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Research Article

A comparison of corneal endothelial cell density between a group of black South Africans with glaucoma and a group of black South African healthy controls

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ABSTRACT

Background: The endothelial layer of the cornea is crucial to corneal clarity and function, and the cell density of this layer gradually decreases with age and due to disease processes. Primary open-angle glaucoma, a subtype of glaucoma, is associated with reduced corneal endothelial cell density in various populations outside of South Africa.

Methods: This cross-sectional, descriptive, observational study assessed the corneal endothelial density of black South Africans with primary open-angle glaucoma on topical medical management only and compared it to a control group with no eye pathology from the same population.

Results: The study included 112 participants, with an equal number in each group. The baseline characteristics of the two groups were similar. Corneal endothelial cell density in cells per square millimetre was significantly lower in the cohort of participants with primary open-angle glaucoma compared to control participants with healthy corneas. The mean endothelial cell density overall was 2323 (SD 331, 95% CI 2261-2385), with the glaucoma group having a mean of 2213 (SD 365, 95% CI 2115-2311) and the control group having a mean of 2433 (SD 251, 95% CI 2365-2500).

Conclusion: The corneal endothelial cell density of a cohort of black South Africans with primary open angle glaucoma being managed with topical mediation alone was found to be significantly lower than a control group from the same population. This is important for managing black patients with primary open-angle glaucoma, as low endothelial cell density can affect long-term post-operative corneal clarity.

Key Words: primary open-angle glaucoma, corneal endothelial cell density, black South African, specular microscopy, topical glaucoma medication

INTRODUCTION

Corneal endothelial cells form a single layer dividing the cornea's stroma from the aqueous humour filled anterior chamber of the eye.(1) The cells maintain the relative dehydration of the corneal stroma, which contributes to corneal clarity.(2) Corneal endothelial cells have a poor ability to divide, and the density of cells decreases gradually throughout life.(2) Endothelial cells in a healthy state are hexagonally shaped; as cells are lost, the remaining cells cover over the gaps and become irregularly shaped.(2)

Corneal endothelial cell density (CECD) is the number of endothelial cells per mm^2.(3) It is measured using a specular microscope, which can assess "cellular size, shape, density, and distribution."(1) Normal adult CECD is between 2000–3000 mm^2 and decreases (0.6% density per year) throughout adult life as part of the ageing process.(3–5) As density is lost, the size and shape of corneal endothelial cells become less uniform; these phenomena are respectively termed polymegathism and pleomorphism.(3)

A specular microscope is a high-powered compound microscope that can obtain an image of the light reflected off the junction of the corneal endothelium and Descemet's membrane.(6) The microscope measures cell size and density and the coefficient of variance of cell size.(1)

Disease processes can cause a significant decline in cell density, leading to corneal oedema, which results in haze and reduced vision.(2) Intra-ocular surgery can also result in a dramatic loss of corneal endothelial cells; the most common surgery to do this is cataract surgery, although glaucoma surgeries that penetrate the anterior chamber can cause significant and ongoing endothelial loss.(5,7–10) Using mitomycin C as a surgical adjunct to reduce fibrosis and increase the chance of surgical success and longevity can also cause loss of endothelial cells.(8) Patients with primary open-angle glaucoma (POAG) who undergo phacoemulsification cataract surgery have been shown to lose an average of 9% of CECD by two years following surgery.(7) This is similar to the 7% CECD loss at six months to one year following phacoemulsification surgery in the non-glaucomatous eyes.(4,11) This loss appears to be due to the single insult of the intraocular surgery, and the rate of loss after surgery slows down to what would be expected with normal aging.(8)

Glaucoma is a unifying classification for various diseases that result in a common outcome of a typical pattern of progressive optic nerve atrophy caused by loss of retinal nerve fibre layer ganglion cells. Glaucoma results in irreversible vision loss. Clinically, glaucoma progression can be seen as a progressive increase in the cup-disc ratio of the optic nerve head as ganglion cells are lost. Primary open-angle glaucoma is the most common type of glaucoma.(12,13) Glaucoma represents a significant burden of disease, especially in Africa, where it is the second largest cause of blindness.(14) It disproportionately affects black people in Africa and is responsible for approximately 15% of blindness in Sub-Saharan Africa and an additional 4% of moderate to severe visual impairment.(15,16) This represents a greater proportional burden of disease than in other parts of the globe, where the average global rate of blindness due to glaucoma is reported to be 8.3%.(16) In addition to higher rates of glaucoma, black people who have the disease tend to develop it earlier in life and have vision loss, which progresses at a faster rate than other race groups.(17,18)

