



## ORIGINAL ARTICLE

## Evaluation of Corneal Transparency in Diabetic Patients Aged 60 Years and Over

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### Abstract

**Purpose:** The aim of the study was to retrospectively evaluate the changes of corneal transparency in diabetic patients across 3 different age groups.

**Materials and methods:** We enrolled 135 diabetes mellitus (DM) patients and 154 control subjects in this retrospective and nonrandomized study. Corneal backward light scattering information was collected from different corneal layers and annuli by using Scheimpflug tomography (Pentacam HR).

**Results:** The corneal densitometry analysis results varied between different age groups. In the 60 to 69 age group, the anterior layer at zone 0 to 2 mm had better corneal clarity in controls than in DM patients. Corneal densitometry values were markedly higher in diabetic eyes compared with control eyes in 70 to 79 age group when considered by central zones of total cornea at the 2 to 6 mm. The corneal transparency increased in 80 to 89 years DM patients in the majority of corneal zones. Besides, a weak correlation was found between the occurrence of DM and corneal densitometry at 0 to 2 mm and 2 to 6 mm concentric radial zones in anterior, posterior and total corneal depth.

**Conclusion:** Diabetic patients showed higher values of corneal densitometry especially in central annuli in anterior layer than controls aged 60 years and over. Corneal transparency decreases differently in DM eyes across 3 age groups.

### Keywords

Corneal backward light scattering, Corneal densitometry, Corneal transparency, Diabetes mellitus, Pentacam scheimpflug system

affect both the anterior and posterior segments of the eye. Besides diabetic retinopathy, corneal epithelium, stroma, and endothelium also change in diabetic patients. Precious studies have shown disruption of epithelial barrier function [2,3], increased polymegathism and polymorphism of endothelial cells [4,5] low density of endothelial cells [6], production and accumulation of advanced glycation end products [7], etc. in the eyes of diabetic patients. These alterations on the cornea could lead to decrease corneal transparency and increase corneal backward light scattering.

Healthy cornea ideally does not absorb visible light and the light that it scatters is minimal [8,9]. Loss of the transmission of light through the cornea give rise to the increasement of cornea backward light scattering. Past researches have verified that corneal densitometry, which describes the level of corneal transparency, could be used as a tool to evaluate corneal health and detect subclinical keratoconus [10,11]. Corneal densitometry also provides objective and quantitative information about corneal backscatter after corneal collagen crosslinking, refractive surgery, cataract surgery, keratoplasty, etc. [12-16], which is helpful for doctors to study the effects on the post-operating recovery of patients.

The Pentacam HR (Oculus, Wetzlar, Germany) employs a rotating Scheimpflug camera to image the anterior segment of the ocular tissues noninvasively and sequentially. The procedure of densitometry analysis measures corneal transparency by backscattered light and applies grayscale units as outputs. The system also provides precise data to describe the degree of corneal clarity at specific zones, allowing us to know the change in value.

### Introduction

Diabetes mellitus is known as a 21<sup>st</sup> century challenge [1] and diabetes is a systemic disease that could even



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The purpose of our study was to evaluate the changes of corneal transparency in diabetic patients aged 60 years and over. We also investigate the differences of corneal densitometry between people with diabetic of different age groups.

## Methods

We retrospectively reviewed the preoperative data of cataract patients who had undergone cataract surgery between august 2019 and November 2019 at Peking University Third Hospital. Only patients who were aged more than 60 years and had no history of ocular surgery were enrolled in our research. Eyes with any ocular diseases such as corneal infections, corneal dystrophies, uveitis and nystagmus, etc. were excluded. Patients who were not able to fully cooperative for Scheimpflug system examinations were also excluded. Both eyes had undergone routine ophthalmic examinations. As a result, 135 patients with DM and 154 patients without DM met the inclusion criteria. 578 eyes were categorized into 3 age groups (60-69, 70-79, 80-89 age groups).

In order to obtain corneal densitometry data, patients were instructed to take examinations following a series of standardized procedures as recommended in the instruction manual. All measurements were performed in dimness and automatically completed with 25 cross-sectional images in 2 seconds. The densitometry images comprises of 4 concentric radial zones around the corneal apex (the central 0-2, 2-6, 6-10, and 10-12 mm zones) and 3 layers (the anterior 120  $\mu$ m, the posterior 60  $\mu$ m and the central corneal layer). The scan-

ning output is expressed in grayscale units (GSU). The GSU level is ranged from 0 (maximum transparency) to 100 (completely opacity), according to the degree of backward light scattering from the cornea. An example of the Scheimpflug optical densitometry output is shown in Figure 1.

