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Research Article

Corneal Endothelial Cell Density and Morphology of Filipino Patients in a Tertiary Level Hospital

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Abstract

The effects of diabetes mellitus and hypertension on the corneal endothelium are often underestimated. Several studies revealed contradictory results on whether there is a statistically significant correlation. This study identified the demographics and corneal endothelial cell density and morphology of diabetic and hypertensive patients 20-83 years old who underwent specular microscopy in one center from January 2021 to January 2023 and compared it with an age-matched control. There was no significant correlation between mean cell density, coefficient of variation and hexagonality in patients with either of the comorbidities and those without across all age groups. However, for patients 60 years old and above, endothelial cell count decreased by an average of 0.78% (18.8003 cells/mm2), and percent hexagonality decreased by an average of 28.2% (-13.31%) compared to age-matched control. The majority of the population with comorbidities was noted to belong to this age group. Therefore, it is highly recommended to include careful evaluation of the corneal endothelium as part of the diabetic and hypertensive patient's eye screening, especially in pre-operative examination.

Keywords: Corneal Endothelium; Cell Density; Cell Morphology; Specular Microscopy; Diabetes Mellitus; Hypertension

Introduction

The most common causes of mortality in the Philippines in the year 2020 are related to specific comorbidities such as ischemic heart diseases, neoplasms, cerebrovascular diseases, diabetes mellitus (DM), and pneumonia [1]. Despite the birth of the notorious COVID-19 virus infection causing the pandemic, the number of deaths due to cerebrovascular disease, diabetes mellitus, and hypertension has still exceeded its rank compared to the morbidity rate of this virus. These diseases' well-established and studied effects in the eye are mainly exhibited on the retina. The cornea, providing the eye's greatest refractive index, has a significant role in maintaining clear vision. It can also be affected by systemic illnesses, but these effects are often underappreciated.

Light must pass through different ocular structures to process images in our visual cortex. Light enters the cornea through the pupil, lens, vitreous humor and the retina. The optic nerve contains millions of axons, which send electrical signals to the brain for processing. Any problem within these structures, especially the cornea, would cause a decrease in vision by inhibiting light from passing through.

This paper aims to identify patients' demographics in a tertiary hospital with comorbidities such as diabetes mellitus and hypertension and compare it with age-matched controls. Previous studies that described the relationship between healthy individuals and those with comorbidities show contradicting results. This study hopes to clarify the correlation using our local data. Providing such a correlation will urge the Filipino ophthalmologist to take extra care in the population of patients with corneal surface disease abnormalities since treatment can avoid irreversible vision problems that can only be treated surgically.

Background of the Study

Vision is one of the 5 major senses. It is the ability to interpret light and process it through the visual cortex. Light in the visible spectrum reflected by objects in the environment passes through the cornea, then through the pupil, lens, and vitreous humor, and then finally the retina.

The cornea is a clear, dome-shaped structure in front of the eye. It's major roles include protection from chemicals and microbes, providing a smooth optical surface, transparency, and clarity to allow light rays to be focused on the retina with minimum scatter and optical degradation; the latter is the primary reason why the cornea provides two-thirds of the refractive power of the eye [2].

The cornea has five layers (from outer to inner): epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. To maintain corneal clarity, the human corneal endothelium functions to sustain a relative state of deturgescence or a steady state of hydration by actively pumping fluid to the corneal stroma, along with the blood-aqueous barrier. This layer, unfortunately, does not proliferate. Trauma, surgery, aging, or specific comorbidities can cause significant cell loss in this single layer of polygonal endothelial cells [4]. The cornea decompensates by covering the defective area with the residual cell hyperplasia via amniotic nucleus division, cellular migration, and badge formation. The result of this extensive repair from its surviving cells is a decrease in mean cell density (MCD), an increase in mean cell area (MCA), and lastly, an increase in variations of cell size or coefficient of variation (CV of cell size or polymegathism) and cell shape (percent of hexagonal cells or pleomorphism) [4]. The mean cell density (MCD) of healthy Filipinos aged 20 to 86 years was found to be 2798 ± 307.2 cells/mm^2 [5]. To date, there has been no reported data regarding the mean cell density of patients with relevant comorbidities such as diabetes mellitus and hypertension in the Philippine setting.