Primary open-angle glaucoma is associated with lower corneal endothelial cell density in multiple populations.(3–5,19,20) The cause of this reduced cell density has been postulated to be multiple factors, including the disease process itself, raised intraocular pressure, topical medications used to treat the condition, and preservatives in these topical medications.(3,8,19) In vitro studies have pointed to benzalkonium chloride (BAK), a commonly used preservative, as a cause of decreased CECD.(4) Surgical and laser procedures form part of the management of primary open angle glaucoma. As discussed above, glaucoma and cataract surgery are associated with significant loss of corneal endothelial cells.(5,7–10) Selective laser trabeculoplasty is a procedure used to reduce intraocular pressure by applying laser spots to the trabecular meshwork situated in the iridocorneal angle. Its effect on corneal endothelial cell density is not certain.(21)

Normative databases of CECD have been described for various African populations.(22–24) These studies show contradictory findings. A Nigerian study of healthy eyes concluded that CECD in Nigerians is lower than "that reported in the Japanese, American and Chinese eyes, and is comparable to that seen in Indian and Malaysian eyes."(22) Similar research done in the Democratic Republic of Congo and Egypt described normative values of CECD in healthy eyes.(23,24) The normative values for the Congolese population are "greater than in most other populations,"(23) while the Egyptian database showed similar CECD to the Nigerian database.(24) A recently published study undertaken in the Western Cape province of South Africa compared CECD, central corneal thickness, and intraocular pressure of three groups (African, ethnically diverse, or European) of healthy participants.(25) The study found that the mean endothelial cell density in the African group was significantly higher than in the ethnically diverse and European patients.

There is no data in South Africa about CECD on populations outside of the Western Cape province of South Africa, nor is there any data on the role of glaucoma and its effect on CECD in South African populations. This study thus aimed to assess whether the corneal endothelial cell density of black South Africans with primary open-angle glaucoma is lower than a comparable group of healthy controls.

METHODS

Study design and setting

This cross-sectional, case-control study was conducted at St John Eye Hospital in Soweto, Johannesburg, South Africa. The study participants were 18 or older and self-identified as black South Africans. The participants in the glaucoma group were confirmed to have a diagnosis of primary open-angle glaucoma and were only on topical mediation (one or more drugs). Participants in the control group were assessed to confirm the absence of pathology in the study eye (including but not limited to glaucoma and corneal disease). However, cataracts, through which the optic nerve head was still visible, were not exclusion criteria.

Convenience sampling was used to recruit study participants who attended St John Eye Hospital for their care (booked follow-up for glaucoma or cataract pre-operative appointments) or to recruit healthy family and friends escorting people with visual complaints to the eye hospital into the control group.

The sample size was calculated by referencing previous studies in other populations. The required sample size was calculated as 112 participants with 1:1 sampling, resulting in 56 in each group. Only one eye of each participant was included in the study; if both eyes were eligible, a random number generator was used to decide which eye to include.

Non-contact specular microscopy was done using the TOMEY EM-4000, and the automated analysis of cell density and size generated by the machine was utilised. (Figure 1)

All participants gave written consent before inclusion. Ethical approval for the study was obtained from the Wits Human Research Ethics Committee.

Participant data were collected on a data collection sheet and then transcribed onto a spreadsheet for data analysis. Data were collected between 23 November 2023 and 1 November 2024. Participant demographic data included age, sex, medical comorbidities, home language, and province of birth in South Africa. Clinical data included visual acuity, intraocular pressure, cup-disc ratio of the optic nerve head, and keratometry. The TOMEY EM-4000 specular microscopy generated data on corneal endothelial cell density, the coefficient of variance, average cell size, standard deviation, maximum and minimum cell sizes, central corneal thickness, and 6A (a measure of the hexagonality of the cells).