## Statistical Analysis

IBM SPSS statistics software package version 24.0 for Windows was used for statistical analysis. Descriptive statistics were presented as the mean  $\pm$  standard deviations (SD). Normality of data distributions was examined using Kolmogorov-Smirnov test. Student-t test for 2 independent samples was used when parametric analysis was possible and the nonparametric of Mann-Whitney *U* test was applied when parametric analysis was not possible. The Spearman's bivariate correlation analysis was performed to determine the relationship between the occurrence of DM and corneal densitometry values. The significance level for all of the tests was set at 5%.

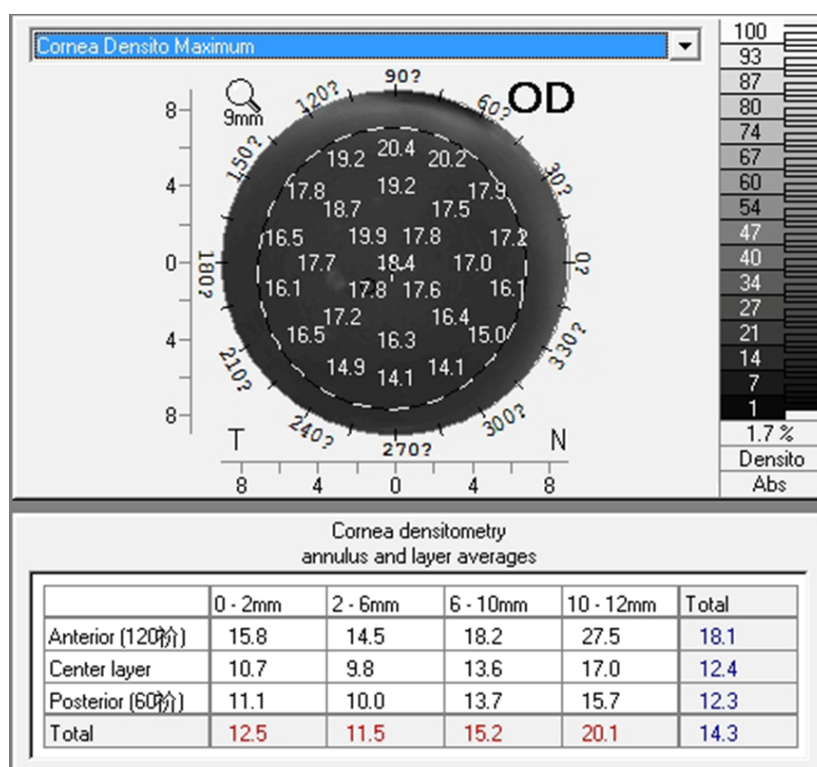
## Results

This retrospective study included 135 patients with

**Table 1:** Demographics of the subjects.

Age group	Diabetic group	Control group	P
60-69 y	58	60	0.982
70-79 y	42	55	0.212
80-89 y	35	39	0.176
Total	135	154	0.891

Data analyzed by Mann-Whitney *U* test.



**Figure 1:** An example of the data output for corneal densitometry assessment.

Table 2: Scheimpflug Measurements in layers and concentric radial zones of diabetic and control eyes.