Specular microscopy measures endothelial morphology analysis through a specular or confocal image. The variables include those mentioned previously, such as MCD, MCA, CV, and percentage of hexagonal cells [6]. This imaging modality is utilized in various primary endothelial diseases such as Fuchs endothelial corneal dystrophy, posterior polymorphous endothelial dystrophy, and Irido-corneal endothelial (ICE) syndrome. Other secondary corneal endothelial disorders include endothelial changes in Pseudoexfoliation syndrome, effects on systemic conditions and medications such as diabetes mellitus, commonly use to specular microscopy to measure endothelial function before and after surgical procedures (e.g., cataract surgery).

It has been long established that the number of cells decreases with age, trauma, and surgery. The correlation between corneal endothelial insufficiency (CEI) and the more common comorbidities such as diabetes mellitus has contradicting results.

A study by Islam, Meebob and Amin compared the corneal morphological parameters of the Israeli population with the duration of diabetes mellitus, glycemic control, and severity of diabetic retinopathy. Patients with diabetes mellitus did not show statistically significant differences in the corneal parameters such as MCA, CV, and percentage of hexagonal cells, compared to the age-matched non-diabetic control subjects. However, among diabetic subjects, the duration of diabetes mellitus of more than ten years significantly correlates with glycemic control, the severity of diabetic retinopathy, MCD, and CV, and the percentage of hexagonal cells. This subgroup has significantly lower MCD compared to the age-matched non-diabetic control subjects [7]. The same parameters were studied in Portuguese eyes. Results show that there is no significant difference between the corneal parameters (MCD, CV, and percentage of hexagonal cells) of diabetic and non-diabetic eyes [8].

Shih., *et al*. emphasized that diabetes mellitus induces progressive damage in end organs, and its effect on the cornea is underappreciated. This study focuses on the effects of diabetes mellitus on the ocular surface – the cornea. Six papers described the correlation between corneal endothelium and diabetes mellitus in a hospital setting. These papers conducted in India, Korea, Malaysia, Hungary, Poland, and Denmark revealed a statistically significant association between type 2 DM and corneal endothelial dysfunction, showing decreased MCD, CV and increased percentage of hexagonal cells [9].

There is limited literature defining the correlation between hypertension and corneal endothelial insufficiency. A Turkish journal investigated patients who underwent cataract surgery with cerebrovascular disease, hypertension and a controlled group. They found that the incidence of corneal endothelial insufficiency after surgery is significantly higher in patients with cerebro-vascular disease and hypertension compared to the control group [10].

Objectives

- **Main Objective:** To describe and correlate the corneal endothelial cell density and morphology of diabetic and hypertensive patients versus an age-matched control.
- **Specific Objectives:** Describe the corneal morphology of patients seen in FEU Eye Center Inc., from January 2021-January 2023 (3 years). Identify the relationship between patients with comorbidities and an agematched control with the corneal endothelial cell density and morphology.

Methodology

This is a cross-sectional, analytic study of Filipino patients aged 20-93 who underwent specular microscopy at FEU Eye Center Inc. from January 2021 to January 2023 using a non-contact specular microscope (USA Tomey Microscope EM4000). Only the charts of eligible subjects were reviewed and analyzed to ensure protected health information is observed. The sample size is calculated based on estimating the population proportion of patients undergoing specular microscopy in FEU Eye Center Inc. from January 2021 to January 2023. The formula is as follows:

$$n = \frac{(z_{!})^{!}\, p^{*}(1-p^{*})}{(E)^{!}} = \frac{(1.96)^{!}\, 0.5(1-0.5)}{(0.05)^{!}} = 385$$

Where

z(α/2) = z tabular value at (1-α)100% confidence level p* = proportion of units of interest from sources other than the sample E = margin of error.

