Published in final edited form as:

Cornea. 2018 June ; 37(6): 712–719. doi:10.1097/ICO.0000000000001575.

A comparative study of central corneal epithelial, stromal and total thickness in males with and without primary open angle glaucoma

Hatim Batawi, MD, MSPH^{1,2,3}, Ivonne Valentina Lollett, MD^{1,2}, Cima Maliakal⁴, Sarah R. Wellik, MD^{1,2}, Michael Anderson, PhD^{5,6}, William Feuer, MS², Carol L. Karp, MD², and Anat Galor, MD, MSPH^{1,2}

¹Miami Veterans Administration Medical Center, Miami, FL

²Bascom Palmer Eye Institute, University of Miami, Miami, FL

³Department of Ophthalmology, King Abdul Aziz University, Jeddah, Saudi Arabia

⁴University of Miami, Miller School of Medicine, Miami, FL

⁵Center for Prevention and Treatment of Visual Loss, Iowa City Veterans Administration Medical Center, Iowa City, IA

⁶Departments of Ophthalmology and Visual Science and Molecular Physiology and Biophysics, University of Iowa, Iowa City, IA

Abstract

PURPOSE—To compare central corneal epithelial thickness (CET), stromal thickness (CST), total thickness (CCT) in males with and without primary open angle glaucoma and to determine factors associated with corneal thickness.

METHODS—A case-control study was conducted to evaluate 116 male patients at the Miami Veterans Affairs Medical Center. Subjects with available anterior segment optical coherence tomography images (Cirrus HD-OCT, Carl Zeiss Meditec Inc., Dublin, California, USA) were retrospectively classified into 2 groups by glaucoma status. CET, CST, CCT measurements between the groups were compared. Associations between thickness and other variables of interest were also evaluated.

RESULTS—The two groups were similar with respect to race and ethnicity. The mean age of patients in the glaucoma group (70.3 ± 8.9) was higher than in the non-glaucoma group (66.0 ± 11.7), $P < 0.03$. Individuals who self-identified as black had lower CST ($447.8 \pm 29.0 \mu\text{m}$) and CCT ($503.0 \pm 30.5 \mu\text{m}$) compared to whites (CST: $470.0 \pm 31.7 \mu\text{m}$; CCT: $525.1 \pm 32.4 \mu\text{m}$), $p = 0.0001$ and $p = 0.0002$, respectively. In a similar manner, individuals with glaucoma had lower CST ($453.4 \pm 32.5 \mu\text{m}$) and CCT ($507.3 \pm 33.8 \mu\text{m}$) compared to those without glaucoma (CST: $465.2 \pm 31.2 \mu\text{m}$; CCT: $521.5 \pm 31.5 \mu\text{m}$), $p = 0.05$ and $p = 0.02$, respectively. CET, CST, and CCT

Corresponding author: Anat Galor, MD, MSPH, 900 NW 17th Street, Miami, FL 33136; agalor@med.miami.edu.

Meeting Presentation: Partially presented in the American Academy of Ophthalmology Annual Meeting, 2016.

Conflicts of interest: No conflicting relationship exists for any author.

were negatively correlated with number of anti-glaucoma medications ($r = -0.20$, $r = -0.22$, and $r = -0.25$, respectively), $P = 0.05$ for all.

CONCLUSIONS—Individuals with glaucoma have lower CST and CCT measurements compared to individuals without glaucoma. An increased number of glaucoma medications associated with lower thickness measurements.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness and the second leading cause of vision loss worldwide. While presently affecting more than 60 million people globally, the number is set to increase to 111.8 million by 2040.^{1, 2} Glaucoma consists of a group of diseases defined by optic nerve damage. Primary open-angle glaucoma (POAG) is the most common sub-type of glaucoma in the United States.³ Early diagnosis and treatment of glaucoma has been shown to slow or prevent disease progression and minimize glaucoma-related vision loss.³

Although the biological mechanisms of POAG are not yet well understood, several significant risk factors have long been linked to POAG including elevated intraocular pressure (IOP), advanced age, black American race, and positive family history of glaucoma.⁴⁻⁷ More recently, central corneal thickness (CCT) has also been shown to be a significant predictor for development of POAG in patients with ocular hypertension.⁸ Other retrospective analyses have indicated that thinner CCT is a risk factor for glaucoma development and progression.⁹⁻¹¹ Several potential mechanisms have been postulated regarding the link between CCT and glaucoma. First, the relationship may be driven by IOP measurement error, as thinner corneas underestimate true IOP and thicker corneas overestimate the measurement.¹²⁻¹⁴ Second, CCT may relate to the biomechanics of the optic nerve head. Due to the continuity of the cornea, sclera, and optic disc lamina, researchers have hypothesized that CCT may reflect the propensity of the sclera and lamina cribrosa to deform.^{15, 16} This latter hypothesis has been questioned however, as some studies found insignificant correlations between CCT and optic disc lamina cribrosa distortion.^{17, 18} Third, lower CCT may allow more oxygen in the anterior chamber angle, leading to oxidative damage to the trabecular meshwork cells, and increased IOP.¹⁹ Fourth, CCT could constitute a biomarker for a glaucomatous genotype, in which some genes influencing CCT may also act in other tissues of more direct glaucoma relevance, such as the trabecular meshwork, retinal nerve fiber layer, or lamina cribrosa.²⁰ Given these discrepancies, it is uncertain whether CCT is an independent risk factor for glaucoma or simply a potential source of error in IOP measurements.²¹

CCT can be measured using a variety of devices, such as ultrasound pachymetry, confocal microscopy, and anterior segment optical coherence tomography (AS-OCT). In most of these devices, CCT is measured as the combined thickness of the three-major corneal histological layers including the epithelium, stroma, and endothelium. An advantage of the AS-OCT is that it is a reliable and reproducible instrument for imaging the central cornea and can measure the corneal epithelium and stromal layer separately.^{22, 23} Because the corneal stromal layer makes up more than 90% of the total corneal thickness, it has been

postulated that disparities in this tissue layer are the primary cause of variability in corneal thickness.^{24, 25} Nonetheless, the association between individual layers of corneal thickness measurements and POAG has not been fully investigated.