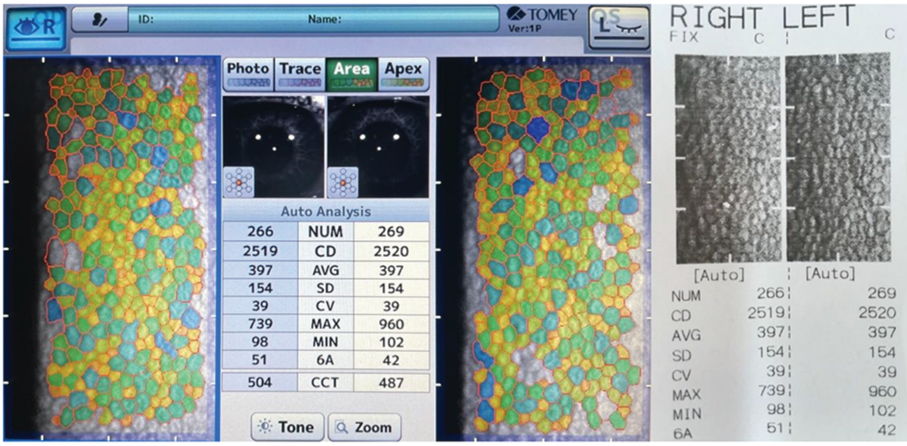

Figure 1: Example of automated corneal endothelial cell density measurement
The images are from the machine used in this study (TOMEY EM-4000)

Table 1: Descriptive statistics of study participants – glaucoma patients and healthy controls

Characteristic	Overall N = 112	Control N = 56	Glaucoma N = 56	p-value
Age, Median[1]	64	65	64	0.70
Sex, n (%)[2]				0.005
Female	57 (51)	36 (64)	21 (38)	
Male	55 (49)	20 (36)	35 (63)	
Eye Examined, n (%)[2]				0.78
Left	49 (44)	25 (45)	24 (43)	
Right	62 (56)	30 (55)	32 (57)	
Self-Reported Comorbidities				
HIV, n (%)[3]	8 (7.1)	2 (3.6)	6 (11)	0.27
Hypertension, n (%)	65 (58)	38 (68)	27 (48)	0.035
Asthma, n (%)[3]	3 (2.7)	2 (3.6)	1 (1.8)	>0.99
Diabetes Mellitus, n (%)	27 (24)	17 (30)	10 (18)	0.12
Clinical Measures				
Visual Acuity in LogMAR, Mean (SD)	0.38 (0.31)	0.37 (0.30)	0.39 (0.32)	0.77
Intraocular pressure (mmHg), Median (IQR)[1]	13.00 (5.00)	13.00 (3.50)	14.00 (5.00)	0.90
Vertical Cup-Disc Ratio, Median (IQR)[1]	0.50 (0.60)	0.30 (0.10)	0.90 (0.20)	<0.001
Keratometry K1, Median (IQR)[1]	42.94 (1.95)	42.81 (1.96)	43.24 (2.05)	0.94
Keratometry K2, Median (IQR)[1]	43.63 (1.96)	43.58 (2.01)	43.77 (1.91)	0.78
Flat Axis, Median (IQR)[1]	95 (114)	94 (100)	95 (123)	0.91

[1]Wilcoxon rank-sum test
[2]Chi-squared test
[3]Fisher's exact test

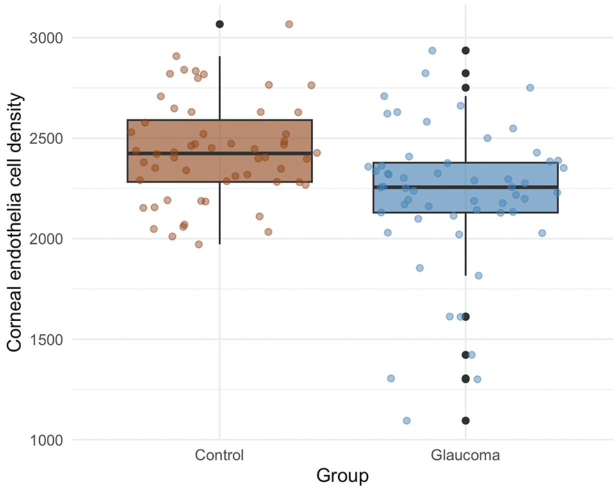

Figure 2: Boxplot of corneal endothelial cell density among patients with glaucoma and healthy controls

Statistical analysis was performed using R version 4.1.2. The Pearson Chi-square and Fisher exact test were used for descriptive categorical analysis, while the Wilcoxon rank-sum test was used for continuous variables. An assessment of whether gender affected the outcome was performed as a sensitivity analysis.