Corneal layer and zone	Age group			70-79			80-89			
	Diabetic group	Control group	P	Diabetic group	Control group	P	Diabetic group	Control group	P	
<b>Anterior</b>	0-2 mm	15.122 ± 1.380	14.628 ± 1.005	<b>0.012<sup>b</sup></b>	15.492 ± 1.458	15.141 ± 1.205	0.051 <sup>b</sup>	16.919 ± 2.477	15.928 ± 2.029	<b>0.001<sup>b</sup></b>
	2-6 mm	14.364 ± 1.219	14.274 ± 1.260	0.527 <sup>b</sup>	15.864 ± 2.123	15.085 ± 1.776	<b>0.003<sup>b</sup></b>	17.364 ± 2.540	16.286 ± 2.391	<b>0.001<sup>b</sup></b>
	6-10 mm	22.717 ± 5.718	24.065 ± 7.500	0.318 <sup>b</sup>	30.208 ± 8.773	28.627 ± 7.439	0.176 <sup>a</sup>	34.573 ± 7.191	33.349 ± 8.362	0.386 <sup>b</sup>
	10-12 mm	34.522 ± 12.696	34.838 ± 11.589	0.619 <sup>b</sup>	40.667 ± 12.898	40.232 ± 13.039	0.840 <sup>b</sup>	44.316 ± 12.264	41.704 ± 12.743	0.135 <sup>b</sup>
	Total	20.207 ± 3.256	20.658 ± 4.003	0.587 <sup>b</sup>	24.060 ± 4.710	23.025 ± 3.854	0.227 <sup>b</sup>	26.861 ± 4.321	25.424 ± 4.805	0.059 <sup>a</sup>
<b>Central</b>	0-2 mm	9.829 ± 0.677	9.798 ± 0.649	0.622 <sup>b</sup>	10.139 ± 0.917	10.055 ± 0.912	0.358 <sup>b</sup>	11.280 ± 1.929	10.423 ± 1.086	<b>0.000<sup>b</sup></b>
	2-6 mm	9.493 ± 0.703	9.628 ± 0.971	0.761 <sup>b</sup>	10.623 ± 1.519	10.123 ± 1.251	<b>0.014<sup>b</sup></b>	11.521 ± 1.676	10.900 ± 1.593	<b>0.005<sup>b</sup></b>
	6-10 mm	16.088 ± 3.764	16.912 ± 4.765	0.355 <sup>b</sup>	21.211 ± 5.605	19.969 ± 4.594	0.092 <sup>a</sup>	23.791 ± 4.956	22.829 ± 5.654	0.329 <sup>b</sup>
	10-12 mm	19.928 ± 5.073	19.964 ± 5.134	0.960 <sup>b</sup>	23.054 ± 6.161	23.278 ± 5.939	0.681 <sup>b</sup>	25.434 ± 6.088	23.212 ± 7.149	<b>0.011<sup>b</sup></b>
	Total	13.289 ± 1.895	13.644 ± 2.386	0.459 <sup>b</sup>	15.871 ± 2.955	15.238 ± 2.227	0.255 <sup>b</sup>	17.579 ± 2.726	16.549 ± 3.073	<b>0.033<sup>a</sup></b>
<b>Posterior</b>	0-2 mm	10.078 ± 0.852	9.990 ± 0.758	0.871 <sup>b</sup>	10.399 ± 0.973	10.405 ± 1.139	0.606 <sup>b</sup>	11.700 ± 1.677	11.118 ± 1.309	<b>0.028<sup>b</sup></b>
	2-6 mm	9.801 ± 0.985	9.845 ± 1.017	0.858 <sup>b</sup>	10.831 ± 1.381	10.456 ± 1.439	<b>0.026<sup>b</sup></b>	11.823 ± 1.748	11.491 ± 1.655	0.209 <sup>b</sup>
	6-10 mm	15.344 ± 2.657	15.650 ± 3.187	0.765 <sup>b</sup>	18.793 ± 3.277	17.971 ± 3.045	0.073 <sup>a</sup>	20.359 ± 3.171	19.751 ± 3.614	0.278 <sup>a</sup>
	10-12 mm	16.903 ± 2.798	17.114 ± 2.679	0.553 <sup>a</sup>	19.289 ± 3.090	19.225 ± 3.041	0.854 <sup>b</sup>	20.669 ± 3.700	19.392 ± 3.785	<b>0.032<sup>b</sup></b>
	Total	12.771 ± 1.472	12.902 ± 1.686	0.985 <sup>b</sup>	14.643 ± 1.871	14.186 ± 1.668	0.144 <sup>b</sup>	15.917 ± 1.799	15.309 ± 2.116	0.107 <sup>b</sup>
<b>Total</b>	0-2 mm	11.682 ± 0.833	11.466 ± 0.689	0.164 <sup>b</sup>	12.001 ± 0.996	11.865 ± 0.981	0.219 <sup>b</sup>	13.300 ± 1.907	12.491 ± 1.298	<b>0.001<sup>b</sup></b>
	2-6 mm	11.224 ± 0.885	11.251 ± 1.026	0.746 <sup>b</sup>	12.437 ± 1.606	11.888 ± 1.417	<b>0.008<sup>b</sup></b>	13.567 ± 1.908	12.894 ± 1.768	<b>0.011<sup>b</sup></b>
	6-10 mm	18.050 ± 3.912	18.879 ± 5.011	0.435 <sup>b</sup>	23.402 ± 5.712	22.187 ± 4.784	0.109 <sup>a</sup>	26.244 ± 4.898	25.313 ± 5.727	0.288 <sup>a</sup>
	10-12 mm	23.697 ± 6.252	23.966 ± 5.997	0.711 <sup>b</sup>	27.666 ± 6.788	27.580 ± 6.706	0.981 <sup>b</sup>	30.141 ± 6.411	28.099 ± 7.287	<b>0.027<sup>b</sup></b>
	Total	15.422 ± 2.107	15.739 ± 2.607	0.617 <sup>b</sup>	18.186 ± 3.066	17.477 ± 2.422	0.198 <sup>b</sup>	20.120 ± 2.797	19.094 ± 3.219	<b>0.041<sup>a</sup></b>