Previous studies have evaluated differences in some, but not all, corneal thickness measurements in patients with glaucoma compared to controls. For example, one study found no significant changes in central corneal epithelial thickness (CET) measurements between POAG and controls.²⁶ A knowledge gap remains, however, regarding differences in epithelial and stromal thicknesses in glaucomatous and non-glaucomatous eyes. To fill in this knowledge gap, in this study we compared epithelial, stromal, and total corneal thickness measurements in men with and without POAG using AS-OCT and evaluated which factors were linked to each individual corneal parameter.

METHODS

Study population

Individuals were identified who had undergone AS-OCT imaging of their central cornea (performed to measure CCT for many indications including pre-cataract planning, glaucoma management, etc.). Of note, ultrasound pachymetry is not used in our clinic for this indication as it requires contact with the cornea and the processing requirement between uses is cumbersome. Individuals were divided into 2 groups based on glaucoma status (POAG versus non-glaucoma group). POAG cases were defined as those with 2 or more of the following: IOP ≥ 21 mm Hg, optic nerve abnormalities (as defined by the treating physician), and/or imaging abnormalities (visual field and/or nerve fiber layer optical coherence tomography). Controls were defined as healthy individuals with no evidence of glaucoma in either eye (no history of elevated IOP; optic nerve or imaging abnormalities). Exclusion criteria included individuals with known corneal abnormalities (keratoconus, corneal scar). We also excluded females from the analysis as they compromised only a small portion of our population ($n=4$). It was determined that 56 individuals were needed in each group to test for differences in mean CCT between individuals with and without POAG. This was based on an expected mean CCT difference of 8 μm (SD 15 μm), power of 80%, and significance level of 0.05. The study was conducted in accordance to the principles of the Declaration of Helsinki and received approval from the Institutional Review Board (IRB) committee at the Miami Veteran Affairs Medical Center (VA).

Data collection

Demographics (age, race, gender, and ethnicity), past medical history (diabetes mellitus, hypertension, and hyperlipidemia), and ocular history (glaucoma severity and glaucoma medication use) were collected from medical records. Glaucoma severity was rated clinically via review of the medical record (including optic nerve photographs, optical coherence tomography images, and visual fields). The severity scale was based on the International Classification of Disease (ICD-9) Staging Criteria²⁷ as follows; Stage 1: Mild or early stage glaucoma which characterized by optic nerve abnormalities consistent with glaucoma but without visual field abnormalities on any visual field test; Stage 2: Moderate stage glaucoma which characterized by glaucomatous visual field abnormalities in one

hemifield and not within 5 degrees of fixation; Stage 3: Severe or late stage glaucoma characterized by glaucomatous visual field abnormalities in both hemifields and/or loss within 5 degrees of fixation in at least one hemifield. The anterior segment module of the Cirrus HD-OCT (Carl Zeiss Meditec Inc, Dublin, California, USA)^{26, 28} with the anterior segment 5-line raster was used to image the central cornea. After imaging, the best scan (of 5 images) was selected based on the clarity of corneal layers after magnification. Although most individuals had images available from both eyes, only the right eye of each was selected given the substantial correlation between corneal thickness measurements in the right and left eyes [central corneal total thickness (CCT); $r=0.9$, central corneal stromal thickness (CST); $r=0.9$, and central corneal epithelial thickness (CET); $r=0.5$, p value=0.00005 for all]. Lubricating drops or local anesthesia was not administered prior to the scan.

Image Analysis

A built-in software caliper tool was used to measure the central epithelial, stromal and total corneal thickness. White and black corneal images were magnified (by 600%-800%) and the corneal thickness was manually measured. 1) To measure CET, cursors were placed perpendicular to the ocular surface epithelium from a point located just beneath the tear film (first hyperreflective layer) to the basal membrane (second hyperreflective layer). 2) To measure CST, cursors were placed perpendicular to the ocular surface stroma from a point located just beneath the basal membrane (second hyperreflective layer) to the Descemet's membrane just above the endothelial layer (third hyperreflective layer). 3) To measure CCT, cursors were placed perpendicular to the ocular surface epithelium from a point located just beneath the tear film (first hyperreflective layer) to a point located just beneath the endothelial layer (third hyperreflective layer). (Figure 1) 4) To calculate relative central epithelial thickness (RCET) and relative central stromal thickness (RCST), CET and CST were divided by CCT and then multiplied by 100. Of note, the minimum distance that can be measured between two points by this software is 4 microns. A single reader, who was masked to clinical data, analyzed all images. The intra-observer reliability for corneal thickness parameter measurement was first evaluated and found to be excellent (Intraclass Correlations 0.97).

Main outcome measure

The main outcome measure was to study whether CET, CST, CCT, RECT, and REST differed by glaucoma status. Secondary outcome measures were correlations between other demographics and co-morbidities with thickness measurements.

Statistical Data Analysis

All statistical analyses were performed using SPSS 21.0 (SPSS Inc, Chicago, IL) statistical package. Frequencies and descriptive statistics were applied to the data, as appropriate. To study the effect of glaucoma on corneal thickness parameters, subjects were first categorized by glaucoma status. Independent t-tests were applied to assess differences in mean epithelial, stromal, and total corneal thickness between the groups. Subsequently, we evaluated which demographics, comorbidities, glaucoma metrics, and glaucoma medications were significantly associated with corneal thickness. Independent t-tests, analyses of variance

(ANOVA) and correlations (Pearson and Spearman) were used for statistical analysis, as applicable. Linear regression analyses were performed to evaluate which factors remained significantly associated with corneal thickness.

