our study. As the accumulation of pseudoexfoliation material has shown to affect CD values, accumulation of pigmented cells might have affect CD. Both Cankaya et al.[12] and Sekeroglu et al.[13] investigated the effect of pseudoexfoliation syndrome (PXS) on CD in their studies. Cankaya et al. investigated the cases with unilateral PXS and observed increased CD in eyes with PXS than control subjects.[12] Also they observed significantly higher CD values of the normal eyes of PXS cases than normal control subjects. Inversely, Sekeroglu et al. did not find significant difference in CD between the eyes with PXS and normal subjects.[13] We observed significantly higher CD values in PG cases especially anterior layers of central zones but there were no significant differences in CD between PDS and normal subjects.

Another hypothesis of our study was the probable effect of glaucoma or glaucoma medications on CD values. There have been no studies about the CD values in different kinds of glaucoma before. Prostaglandins are known to have many effects on the ocular surface structures.[14,15] Sen et al. investigated the effect of topical latanoprost on corneal clarity in glaucoma cases.[16] Decrease in CD was observed in their study and it was thought to be related with long-term use of latanoprost and the IOP reduction. In our study, all of our PG cases were under prostaglandin treatment during the study and maybe they had had higher CD values before treatment at the diagnosis of PG.

There are conflicting reports regarding the effect of LPI on the corneal endothelium in the literature. Meyer et al. suggested that the high energy and heat generated after LPI triggered the loss of corneal endothelial cells.[17] Similar to this study, Wu et al. demonstrated significant endothelial cell loss at 1-year follow-up after LPI.[18] However, in recent studies, Kumar et al. reported that there was no significant loss of ECD in the 3-year follow-up of the patients after LPI.[19] Similarly, Ono et al. declared that the loss of ECD 1- year after LPI was not significant and was at a negligible level.[20] Because we neglected the effects of LPI on the endothelium in the line of current information, endothelial cell count were not performed before and after the procedure. This situation is one of the limiting factors of our study. If we performed specular microscopy before and after LPI procedure, we could provide clear data.

We excluded the cases with any corneal diseases and also diabetic cases. Koc et al. stated that increase in CD especially in anterior layers of the central zones might be an early finding of subclinical keratoconus.[21] As abnormal glucose metabolism might affect corneal and lens density, corneal and lens clarity in children with type 1 diabetes

mellitus have been reported in the study by Tekin et al.[22] They observed decreased lens clarity in diabetic children but no significant changes were observed in CD.

In the current study, we observed significantly higher CD values in PG cases than PDS cases and normal subjects. We observed these increases in CD especially anterior layers of central zones. But we didn't observe any significant differences in CD between PDS and normal subjects. The lifetime conversion from PDS to PG has been reported to be between 35-50%.[1] No significant effects of age, sex, diopters of myopia and family history were reported on conversion to glaucoma. Also the presence of Krukenberg spindle have been reported to be related with the conversion to glaucoma but not confirmatory, in addition to genetic predisposition.[23] There are two possible reasons for the results of our study. Glaucoma and glaucoma treatment are well-known to have some negative effects on the health of cornea.[24,25] May be the presence of glaucoma and/or antiglaucoma treatment might have caused higher CD values in PG cases. Another possible reason is the presence of Krukenberg spindle. But Krukenberg spindle is also found in PDS cases. May be more Krukenberg spindle in PG cases might have caused higher CD values. We found that CD values were highest in the anterior layer and lowest in the posterior layer in all zones like in previous studies and thought that it was related with the fact that corneal epithelium was the main source for backscattering.[4,5] Asena et al. demonstrated that ocular surface or tear film abnormalities associated with dry eye disease could affect the measurements by Scheimpflug Imaging.[26] Because of that, we excluded the cases with dry eye or any ocular surface diseases.

As conclusion, we observed significantly higher CD values in PG cases than PDS and normal subjects. The presence of Krukenberg spindle, the probable effect of higher age and the probable effects of glaucoma might cause corneal backscatter of light and increased CD especially in anterior layers in central zones of cornea. To the best of our knowledge, this is the first study about CD measurements in PG and PDS. In order to investigate the possible effects of glaucoma on CD values, further investigations about the effects of different types of glaucoma on CD should be encouraged.

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Conflicts of Interest

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