All corneal densitometry values represented in grayscale units. Data are expressed as mean ± SD.

<sup>a</sup>Independent sample *t* test.

<sup>b</sup>Mann-Whitney *U* test.

DM and 154 controls (112 Male, 177 Female) that were divided into 3 age groups. The mean age of DM patients was 72.71 with SD 8.15. The controls' mean age was 72.69 with a SD of 7.67 and there was no significant difference in mean age between 3 age groups. The demographics of the subjects are summarized [Table 1](#).

The mean corneal densitometry results are summarized in [Table 2](#). The corneal densitometry analysis results varied between different age groups. In the 60 to 69 age group, the anterior layer at zone 0 to 2 mm has better corneal clarity in controls than in DM patients while corneal densitometry in other zones shows no significant difference. In corneal central zones of 2 to 6 mm, corneal densitometry values were markedly higher in diabetic eyes compared with control eyes in 70 to 79 age group in full depth. The corneal transparency increased in 80 to 89 years DM patients in specific corneal zones including the anterior layer at 0 to 2 mm and 2 to 6 mm, the central layer at 0 to 2 mm, 2 to 6 mm, 10 to 12 mm and 0 to 12 mm and the posterior layer at 0 to 2 mm and 10 to 12 mm regions. Moreover, the total light backscatter at total corneal thickness was higher at 0 to 2 mm, 2 to 6 mm, 10 to 12 mm and 0 to 12 mm concentric radial zones. A weak correlation was found between the occurrence of DM and corneal densitometry at 0 to 2 mm and 2 to 6 mm corneal zones in anterior, posterior and total corneal depth. The correlation coefficients between the occurrence of DM and corneal densitometry are given in [Table 3](#).

## Discussion

This study demonstrated that corneal densitometry increases in DM eyes in different age groups and the affected area tends to expand with age. A previous research revealed a significant increase in corneal densitometry in the 0 to 10 mm zone of the anterior layer and 0 to 2 mm zone of the total cornea in diabetic eyes versus the eyes of controls aged 40 to 60 [17]. A pilot study collected corneal backscatter in seven meridians for each eye, with orientations ranging from 70° to 110° and concluded that the corneal backscatter in corneal 3 mm and 5 mm central zones of insulin-dependent and non-insulin-dependent DM patients was higher than that of controls [18]. Whereas, there was no statistically significant difference in corneal clarity between children with type 1 DM and control subjects [19]. The intraocular straylight level in pseudophakic eyes was higher in diabetic patients than in nondiabetic patients and had a

tendency to increase as the severity of diabetic retinopathy increased [20]. We speculated that the difference of population samples causes the different outcomes.

In the present study, corneal backscattering of different layers in many zones in diabetic eyes was markedly higher than in controls' eyes aged 70 and over. Previous studies revealed that diabetic patients seemed to have thicker corneas, less cell density and hexagonality, and more irregular cell size of the corneal endothelium cells than those of the controls [4-6]. Abnormal morphology of the corneal endothelial cells combined with increased central corneal thickness is an indicator of alterations of endothelial pump function, which decrease corneal transparency [5]. Moreover, Anbar, et al. [21] and Islam, et al. [22] found a significant correlation between the duration of diabetes and polymegathism and polymorphism of corneal endothelium cells, supporting the idea that the longer the disease evolution, the higher endothelial loss. As these changes in corneal endothelial cells are age-related, corneal densitometry in the posterior layer also increases with age in all concentric radial zones [23,24].