RESULTS

Study population

A total of 116 right eyes of 116 males were included in this study; 58 eyes had a documented history of POAG while 58 eyes had no history of POAG. The mean age of all participants was 68.20 ± 10.62 (range 26–90) years. The majority of subjects were non-Hispanic (83%) and 48% were black. More than half of the group had hypertension (67%) and hyperlipidemia (67%), while 38% had diabetes.

Corneal thickness parameters in POAG versus healthy controls

There were no significant differences in demographics (race, and ethnicity), and comorbidities (diabetes, hypertension, and hyperlipidemia) among glaucoma and non-glaucoma group. However, individuals in the glaucoma group were older (mean: 70.3 ± 8.9 years) compared to those without glaucoma (mean: 66.0 ± 11.7 years), $P < 0.03$. Individuals with glaucoma had lower mean CST ($453.4 \pm 32.5 \mu\text{m}$) and CCT ($507.3 \pm 33.8 \mu\text{m}$) compared to controls (CST: $465.2 \pm 31.2 \mu\text{m}$ and CCT: $521.5 \pm 31.5 \mu\text{m}$) $p = 0.05$ and $p = 0.02$, respectively. CET measurements were also lower, but the difference did not reach statistical significance. On the other hand, we did not find any significant differences in RCET and RCST between the glaucoma group (RCET: 9.06 ± 0.67 , and RCST: 89.35 ± 0.73) and the control group (RCET: 9.02 ± 0.86 , and RCST: 89.16 ± 1.0) $p = 0.77$, and $p = 0.24$, respectively. (Table 1)

Glaucoma severity correlated with thickness, as those with severe glaucoma ($n = 5$) had the thinnest corneas (CST $427.2 \pm 31.6 \mu\text{m}$; CCT $480.8 \pm 31.4 \mu\text{m}$). Participants with moderate glaucoma ($n = 39$) had the second lowest values (CST $453.5 \pm 32.3 \mu\text{m}$; CCT $507.5 \pm 33.6 \mu\text{m}$) followed by those with mild glaucoma ($n = 14$) (CST $462.5 \pm 30.2 \mu\text{m}$; CCT $516.2 \pm 32.2 \mu\text{m}$) (Table 2). In a similar manner, CST and CCT inversely correlated with cup-to-disc ratio (CDR) ($r = -0.24$, and $r = -0.26$) $p = 0.009$, and $p = 0.001$, respectively. Whereas IOP was positively correlated with both CST and CCT ($r = 0.18$, and $r = 0.19$) $p = 0.04$, and $p = 0.03$, respectively. CET, RCET, and RCST did not correlate with glaucoma severity, CDR, or IOP (Table 3).

Corneal thickness parameters by anti-glaucoma medications

CET, CST, and CCT were all negatively correlated with the number of anti-glaucoma medications ($r = -0.20$, $r = -0.22$, and $r = -0.25$, respectively, p -value < 0.05 for all). There was no significant correlation between number of anti-glaucoma medications and RECT or REST (Table 4). Changes in corneal thickness parameters by different types of anti-glaucoma medications are summarized in (Table 4). Considering only those individuals with glaucoma, those using timolol eye drops had lower mean CET ($45.0 \pm 3.0 \mu\text{m}$) compared to individuals who did not use timolol ($47.2 \pm 3.2 \mu\text{m}$), $p = 0.015$. Both CST and CCT measurements were also lower, but the difference did not reach statistical significance. No

significant differences were noted in corneal thickness parameters in those using versus not using dorzolamide, latanoprost and brimonidine (Table 4).

Corneal thickness parameters by demographics and comorbidities

Age was negatively correlated with RCET ($r=-0.18$, $p=0.047$), but not CET ($r=-0.15$, $p=0.09$), CST ($r=0.12$, $p=0.18$), or CCT ($r=0.09$, $p=0.30$). RCST was positively correlated with age ($r=0.21$, $p=0.02$) (Table 3). Blacks had lower CST $447.8 \pm 29.0 \mu\text{m}$, CCT $503.0 \pm 30.5 \mu\text{m}$, and RCST 89.01 ± 0.80 compared to whites (CST: $470.0 \pm 31.7 \mu\text{m}$, CCT: $525.1 \pm 32.4 \mu\text{m}$, and RCST: 89.48 ± 0.90), $p=0.0001$, $p=0.0002$, and $p=0.004$, respectively. CET and RCET were not significantly affected by race. No significant differences in thickness were seen by ethnicity, diabetes, hypertension, and hyperlipidemia. (Table 5)

Regression analysis

Multivariable regression analysis was performed to determine which factors remained significantly associated with corneal thickness. When considering demographics (age and race), glaucoma status (IOP, CDR, and stage), and anti-glaucoma medications (number and type), the number of glaucoma medications remained significantly correlated with CET (beta: -0.20 , standard error (SE): 0.21 , $p=0.03$). For CST, when considering these parameters, race (-0.33 , 5.7 , 0.0002) and IOP (0.24 , 0.72 , 0.006) remained significant in the analysis (Table 6). When examining the relationship between corneal thickness and glaucoma within race, white individuals with glaucoma ($n=26$) had thinner CST $464.2 \pm 32.3 \mu\text{m}$ compared to their counterparts without glaucoma ($n=34$) CST $474.4 \pm 30.9 \mu\text{m}$ but the difference did not reach statistical significance ($p=0.21$). While blacks had lower CST values than whites, there were no significant difference in measurement between those with ($n=32$) and without ($n=24$) glaucoma (CST $444.7 \pm 30.4 \mu\text{m}$; CST $452.0 \pm 27.1 \mu\text{m}$), respectively, ($p=0.35$). (Figure 2).