RESULTS

The baseline characteristics, including age, sex, the eye examined, and medical comorbidities of the 122 study participants, are detailed in Table 1. The glaucoma and control groups were similar regarding participant age and the eye examined. Although there was a difference in the proportion of male to female participants in each group, this was later sub-analyzed to assess whether this difference introduced any bias. Hypertension was self-reported as a comorbidity significantly more in the control group (68%) versus 48% of glaucoma participants. A multivariate analysis to assess whether this affected the primary outcome showed no effect ($p = 0.24$).

Visual acuity, intraocular pressure, and keratometry were similar in the two groups (Table 1). The mean vertical cup-disc ratio of the control group was 0.3 (SD 0.08, 95% CI 0.28-0.33), while that of the glaucoma group was 0.9 (SD 0.17, 95% CI 0.8-0.9); with a $p < 0.001$ for this comparison.

All participants in the glaucoma group were asked which topical medications they were using. The topical medications available for managing primary open-angle glaucoma at St John Eye Hospital fall into one of four categories: alpha agonists, beta-blockers, prostaglandin analogues, and carbonic anhydrase inhibitors. Table 2 details participants' medications, showing that beta blockers and prostaglandin analogues were commonly used. Univariate models were designed to assess whether topical medication was associated with lower CECD and whether increasing numbers of topical medicines were associated with lower CECD. These models showed wide confidence intervals and insignificant p-values. Controlling for time from diagnosis of glaucoma to inclusion in the study also did not affect this analysis.

The primary outcome of the study, corneal endothelial cell density was 2433 (SD 251, 95% CI 2365-200) in the control group, while it was 2213 (SD 365, 95% CI 2115-2311) in the glaucoma group ($p<0.001$). Figure 2 is a box and whisker diagram which illustrates this primary outcome.

Table 2: Table of medications among patients with glaucoma

Characteristic	**N = 56**
Beta Blocker, n (%)	52 (93)
Prostaglandin Analogue, n (%)	52 (93)
Alpha Blocker, n (%)	45 (80)
Carbonic Anhydrase Inhibitor, n (%)	19 (34)

Table 3: Descriptive analysis of endothelial cell variables

	Overall N = 112	**Control N = 56**	**Glaucoma N = 56**	**p-value[1]**
Corneal Endothelial Cell Density, Mean (SD)	**2,323 (331)**	**2,433 (251)**	**2,213 (365)**	**<0.001**
Coefficient Of Variation, Mean (SD)	40.7 (8.3)	40.8 (5.9)	40.6 (10.3)	0.49
Average Cell Size, Mean (SD)	446 (88)	422 (51)	470 (108)	0.003
Standard Deviation, Mean (SD)	181 (51)	173 (41)	188 (59)	0.33
Maximum Cell Size, Mean (SD)	1,177 (413)	1,120 (264)	1,233 (518)	0.53
Minimum Cell Size, Mean (SD)	112 (32)	106 (22)	117 (39)	0.040
Central Corneal Thickness, Mean (SD)	481 (46)	489 (58)	473 (28)	0.002
Hexagonality, Mean (SD)	44 (8)	43 (9)	45 (8)	0.13

[1]Wilcoxon rank sum test

Central corneal thickness was also significantly lower in the glaucoma group [473µm (SD 28, 95% CI 466-481)] compared to the control group [489µm (SD 58, 95% CI 474-505)] ($p = 0.002$). The cell size measurements in the two groups are also detailed in Table 3.

As a result of the differing proportions of baseline sex composition of the two groups, a sensitivity analysis was performed to assess the effect of sex on corneal endothelial cell density and other measured corneal variables. The study showed that sex did not impact the outcomes ($p > 0.05$).