Given the maximum allowable error of 5% and reliability of 95%, the minimum sample size is 385. Data collected were statistically analyzed using Statistica Version 14.0.0.15, and rejection of the null hypothesis was set at alpha 0.05.

The sampling method is a total enumeration of all the patients who underwent specular microscopy at FEU Eye Center Inc. from January 2021 to January 2023. Inclusion criteria include patients more than twenty years old who consulted with any consultant staff in FEU Eye Center Inc. Records were reviewed, and relevant history, such as comorbidities: hypertension or diabetes mellitus, was documented. Note that the control of comorbidities or the presence or absence of medications for these comorbidities is beyond the scope of the study. Exclusion criteria include the history of corneal trauma, the presence of corneal opacity and evidence of corneal dystrophy, as stated in their patient records.

The human corneal endothelium does not regenerate. Specific measures, such as the percentage of hexagonal endothelial cells (6A), the coefficient of variation of cell area (CV), and the endothelial cell density (CD), are used to interpret the state of the endothelium. Polymegathism is the term used to describe an increase in cell area variability or CV, which is normally less than 0.30. Pleomorphism is the term used to describe the percentage of hexagonal cells or increased variability in cell shape. This value is directly proportional to endothelial health, lower percentages mean poorer endothelial health. Age and endothelial cell attrition from different causes produce a rise in the coefficient of variation of cell area (polymegathism) and diminishing the percentage of hexagonal cells (pleomorphism).

Specular microscopy describes the endothelial cell morphology, which includes the following: cell area ± SD (square micrometers, μm^2), cell density or CD (cells/mm^2), polymegathism (Coefficient of Variation or CV), pleomorphism (percentage of hexagonal cells or 6A). Figure 1 shows the result of a healthy 70-year-old female with endothelial cell parameters – CD, CV, and 6A within normal parameters.

The following data were collected from patient records: cell density or CD (cells/mm^2), polymegathism (Coefficient of Variation or CV), pleomorphism (percentage of hexagonal cells or 6A) in each eye. To observe utmost confidentiality in data recording, the patient's name was not recorded. Instead, the unique patient ID assigned by the machine was used. Age is automatically computed based on a patient's date of birth. These data were documented in an Excel file, as seen in Figure 2. A binary coding representing the presence (1) or absence (0) of comorbidities such as diabetes mellitus or hypertension was logged.

A frequency distribution table was analyzed to get the endothelial cell characteristics of different age groups. Other information such as the number of subjects, percentage of males and females, average CD of the population, CV in cell size, and mean percentage of hexagonality was also gathered. Lastly, the percentage of subjects with hypertension and diabetes Mellitus was recorded.

The Mann-Whitney test was used to identify the comparison between genders (male versus female) and the standard control versus those with comorbidities. The null hypothesis states that patients with at least one of the comorbidities (hypertension and diabetes mellitus) and patients without any of the comorbidities have no significant difference in their mean/ median in the CD, CV, and Percentage of Hexagonality. Marked tests are significant at p <.05000. Spearman's test was used to identify whether numeric variables such as CD, CV, and Percentage of Hexagonality have a significant linear relationship between age groups.

Ethical considerations

This study had no financial, familial, or proprietary interests of the principal investigator or FEU Eye Center, Inc. The provisions in RA 10713 on Data Privacy were well understood and considered. There was utmost confidentiality in retrieving information from the eye center. Only eligible charts were reviewed, and an identifier assigned randomly by the machine was used, including the patient's age, gender, and the results of the specular microscopy, such as CD, CV of cell size, and percentage of hexagonality (6A). The records were password-protected on the primary investigator's laptop. Data will be retained until the study has been completed, which will take approximately one month. The Data Privacy Officer's permission was obtained before the data collection. A seminar regarding the technicalities of RA 10713 provided by an in-house Data Privacy Officer was done before commencing data collection. Details of the study were carefully analyzed and approved. Since this was chart review, neither a face-to-face interview nor a questionnaire was needed for the study. A request for waiver of informed consent was provided. The study did not involve medical records of vulnerable groups, nor did it collect stigmatizing information from the medical records. This study had minimal risk as it only involved a chart review, and no personal data was obtained. Lastly, as this study will have great potential to yield general knowledge, results may be shared through local and international publications.