DISCUSSION

This study aimed to investigate five specific corneal parameters; central corneal epithelial thickness (CET), stromal thickness (CST), total thickness (CCT), relative epithelial thickness (RCET) and, relative stromal thickness (RCST), assessing how these measurements differed with glaucoma status and topical medication use. We found an association between CCT and glaucoma, driven by CST rather than CET. Furthermore, similar to previous reports,^{29, 30} we found a correlation between decreased CCT and increased glaucoma severity. However, when controlling for race, we found that black race was more significantly associated with CST than the presence or absence of glaucoma. Conversely, our results showed no significant correlation between relative corneal thicknesses measurements (RCET, and RCST) and glaucoma. Although glaucoma patients had lower absolute corneal thicknesses measurements compared to controls, the relative corneal thicknesses measurements were not different between the two groups. Similar to previous studies^{24,25}, we found that the CST was the major contributor to the CCT (about 90%), regardless of demographics, comorbidities, or glaucoma status.

Our findings demonstrating an association between CCT and glaucoma are in line with those of prior reports. In one study of 50 individuals with glaucoma, CCT, and CST, but not CET, showed a positive correlation with IOP ($\sim r = 0.65$).³¹ Another study that compared eyes within an individual found that the eye with the thinner CCT exhibited greater visual field loss compared to the eye with the thicker CCT.³² Yet another group described a similar phenomenon with respect to optic nerve cupping, but interestingly, did not note IOP differences by CCT.³³ As such, they hypothesized that the connection between CCT and glaucoma severity was driven by inaccuracies in IOP measurement.

The finding of an association between black race and decreased CCT has likewise been described in previous studies.^{11, 34, 35} Mechanisms underlying the lower CCT in blacks remain unknown, but have been hypothesized to include genetic disposition and structural differences in the optic nerve. In fact, genetic predisposition has been shown to influence epithelial, stromal and total corneal thickness.³⁶ For example, cell adhesion molecules, such as neurotrimin (*NTM*), contactin-associated protein-like 4 (*CNTNAP4*), and collagen genes, *COL5A1* and *COL8A2* have been implicated in CCT variability.³⁷ In mice, the genetic components that influence epithelial thickness appear to be different from those that influence stromal thickness. For example, the quantitative trait loci named *Cctq5* (chr 11) and *Cctq6* (chr 14) demonstrated an association specifically with ST, while *Cctq4* (chr 3) correlated with epithelial thickness. It is clear then that CCT is a complex trait with multiple genes contributing to it, but the mechanisms connecting CCT to glaucoma needs further exploration.

In our study, CET negatively correlated with anti-glaucoma medication use. Epithelial thickness is in part a measure of the number and regenerative capabilities of limbal epithelial stem cells. Over the course of a lifetime, the eye undergoes many periods of stress, during which time stem cells proliferate and re-establish normal homeostasis of epithelial thickness. Not surprisingly, as age increases, the number and proliferative capacity of these stem cells diminishes, potentially leading to a decreased epithelial thickness.³⁸ A similar phenomenon is found throughout the body with decreased function of epithelial stem cells on the skin and viscera,²³ leading to decreased epithelial thicknesses. For instance, age halts epithelial repair in the olfactory cells in a similar manner as the corneal epithelium.³⁹ Some prior studies have reported a negative association between age and absolute epithelial thickness³⁸ while others have not.⁴⁰ The association between glaucoma medications and epithelial thickness may also be explained by the regenerative potential of limbal stem-cells. Glaucoma medications contain preservatives, such as benzalkonium chloride (BAK), that are toxic to epithelial cells and can lead to a dysfunction or depletion of limbal stem cells.⁴¹

As with all studies, our findings must be considered bearing in mind the innate limitations, which include a retrospective design and a male population defined by availability of AS-OCT images. Furthermore, the OCT utilized did not have automated software for measuring corneal thickness. However, we did find excellent intra-reader reliability when measuring these parameters repeatedly within the same image. Despite these caveats, the study contributes vital information to the future of CCT interpretation in glaucoma patients. Our results highlight that while central corneal stromal thickness is decreased in individuals with glaucoma as compared to those without glaucoma, this difference is driven more by race

than glaucoma status. Furthermore, our study highlights the potential effects of glaucoma medication usage, especially timolol, on central corneal epithelial thickness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Drs. Anna Junk and Jennifer Hu for their generous input and support.

Financial support: Supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Clinical Sciences Research EPID-006-15S (Dr. Galor), R01EY026174 (Dr. Galor), NIH Center Core Grant P30EY014801, Research to Prevent Blindness Unrestricted Grant, US Dept. of Veterans Affairs, RR&D (I01RX001481) and National Institutes of Health, NEI (R01EY017673) grants (Dr. Anderson). Ronald and Alicia Lepke Grant, The Lee and Claire Hager Grant, The Jimmy and Gaye Bryan Grant, The H. Scott Huizenga Grant, The Grant and Diana Stanton-Thornbrough, The Robert Baer Family Grant, The Emilyn and Mark Feldberg Grant, The Gordon Charitable Foundation and the Richard Azar Family Grant (institutional grants). The sponsors or funding organizations had no role in the design or conduct of this research. The contents do not represent the views of the U.S. department of veterans Affairs or the United States Government.