DISCUSSION

Primary open-angle glaucoma is a common eye disease. In black patients, it is a more severe disease with an earlier age of onset and causes more blindness than in other race groups.(17,18) This study highlights the severe and frequently advanced nature of the glaucomatous disease seen in this population. The mean vertical cup-disc ratio of 0.9 illustrates this. The fact that the mean intraocular pressure in the glaucoma group was 13.71 demonstrates that this group of participants had an acceptable intraocular pressure on the day of inclusion into the study. An analysis of the Advanced Glaucoma Intervention Study (AGIS) data concluded that "low intraocular pressure is associated with reduced progression of visual field defect" in patients with open-angle glaucoma.(26) Average intraocular Pressure of less than 14 mmHg over a follow-up period of 7 years was protective against worsening loss of visual field, and intraocular pressure below 18 mmHg at all visits over 6 years prevented glaucoma progression.(26) The current study cannot assess whether this group of participants, whose mean intraocular pressure fell within the desired range according to this AGIS analysis, had progressive glaucomatous visual field loss.

In this study, the first of its kind in a black South African population, we found that the corneal endothelial cell density of black South Africans with primary open angle glaucoma is lower than age-matched healthy controls. This mirrors studies undertaken outside of South Africa, which showed a difference between endothelial cell density between eyes with glaucoma on medical management and healthy eyes.(4,19) A 2021 review of all glaucoma therapies on endothelial cell density concluded that high intraocular pressure in glaucoma was associated with increased loss of endothelial cells; in addition, other glaucoma subtypes, such as angle closure glaucoma can result in very high pressure and a significant reduction in corneal endothelial cell density over a short period of raised pressure.(4)

The difference in baseline rate of hypertension between the two groups is a potential confounder. However, a multivariate analysis showed that this difference did not affect the primary outcome.

The lower central corneal thickness in the glaucoma group is a finding that is in keeping with the current understanding of lower central corneal thickness being associated with and possibly a risk factor for the development of primary open-angle glaucoma.(27)

The medications (in drop formulation) used to lower intra-ocular pressure and the compounds used to preserve them have not conclusively been found to contribute to the loss of endothelial cells.(4) The drops available for lowering intraocular pressure at St John Eye Hospital are all preserved with BAK. BAK has been associated with corneal decompensation due to significant endothelial cell loss, but other studies have not found this association.(28) The effects of individual drug classes on endothelial cell density have been studied, and, in a review by Realini et al., no single glaucoma medication has been shown to reduce endothelial cell density significantly.(4) Janson notes that the studies of individual medications on corneal endothelial cells are generally undertaken for weeks or months and that years or decades of use of these medications may be having effects that are not fully understood.(8) A 2019 study found significantly lower endothelial cell density in participants with primary open-angle glaucoma compared to healthy controls; this study also included glaucoma participants not yet on topical medication and found that glaucoma medication use was associated with lower corneal endothelial cell density – the authors concluded that this difference might be attributable to glaucoma medication toxicity.(19) This study was not designed to assess the association of individual anti-glaucoma medications on CECD, and when this association was assessed, no association was found. Additionally, an association between CECD and the number of medications used was not found.

With the increase in the use of selective laser trabeculoplasty for the management of primary open-angle glaucoma (as driven by the results of the LiGHT trial (29)), there are likely to be fewer patients with primary open-angle glaucoma who will only be on topical medical treatment for the disease.

Rho kinase (ROCK) inhibitors are a relatively new class of drugs developed to lower intraocular pressure and manage glaucoma.(30) They have been found to "promote corneal endothelial cell proliferation, increase intercellular adhesion, and suppress apoptosis". They thus have applications in the treatment of endothelial pathology and glaucoma management. They are not yet licenced in South Africa, so no study participants were using them. Once commercially available, their effect on corneal endothelium in this population is a potential study area.

LIMITATIONS

There are several limitations to this study. As this study only assessed CECD at a single time, it could not determine the rate of loss of endothelial cell density. Only participants in topical medical management were included in the glaucoma arm of the study. Thus, a significant proportion of the population with primary open-angle glaucoma was ineligible to participate as they had either undergone intraocular surgery or had a laser procedure for the management of their glaucoma. Currently, there is no established normative database of corneal endothelial cell density in the black population of South Africa; thus, our results may not be generalisable to the black population as a whole.

CONCLUSION

This study shows that black South African patients with glaucoma treated only with topical medication had lower corneal endothelial density when compared to race and age-matched control participants. These findings are similar to published reports in other race groups. This parameter is essential for an ophthalmologist when managing patients with primary open-angle glaucoma, as endothelial cell density will affect surgical decision-making and long-term post-operative corneal clarity. We also recommend a larger study to establish a normative database of corneal endothelial cell density in the black South African population, as it would add to the understanding of glaucoma in this group of patients.

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