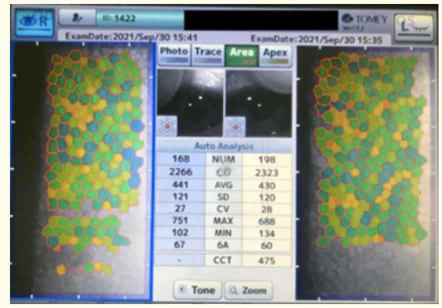

Figure 1: Specular microscopy result of a healthy 70-year-old female with normal endothelial parameters.

					RIGHT EYE				LEFT EYE			
PATIENT ID	AGE	SEX	DM	HTN	CD	CV	6A	CCT	CD	CV	6A	CCT
1422	62	FEMALE	1	1	2338	51	39	610	2372	67	36	548
1454	59	FEMALE	0	0	2854	33	52	538	2568	32	45	535
1475	60	MALE	0	0	2380	39	52	495	2454	38	42	500
1432	67	FEMALE	0	0	2675	41	43	566	2518	49	41	525
1448	85	MALE	0	0	2038	46	45	563	2117	44	41	539
1498	69	MALE	0	0	2396	32	47	470	2377	29	54	478
1571	31	FEMALE	0	0	2937	36	56	556	2986	38	41	544

Figure 2: Sample raw data logging of patients in the study.

Results

The study population consists of 759 subjects aged 20-83 years old (mean age 62 ± 14). Of this population, 281 (36.9%) were male and 478 (62.8%) were female. A total of 922 eyes were studied. The MCD of the population is 2748.857 cells/mm^2 (range 2633.885 - 2863.829 cells/mm^2) for ages 20-39; 2581.681 cells/mm^2 (range 2511.911 - 2651.450) for ages 40-59 and 2406.829 cells/mm^2 (range 2349.931 - 2463.727) for ages more than 60 years old. The mean CV in cell size and the mean hexagonality among different age groups are listed in Table 1. Among the 759 subjects, 255, or 33%, had diabetes mellitus, and 237 or 31% had hypertension.

There was no statistically significant relationship between the MCD, CV, and percent hexagonality in patients with either of the comorbidities – diabetes mellitus and hypertension compared with age-matched controls (all p values>0.05000). Furthermore, there was no statistically significant difference between male and female patients with comorbidities and the age-matched controls (all p values>0.05000), as seen in Table 2. However, age significantly correlates with the endothelial cell count (ρ = -0.324150) starting at age 60 and above. Regression analysis showed that starting at 60,

Age Group	Variables	Mean	SD	Lower Limit	Upper Limit
20-39	Mean Cell Density (cells/mm^2)	2748.857	296.5027	2633.885	2863.829
	CV in Cell Size (%)	50.143	6.67137	25	38.9
	Hexagonality (%)	48.679	8.798	45.267	52.090
40-59	Mean Cell Density (cells/mm^2)	2581.681	384.338	2511.911	2651.450
	CV in Cell Size (%)	37.403	6.0413	36.307	38.500
	Hexagonality (%)	58.076	11.85525	36.555	79.597
> 60	Mean Cell Density (cells/mm^2)	2406.829	504.1392	2349.931	2463.727
	CV in Cell Size (%)	38.339	6.6512	37.588	39.089
	Hexagonality (%)	46.207	8.5831	45.239	47.176

Table 1: Endothelial Cell Characteristics in Different Age Groups.