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006; 90:262–7. [PubMed: 16488940]
2. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014; 121:2081–90. [PubMed: 24974815]
3. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet*. 2004; 363:1711–20. [PubMed: 15158634]
4. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol*. 1991; 109:1090–5. [PubMed: 1867550]
5. Ko F, Boland MV, Gupta P, et al. Diabetes, Triglyceride Levels, and Other Risk Factors for Glaucoma in the National Health and Nutrition Examination Survey 2005–2008. *Invest Ophthalmol Vis Sci*. 2016; 57:2152–7. [PubMed: 27111561]
6. Tielsch JM, Sommer A, Katz J, et al. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *Jama*. 1991; 266:369–74. [PubMed: 2056646]
7. Wolfs RC, Klaver CC, Ramrattan RS, et al. Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. *Arch Ophthalmol*. 1998; 116:1640–5. [PubMed: 9869795]
8. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002; 120:714–20. discussion 829–30. [PubMed: 12049575]
9. Mehdizadeh A, Hoseinzadeh A, Fazalzadeh A. Central corneal thickness as a risk factor for glaucoma. *Med Hypotheses*. 2007; 69:1205–7. [PubMed: 17566668]
10. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007; 114:1965–72. [PubMed: 17628686]
11. Herndon LW, Weizer JS, Stinnett SS. Central corneal thickness as a risk factor for advanced glaucoma damage. *Arch Ophthalmol*. 2004; 122:17–21. [PubMed: 14718289]
12. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Surv Ophthalmol*. 2000; 44:367–408. [PubMed: 10734239]
13. Brandt JD, Beiser JA, Kass MA, et al. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). *Ophthalmology*. 2001; 108:1779–88. [PubMed: 11581049]

14. Shih CY, GraffZivin JS, Trokel SL, et al. Clinical significance of central corneal thickness in the management of glaucoma. *Arch Ophthalmol*. 2004; 122:1270–5. [PubMed: 15364705]
15. Tezel G, Trinkaus K, Wax MB. Alterations in the morphology of lamina cribrosa pores in glaucomatous eyes. *Br J Ophthalmol*. 2004; 88:251–6. [PubMed: 14736786]
16. Mokbel T, Ghanem A. Correlation of central corneal thickness and optic nerve head topography in patients with primary open-angle glaucoma. *Oman J Ophthalmol*. 2010; 3:75–80. [PubMed: 21217900]
17. Jonas JB, Holbach L. Central corneal thickness and thickness of the lamina cribrosa in human eyes. *Invest Ophthalmol Vis Sci*. 2005; 46:1275–9. [PubMed: 15790890]
18. Ren R, Li B, Gao F, et al. Central corneal thickness, lamina cribrosa and peripapillary scleral histomorphometry in non-glaucomatous Chinese eyes. *Graefes Arch Clin Exp Ophthalmol*. 2010; 248:1579–85. [PubMed: 20495817]
19. Siegfried CJ, Shui YB, Bai F, et al. Central corneal thickness correlates with oxygen levels in the human anterior chamber angle. *Am J Ophthalmol*. 2015; 159:457–62.e1. [PubMed: 25461296]
20. Lively GD, Koehn D, Hedberg-Buenz A, et al. Quantitative trait loci associated with murine central corneal thickness. *Physiol Genomics*. 2010; 42:281–6. [PubMed: 20423963]
21. Medeiros FA, Weinreb RN. Is corneal thickness an independent risk factor for glaucoma? *Ophthalmology*. 2012; 119:435–6. [PubMed: 22385483]
22. Sin S, Simpson TL. The repeatability of corneal and corneal epithelial thickness measurements using optical coherence tomography. *Optom Vis Sci*. 2006; 83:360–5. [PubMed: 16772894]
23. Yang Y, Hong J, Deng SX, et al. Age-related changes in human corneal epithelial thickness measured with anterior segment optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2014; 55:5032–8. [PubMed: 25052994]
24. Reinstein DZ, Archer TJ, Gobbe M, et al. Stromal thickness in the normal cornea: three-dimensional display with artemis very high-frequency digital ultrasound. *J Refract Surg*. 2009; 25:776–86. [PubMed: 19772263]
25. Ehlers N, Hjortdal J. Corneal thickness: measurement and implications. *Exp Eye Res*. 2004; 78:543–8. [PubMed: 15106933]
26. Francoz M, Karamoko I, Baudouin C, et al. Ocular surface epithelial thickness evaluation with spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2011; 52:9116–23. [PubMed: 22025572]
27. Parekh AS, Tafreshi A, Dorairaj SK, et al. Clinical applicability of the International Classification of Disease and Related Health Problems (ICD-9) glaucoma staging codes to predict disease severity in patients with open-angle glaucoma. *J Glaucoma*. 2014; 23:e18–22. [PubMed: 24370808]
28. Pekel G, Yagci R, Acer S, et al. Comparison of Corneal Layers and Anterior Sclera in Emmetropic and Myopic Eyes. *Cornea*. 2015; 34:786–90. [PubMed: 25811725]
29. Meirelles SH, Alvares RM, Botelho PB, et al. Relationship between corneal thickness and severity of visual field loss in primary open-angle glaucoma. *Arq Bras Oftalmol*. 2006; 69:313–7. [PubMed: 16936951]
30. Janicijevic-Petrovic MA, Sarenac-Vulovic TS, Janicijevic KM, et al. Evaluation of central corneal thickness in patients with ocular hypertension and primary open-angle glaucoma. *Med Glas*. 2014; 11:115–9.
31. Lee M, Ahn J. Effects of Central Corneal Stromal Thickness and Epithelial Thickness on Intraocular Pressure Using Goldmann Applanation and Non-Contact Tonometers. *PLoS One*. 2016; 11:e0151868. [PubMed: 26998838]
32. Sullivan-Mee M, Gentry JM, Qualls C. Relationship between asymmetric central corneal thickness and glaucomatous visual field loss within the same patient. *Optom Vis Sci*. 2006; 83:516–9. [PubMed: 16840876]
33. Iester M, Telani S, Frezzotti P, et al. Differences in central corneal thickness between the paired eyes and the severity of the glaucomatous damage. *Eye*. 2012; 26:1424–30. [PubMed: 22975658]
34. Muir KW, Duncan L, Enyedi LB, et al. Central corneal thickness in children: Racial differences (black vs. white) and correlation with measured intraocular pressure. *J Glaucoma*. 2006; 15:520–3. [PubMed: 17106365]