The results additionally revealed that corneal backscatter increased to various extents in DM eyes in the 0 to 2 mm circular zone in different age groups and the evolution of DM could possibly increase the corneal densitometry at 0 to 2 mm and 2 to 6 mm in anterior, central and total corneal depth. The visual effect of increased corneal densitometry at pupillary zone is not clear. Prior researches showed intraocular scattering increased in the diabetic eyes compared with controls and the level of intraocular straylight had a tendency to increase as the severity of diabetic retinopathy increased [20,21]. Besides, optical quality of the diabetic eyes was reduced simultaneously in comparison with the control group [21]. There is not a precise relation between the level of backward light scattering and the level of forward light scattering in the cornea [9]. More investigations should be focused on the level of corneal backscatter and its effect on visual quality in clear cornea of diabetic patients.

We also observed a weak correlation between corneal densitometry and the occurrence of DM at 0 to 2 mm and 2 to 6 mm in anterior, posterior and total corneal depth in all patients we enrolled. The speculation may be concluded that the anterior layer was the most susceptible layer in cornea under hyperglycemia

**Table 3:** Spearman correlation between the occurrence of diabetes mellitus and corneal densitometry.

	0-2 mm		2-6 mm		6-10 mm		10-12 mm		0-12 mm	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
<b>Anterior</b>	<b>0.175</b>	<b>0.000</b>	<b>0.139</b>	<b>0.001</b>	0.004	0.926	0.013	0.755	0.035	0.397
<b>Central</b>	<b>0.083</b>	<b>0.046</b>	<b>0.093</b>	<b>0.025</b>	0.007	0.866	0.032	0.443	0.030	0.474
<b>Posterior</b>	0.053	0.199	0.071	0.087	0.028	0.501	0.031	0.454	0.051	0.221
<b>Total</b>	<b>0.123</b>	<b>0.003</b>	<b>0.110</b>	<b>0.008</b>	0.010	0.819	0.022	0.605	0.040	0.338



and the corneal backward light scattering of the anterior layer increased in DM patients in the same age group. As defined with corneal densitometry software, the anterior layer corresponds to corneal epithelial and anterior stromal. Loss of the subbasal nerve plexus, corneal epithelial thinning and a reduction in basal epithelial cell density was determined using *In vivo* confocal microscopy in type I diabetic rats [2,3]. Alterations of corneal subbasal plexus was also found in patients with type I diabetes [21]. Production and accumulation of advanced glycation end products leads to the morphological disorders including increase of membrane thickness and multilamination [22]. A series of proteins of epithelial basement membrane such as laminin-I, entactin/nidogen and laminin-10 also change in DM eyes [23,24]. In addition, DM is associated with increased collagen crosslinking mediated by glycated proteins *in situ* [25,26]. These alterations may account for the increase of corneal densitometry in corneal anterior layer. And a recent research showed a loss in corneal keratocyte density is associated with corneal sub-basal plexus nerve damage in patients with and without diabetic neuropathy by using corneal confocal microscopy [27]. Corneal confocal microscopy has been recognized as one potentially useful method for diagnosing diabetic peripheral neuropathy [28]. We believe corneal densitometry using Scheimpflug system may also provide a method of diabetic peripheral neuropathy in early screening, diagnosis and intervention.

It is worth noting that the obvious rise of corneal densitometry at 6 to 10 mm and 10 to 12 mm concentric radial zones may have low clinical significance in the same age group. As the possible existence of marginal corneal degenerations (influenced by environmental and genetic factors) such as cornea arcus senilis and white limbus girdle of Vogt [29] cannot be ignored, corneal densitometry value of peripheral cornea at 6 to 10 mm is certainly high. Because of natural variability in total corneal diameter [30], the 10 to 12 mm concentric radial zones is possibly part of the limbus or sclera, resulting to high level of corneal backward light scattering. Due to these factors, the increase in corneal backscatter at 6 to 10 mm and 10 to 12 mm region cannot be definitively attributed to the duration of DM.

## Limitations

The current study had numerous limitations. We did not distinguish the type of diabetes as all subjects aged 60 years and over. Another limitation is that the diabetic retinopathy stages were not taken into account. It is generally known that three major risk factors for diabetic retinopathy are diabetes duration, hemoglobin A1c (HbA1c) and blood pressure [31]. Further studies are needed to investigate all the interaction between these above-mentioned factors and corneal densitometry in patients with DM.

## Conclusions

In summary, corneal densitometry provides a beneficial means for quantitative evaluation of the corneal transparency. As results shows, corneal densitometry is higher especially in central annuli in anterior layer in DM eyes when compared with controls aged 60 years and over. Moreover, corneal transparency decreases to various extents in DM eyes in different age groups and the affected region tends to expand with age.

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