Age Group	Variables	U	p-value
20-39	Mean Cell Density (cells/mm^2)	29.00000	0.224525
	CV in Cell Size (%)	32.00000	0.308857
	Hexagonality (%)	45.00000	0.869627
40-59	Mean Cell Density (cells/mm^2)	1441.500	0.221696
	CV in Cell Size (%)	1359.500	0.094646
	Hexagonality (%)	1319.000	0.058315
> 60	Mean Cell Density (cells/mm^2)	10514.50	0.748533
	CV in Cell Size (%)	10737.00	0.984352
	Hexagonality (%)	10487.00	0.720514

Table 2: Comparison of Endothelial Cell Characteristics between Comorbidities – Hypertension or Diabetes Mellitus in Different Age Groups (Mann-Whitney U Test).

Age Group	Variables	ρ
20-39	Mean Cell Density (cells/mm^2)	0.159622
	CV in Cell Size (%)	-0.194853
	Hexagonality (%)	0.274364
40-59	Mean Cell Density (cells/mm^2)	0.000982
	CV in Cell Size (%)	-0.065225
	Hexagonality (%)	0.059846
> 60	Mean Cell Density (cells/mm^2)	-0.215441
	CV in Cell Size (%)	0.039248
	Hexagonality (%)	-0.039591

Table 3: Comparison of Endothelial Cell Characteristics between Age-Matched Control (Spearman Rank Order Correlation).

age explains the decrease in CD count (b =-12.804) and the percentage of hexagonality (b = --0.13307). Age did not correlate with the other parameters, such as CV in cell size (see table 3).

Discussion

Providing the greatest refractive index of the eye, the cornea plays a significant role in transmitting clear images to the retina. It is, therefore, essential to maintain its clarity. The innermost layer of the cornea is the endothelium. It has been well established that there is a relationship between age, gender, ethnicity, history of trauma or surgery, and specific comorbidities and CEI [5].

The results of our study showed a mean cell density of 2748.8 cells/mm^2, 2581.6 cells/mm^2 and 2406.8 cells/mm^2 for age groups 20-39, 40-50 and >60 respectively. These values are still within the average value of 2798 ± 307.2 cells/mm^2 described in healthy Filipino eyes [5]. Furthermore, the normal attrition rate averaged 0.6% per year, yielding approximately 2300 cells/mm^2 at the age of 85.3 Our data shows that the lower limit among all age groups is still greater than the approximate decrease with normal aging. Given these data, we can infer that the patients included in the study are within normal limits.

For the younger age group of 20-39, we expect normal endothelial cell parameters. However, the results of our study show that the mean coefficient of variation (50.143%) is significantly higher than normal (less than 30%), implying that some of the participants in this group have polymegathism. Only the upper 10% (6 out of 58) of this population have approximately 47% CV in cell size, indicating that the 6 participants in this age group have significantly increased CV that mean was pulled up towards the higher value. The median and mode of this population is 29%, which is probably a more reliable representative of CV in ages 20-39. In other age groups, the values of the mean, median, and mode are close to each other, meaning there are no outliers in this subset significant enough to skew the data to the right, see Table 4.

Age Group	Variables	Mean	SD	Mean	SD
		Normal Filipino Eyes		Our Study	
20-39	Mean Cell Density (cells/mm^2)	2946	270	2748.857	296.5027
	CV in Cell Size (%)	343	34.1	50.143	6.67137
	Hexagonality (%)	32.5	3.1	48.679	8.798
40-59	Mean Cell Density (cells/mm^2)	2761	333	2581.681	384.338
	CV in Cell Size (%)	393.6	33.3	37.403	6.0413
	Hexagonality (%)	31.9	4.3	58.076	11.85525
> 60	Mean Cell Density (cells/mm^2)	2846	467	2406.829	504.1392
	CV in Cell Size (%)	367.7	39.7	38.339	6.6512
	Hexagonality (%)	35.3	3.8	46.207	8.5831

Table 4: Endothelial Cell Characteristics in our Study compared with Normative Age Group.