35. Leite MT, Alencar LM, Gore C, et al. Comparison of corneal biomechanical properties between healthy blacks and whites using the Ocular Response Analyzer. *Am J Ophthalmol.* 2010; 150:163–8.e1. [PubMed: 20538248]
36. Koehn DR, Meyer KJ, Anderson MG. Genetic Evidence for Differential Regulation of Corneal Epithelial and Stromal Thickness. *Invest Ophthalmol Vis Sci.* 2015; 56:5599–607. [PubMed: 26305532]
37. Ulmer M, Li J, Yaspan BL, et al. Genome-wide analysis of central corneal thickness in primary open-angle glaucoma cases in the NEIGHBOR and GLAUGEN consortia. *Invest Ophthalmol Vis Sci.* 2012; 53:4468–74. [PubMed: 22661486]
38. Kim BJ, Ryu IH, Kim SW. Age-related differences in corneal epithelial thickness measurements with anterior segment optical coherence tomography. *Jpn J Ophthalmol.* 2016; 60:357–64. [PubMed: 27324656]
39. Blanks, JD. CK Sensory Aging: Vision. Hof, P., editor. New York, NY: Elsevier; 2009. p. 208-9.
40. Korey M, Gieser D, Kass MA, et al. Central corneal endothelial cell density and central corneal thickness in ocular hypertension and primary open-angle glaucoma. *Am J Ophthalmol.* 1982; 94:610–6. [PubMed: 7148942]
41. Rosin LM, Bell NP. Preservative toxicity in glaucoma medication: clinical evaluation of benzalkonium chloride-free 0.5% timolol eye drops. *Clin Ophthalmol.* 2013; 7:2131–5. [PubMed: 24204115]

Figure 1.

A magnified anterior segment optical coherence tomography scan showing a) the measurements of central corneal epithelial thickness = 48 μm and b) stromal thickness = 476 μm.

Figure 2.
Histogram examining stromal thickness differences between those with and without glaucoma, separated by race.

Table 1

Corneal thickness parameters in glaucoma versis non glaucoma group.

Group	Glaucoma group (N=58)	Control group (N=58)	P-Value
Demography			
Age, mean ± SD, (min-max)	70.3 ± 8.9 (46 - 90)	66.0 ± 11.7 (26 - 86)	0.03
Race, n (%) black	32 (55.17)	24 (41.37)	0.13
Ethnicity, n (%) Hispanic	9 (15.51)	11 (18.96)	0.62
Co-Morbidities			
Diabetes mellitus, n (%)	32 (55.17)	21 (36.20)	0.70
Hypertension, n (%)	40 (68.96)	40 (68.96)	1.00
Hyperlipidemia, n (%)	37 (63.79)	43 (74.13)	0.22
Medication (eye drops)			
Artificial tears, n (%)	10 (17.24)	12 (20.68)	0.63
Brimodine, n (%)	22 (37.93)	NA	
Dorzolamide, n (%)	33 (56.89)	NA	
Timilol, n (%)	37 (63.79)	NA	
Latanoprost, n (%)	49 (84.48)	NA	
Corneal thickness parameters[*]			
CET, mean ± SD (min-max), μm	45.8 ± 3.2 (40 - 52)	46.9 ± 3.9 (40 - 56)	0.10
CST, mean ± SD (min-max), μm	453.4 ± 32.5 (388 - 544)	465.2 ± 31.2 (402 - 556)	0.05
CCT, mean ± SD (min-max), μm	507.3 ± 33.8 (440 - 604)	521.5 ± 31.5 (454 - 608)	0.02
RCET, mean ± SD (min-max)	9.06 ± 0.67 (7.7 - 10.9)	9.02 ± 0.86 (7.2 - 10.5)	0.77
RCST, mean ± SD (min-max)	89.35 ± 0.73 (87.4 - 90.7)	89.16 ± 1.0 (86.6 - 91.4)	0.24

CET=absolute central epithelial thickness; CST=absolute central stromal thickness, CCT=absolute central corneal thickness; RCET=relative central epithelial thickness; RCST=relative central stromal thickness; SD=standard deviation; Min=minimum; Max=maximum; N=number of participants.

* measured in right eye.

Table 2

Corneal thickness parameters by glaucoma stage.

Group	Control group (N=58)	Mild glaucoma (N=14)	Moderate glaucoma (N=39)	Severe glaucoma (N=5)	P value
<i>Corneal thickness parameters*</i>					
CET, mean $\pm$ SD (min-max), μm	46.9 $\pm$ 3.9 (40 - 56)	45.7 $\pm$ 3.0 (40 - 52)	45.9 $\pm$ 3.5 (40 - 52)	45.6 $\pm$ 2.1 (44 - 48)	0.44
CST, mean $\pm$ SD (min-max), μm	465.2 $\pm$ 31.2 (402 - 556)	462.5 $\pm$ 30.2 (412 - 508)	453.5 $\pm$ 32.3 (388 - 544)	427.2 $\pm$ 31.6 (388 - 472)	0.03
CCT, mean $\pm$ SD (min-max), μm	521.5 $\pm$ 31.5 (454 - 604)	516.2 $\pm$ 32.2 (464 - 564)	507.5 $\pm$ 33.6 (440 - 604)	480.8 $\pm$ 31.4 (440 - 524)	0.02
RCET, mean $\pm$ SD (min-max)	9.02 $\pm$ 0.86 (7.2 - 10.5)	8.86 $\pm$ 0.43 (8.2 - 9.5)	9.07 $\pm$ 0.72 (7.7 - 10.9)	9.51 $\pm$ 0.77 (8.4 - 10.3)	0.43
RCST, mean $\pm$ SD (min-max)	89.16 $\pm$ 1.0 (86.6 - 91.4)	89.58 $\pm$ 0.47 (88.8 - 90.3)	89.34 $\pm$ 0.77 (87.4 - 90.7)	88.81 $\pm$ 0.86 (87.9 - 90.1)	0.24

CET=absolute central epithelial thickness; CST=absolute central stromal thickness, CCT=absolute central corneal thickness; RCET=relative central epithelial thickness; RCST=relative central stromal thickness; SD=standard deviation; Min=minimum; Max=maximum; N=number of participants.

* measured in right eye.

Table 3

Correlations between age, intraocular pressure (IOP), cup-to-disc ratio, number of anti-glaucoma medications, and corneal thickness parameters.

	CET (Pearson r/Spearman rho)	CST (Pearson r/Spearman rho)	CCT (Pearson r/Spearman rho)	RCET (Pearson r/Spearman rho)	RCST (Pearson r/Spearman rho)
Age	-0.13/-0.15	0.05/0.12	0.03/0.09	-0.120/-0.18 *	0.18 */0.21 *
IOP	-0.01/-0.01	0.18 */0.21 *	0.19 */0.23 *	-0.16/-0.18	0.03/0.06
Cup-to-disc ratio	-0.13/-0.10	-0.24 **/-0.20 *	-0.26 **/-0.23 **	0.08/0.05	0.03/0.05
N. of glaucoma medications	-0.20 */-0.16	-0.22 */-0.19 *	-0.25 */-0.23 **	0.01/0.01	0.09/0.09

CET=absolute central epithelial thickness; CST=absolute central stromal thickness, CCT=absolute central corneal thickness; RCET=relative central epithelial thickness; RCST=relative central stromal thickness; N=number.

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 4

Corneal thickness parameters by different types of anti-glaucoma medications in individuals with glaucoma.

Factor	Number, (%)	CET mean $\pm$ SD (min-max)	P	CST mean $\pm$ SD (min-max)	P	CCT mean $\pm$ SD (min-max)	P	RCET mean $\pm$ SD (min-max)	P
Brimonidine	Yes N=22 (37.93)	45.2 $\pm$ 2.8 (40 - 52)	0.28	449.9 $\pm$ 35.7 (388 - 508)	0.51	503.1 $\pm$ 36.6 (440 - 564)	0.46	89.37 $\pm$ 0.79 (87.9 - 90.7)	0.78
	No N=36 (62.02)	46.2 $\pm$ 3.5 (40 - 52)		455.6 $\pm$ 30.7 (392 - 544)		509.8 $\pm$ 32.2 (440 - 604)		89.34 $\pm$ 0.71 (87.4 - 90.6)	
Dorzolamide	Yes N=33 (56.89)	45.2 $\pm$ 3.0 (40 - 52)	0.08	451.5 $\pm$ 32.3 (388 - 508)	0.61	504.7 $\pm$ 33.0 (440 - 564)	0.51	89.42 $\pm$ 0.81 (87.4 - 90.7)	0.32
	No N=25 (43.10)	46.7 $\pm$ 3.4 (40 - 52)		456.0 $\pm$ 33.2 (388 - 544)		510.7 $\pm$ 35.2 (440 - 604)		89.26 $\pm$ 0.63 (88.2 - 90.3)	
Latanoprost	Yes N=49 (84.48)	45.8 $\pm$ 3.0 (40 - 52)	0.93	454.1 $\pm$ 33.2 (388 - 544)	0.71	508.0 $\pm$ 34.47 (440 - 604)	0.71	89.36 $\pm$ 0.71 (87.9 - 90.7)	0.83
	No N=9 (15.51)	45.7 $\pm$ 4.5 (40 - 52)		449.7 $\pm$ 30.1 (412 - 512)		503.5 $\pm$ 31.5 (464 - 572)		89.30 $\pm$ 0.92 (87.4 - 90.6)	
Timolol	Yes N=37 (63.79)	45.0 $\pm$ 3.0 (40 - 52)	0.015	449.1 $\pm$ 33.8 (388 - 508)	0.17	502.2 $\pm$ 34.7 (440 - 564)	0.12	89.39 $\pm$ 0.79 (87.4 - 90.7)	0.40
	No N=21 (36.20)	47.2 $\pm$ 3.2 (40 - 52)		461.1 $\pm$ 29.3 (416 - 544)		516.3 $\pm$ 30.8 (468 - 604)		89.28 $\pm$ 0.63 (88.3 - 90.3)	

CET=absolute central epithelial thickness; CST=absolute central stromal thickness, CCT=absolute central corneal thickness; RCET=relative central epithelial thickness; RCST=relative central stromal thickness; SD=standard deviation; Min=minimum; Max=maximum; N=number of participants.

* All Corneal thickness parameters (μm) were measured in right eye.

Table 5

Corneal thickness parameters by demographics and comorbidities.