Across all age populations, the value for the percentage of hexagonality is more or less within the normal range (approximately 50-60%), signifying that there is no pleomorphism in our study population. However, there is a higher mean percentage of hexagonality in ages 40-59 with an average of (58.076%) compared to the other age groups meaning that this population probably has a healthier endothelial function. This study did not evaluate corneal endothelial function in connection to the factors measured, thus further research is necessary to confirm this speculation, see Table 4.

The study by Padilla., *et al*. defined the normative value of Filipino eyes aged 20-86 years old. It specifically described an inversely proportional relationship between the mean cell density, percentage of hexagonality, and age. On the other hand, there is a proportional relationship between CV in cell size and age. 5 However, another essential factor to consider is defining the correlation between certain diseases commonly seen in Filipino patients, such as diabetes Mellitus and hypertension.

This study's results revealed no significant difference in the MCD, CV in size, and percentage of hexagonality in patients with specific comorbidities such as diabetes mellitus and hypertension compared to age-matched control. The same results were seen in the Israeli and Portuguese studies [7,8]. However, upon reaching 60 years old and above, the endothelial cell count decreased by 18.8003 cells/mm^2, while percentage of hexagonality decreased by -13.31% compared to age-matched control. Although only 24% of this population claimed to be diabetic, this decline may be due to several hypotheses, such as the formation of advanced glycation end products (AGEs) in the epithelium basement membrane or Descemet's membrane, aberrant F-actin fiber patterns, and excessive sorbitol accumulation in the corneal endothelium linked to cause diabetic keratopathy. These reasons may prove the possible negative correlation of CEI with diabetes mellitus [11,12].

There are limited studies involved in the correlation of hypertension with CEI. In our study, however, there is no significant difference in the MCD, CV in size, and percentage of hexagonality in patients with hypertension compared to the age-matched controls. However, the majority of hypertensive patients are seen in the 60year-old and above age group. 59.2% of the aged 60 years old and above claimed to be hypertensive. Olsen., *et al*. revealed that the group with Fuchs' endothelial dystrophy had a considerably higher frequency of cardiovascular illness than the control group. This study shows that vascular mesenchymal and corneal endothelial cells form a close developmental association, and the two types of endothelium share biological characteristics [13]. Other hypothesized theory states that the reduced blood supply linked to hypertension and vascular disorders could lead to a decrease in aqueous flow, resulting in ocular endothelial dysfunction. The nutrition of the cornea may be adversely affected by a reduction in aqueous flow [10]. The possible reasons for the negative correlation between patients aged 60 above mean cell density and percentage of hexagonality were discussed thoroughly previously.

Our study is limited to subjects in a single center tertiary hospital. Furthermore, it defines the presence or absence of the disease (hypertension or diabetes Mellitus) without considering the duration, level of diabetic retinopathy or hypertensive retinopathy, glucose control (HbA1c or plasma glucose), and blood pressure control (mean systolic and diastolic BP). The statistical tests assigned each of the comorbidities – hypertension or diabetes mellitus with equal weights and therefore cannot assume the likelihood of CEI with one or both comorbidities present. Prospective research studies with adequate statistical power may provide more insight into the effects of plasma glucose or blood pressure on endothelium and corneal structural alterations.

Conclusion

Although there is no statistically significant difference in the MCD, CV in size, and percentage of hexagonality in patients with diabetes mellitus and hypertension compared to age-matched controls, most of the hypertensive and diabetic population belonged to the age group of 60 years old and above. In this age group, the endothelial cell count decreased by 18.8003 cells/mm^2, and the percentage of hexagonality decreased by -13.31% compared to age-matched control.

Therefore, it is still highly recommended to include careful evaluation of the corneal endothelium as part of the diabetic and hypertensive patient's eye screening, especially in pre-operative examination.

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