Factor	N (%)	CET mean $\pm$ SD (min-max)	P	CST mean $\pm$ SD (min-max)	P	CCT mean $\pm$ SD (min-max)	P	RCET mean $\pm$ SD (min-max)	P	RCST mean $\pm$ SD (min-max)	P
Gender	Male	118 (100.0)	46.4 $\pm$ 3.6 (40 - 56)	NA	459.3 $\pm$ 32.2 (388 - 556)	NA	514.4 $\pm$ 33.3 (440 - 608)	NA	9.0 $\pm$ 0.77 (7.2 - 10.9)	89.2 $\pm$ 0.88 (86.6 - 91.4)	NA
	Female	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Race	Black	56 (48.27)	45.8 $\pm$ 3.3 (40 - 52)	0.11	447.8 $\pm$ 29.0 (388 - 504)	0.0001	503.0 $\pm$ 30.5 (440 - 608)	0.0002	9.12 $\pm$ 0.74 (7.2 - 10.5)	89.01 $\pm$ 0.80 (86.6 - 91.4)	0.004
	White	60 (51.72)	46.9 $\pm$ 3.8 (40 - 56)		470.0 $\pm$ 31.7 (388 - 556)		525.1 $\pm$ 32.4 (440 - 560)		8.95 $\pm$ 0.79 (7.4 - 10.9)	89.48 $\pm$ 0.90 (86.6 - 90.6)	
Ethnicity	H	20 (17.24)	47.6 $\pm$ 3.8 (40 - 56)	0.11	470.2 $\pm$ 28.5 (428 - 544)	0.09	525.8 $\pm$ 30.0 (476 - 604)	0.09	9.03 $\pm$ 0.79 (8.0 - 10.5)	89.41 $\pm$ 0.71 (87.9 - 90.6)	0.39
	NH	96 (82.75)	46.1 $\pm$ 3.5 (40 - 56)		457.0 $\pm$ 32.7 (388 - 556)		512.0 $\pm$ 33.6 (440 - 608)		9.06 $\pm$ 0.68 (7.2 - 10.9)	89.22 $\pm$ 0.91 (86.6 - 91.4)	
Diabetes	Yes	44 (37.93)	45.7 $\pm$ 3.2 (40 - 56)	0.11	461.7 $\pm$ 37.6 (388 - 566)	0.52	516.0 $\pm$ 38.6 (440 - 608)	0.68	8.89 $\pm$ 0.75 (7.2 - 10.3)	89.44 $\pm$ 0.80 (88.1 - 91.4)	0.08
	No	72 (62.06)	46.8 $\pm$ 3.8 (40 - 56)		457.8 $\pm$ 28.7 (388 - 544)		513.4 $\pm$ 29.8 (440 - 604)		9.12 $\pm$ 0.77 (7.7 - 10.9)	89.14 $\pm$ 0.91 (86.6 - 90.8)	
Hypertension	Yes	80 (68.96)	46.3 $\pm$ 3.5 (40 - 56)	0.61	457.9 $\pm$ 34.4 (388 - 556)	0.48	513.0 $\pm$ 35.5 (440 - 608)	0.49	9.05 $\pm$ 0.78 (7.2 - 10.9)	89.22 $\pm$ 0.93 (86.6 - 91.4)	0.56
	No	36 (31.03)	46.6 $\pm$ 3.8 (40 - 56)		462.5 $\pm$ 27.0 (412 - 544)		517.6 $\pm$ 27.9 (464 - 604)		9.01 $\pm$ 0.75 (7.7 - 10.5)	89.32 $\pm$ 0.76 (87.9 - 90.8)	
Hyperlipidemia	Yes	80 (68.96)	46.4 $\pm$ 3.5 (40 - 56)	0.95	462.6 $\pm$ 33.9 (388 - 556)	0.10	517.5 $\pm$ 34.9 (440 - 608)	0.13	8.99 $\pm$ 0.74 (7.2 - 10.4)	89.35 $\pm$ 0.84 (86.6 - 91.4)	0.07
	No	36 (31.03)	46.4 $\pm$ 3.9 (40 - 56)		452.0 $\pm$ 27.3 (388 - 500)		507.6 $\pm$ 28.6 (440 - 560)		9.14 $\pm$ 0.82 (7.7 - 10.9)	89.03 $\pm$ 0.93 (86.6 - 90.7)	

CET=absolute central epithelial thickness; CST=absolute central stromal thickness, CCT=absolute central corneal thickness; RCET=relative central epithelial thickness; RCST=relative central stromal thickness; SD=standard deviation; Min=minimum; Max=maximum; H=Hispanic; NH=non-Hispanic.

* All Corneal thickness parameters (μ m) were measured in right eye.

Table 6

Multivariable regression analysis evaluating factors associated with CET, CST, CCT, RCET, and RCST.

	CET (β, SE, p)	CST (β, SE, p)	CCT (β, SE, p)	RCET (β, SE, p)	RCST (β, SE, p)
Age	(-0.14, 0.03, 0.13)	(0.04, 0.26, 0.64)	(0.02, 0.27, 0.78)	(-0.11, 0.07, 0.22)	(0.14, 0.008, 0.13)
Race	(-0.14, 0.70, 0.13)	(-0.33, 5.7, 0.0002)	(-0.32, 5.8, 0.0004)	(0.10, 0.14, 0.22)	(-0.28, 0.16, 0.0004)
IOP	(-0.0001, 0.08, 0.99)	(0.24, 0.72, 0.006)	(0.25, 0.74, 0.004)	(-0.19, 0.01, 0.04)	(0.07, 0.02, 0.40)
Cup-to-disc ratio	(0.02, 2.54, 0.89)	(-0.03, 20.7, 0.84)	(-0.03, 21.2, 0.89)	(0.03, 0.45, 0.78)	(0.02, 0.70, 0.87)
Glaucoma stage	(0.06, 0.66, 0.74)	(-0.16, 5.4, 0.33)	(-0.16, 5.5, 0.32)	(0.19, 0.14, 0.30)	(-0.08, 0.15, 0.62)
N. of glaucoma medications	(-0.20, 0.21, 0.03)	(-0.01, 2.8, 0.90)	(-0.04, 2.9, 0.73)	(-0.16, 0.07, 0.29)	(0.17, 0.08, 0.24)

CET=absolute central epithelial thickness; CST=absolute central stromal thickness, CCT=absolute central corneal thickness; RCET=relative central epithelial thickness; RCST=relative central stromal thickness; P=p-value; SE=Standard error; β =Regression coefficients.

* All Corneal thickness parameters (μm) were measured in right eye.