Original Investigation

Ethnic Differences in Trabecular Meshwork Height by Optical Coherence Tomography

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IMPORTANCE Differences in ocular anatomy may contribute to ethnic differences in glaucoma risk. Because the trabecular meshwork (TM) plays an important role in aqueous outflow, its anatomy in relation to at-risk populations may provide insight into a potential contributor to elevated intraocular pressure and thus to probability of glaucoma development.

OBJECTIVE To investigate whether differences exist in TM height between ethnic groups.

DESIGN, SETTING, AND PARTICIPANTS This prospective study took place from January 1, 2012, to December 31, 2013. Adult patients who self-reported as being of white, Asian, Hispanic, or African American ethnicity were recruited from ophthalmology clinics at the University of California, San Francisco. The TM height was assessed using spectral-domain anterior segment optical coherence tomography.

MAIN OUTCOMES AND MEASURES Trabecular meshwork height was measured from the scleral spur to the Schwalbe line. We hypothesized that ethnicities with a higher prevalence of glaucoma would tend to have shorter TM heights.

RESULTS We collected data from 460 eyes of 291 participants after excluding 34 optical coherence tomographic scans owing to poor image quality. The final sample was 32.2% white, 45.1% Asian, 10.5% African American, and 12.1% Hispanic. There were 64.2% women, and the mean age was 68.1 years. The mean (SD) TM height among all eyes included in the study was 836 (131) μm. The mean (SD) TM height was characterized among white (851 [131] μm), Asian (843 [126] μm), Hispanic (822 [147] μm), and African American (771 [118] μm) persons. Ethnicity was not associated with TM height overall (P = .23, linear mixed regression model). However, the TM heights of African American participants (771 μm) were shorter than those of white (851 μm; adjusted difference 95% CI, -119.8 to -8.1; P = .02) and Asian (843 μm; adjusted difference 95% CI, -174.4 to -10.8; P = .02) participants.

CONCLUSIONS AND RELEVANCE Although TM height is not associated with ethnicity overall, African American individuals have shorter TM heights compared with Asian and white persons. Trabecular meshwork size may play a role in ethnic differences of glaucoma risk and be a new risk factor to consider in primary open-angle glaucoma.

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Glaucoma is the second leading cause of blindness worldwide and the leading cause of irreversible blindness. Glaucoma is a form of progressive optic neuropathy that causes retinal ganglion cell loss, resulting in visual field defects and characteristic anatomical changes.2-3

Primary open-angle glaucoma (POAG) is the most common type of glaucoma and displays substantial variation in its interethnic distribution.4-5 African American individuals have the highest prevalence of POAG, approximated at 5.6%, and are more likely to progress to blindness compared with other ethnic groups.6-9 Hispanic persons have the second highest prevalence of POAG at 4.7%, followed by Asian and non-Hispanic white individuals at 2.4% and 1.7%, respectively.9

Elevated intraocular pressure is an important modifiable risk factor associated with glaucoma development and progression.10-13 The trabecular meshwork (TM) is the dominant aqueous outflow pathway and actively self-regulates the outflow.14 Because the TM plays an important role in aqueous outflow, its anatomy in relation to at-risk populations may provide insight into a potential contributor to elevated intraocular pressure and thus to probability of glaucoma development.

In this study, we compare the anatomical features of the TM among white, Asian, African American, and Hispanic persons. A smaller TM could diminish aqueous outflow facility. We hypothesize that a shorter TM height is associated with ethnicities that are at higher risk of developing POAG.

Methods

Study Design
This was a prospective, cross-sectional study of the relationship between TM height and ethnicity. Approval from the University of California, San Francisco, Committee on Human Research was obtained, and this study followed the tenets of the Declaration of Helsinki. We recruited consecutive patients from the comprehensive and glaucoma ophthalmology clinics at the University of California, San Francisco, for participation in this study. The recruitment period was from January 1, 2012, to December 31, 2013. All enrolled participants provided written informed consent after explanation of the study and possible consequences.

The ethnicities of study participants included white, Asian, African American, and Hispanic. Ethnicity was assessed by self-report. The Asian cohort included individuals of self-reported Chinese, Japanese, Korean, Filipino, and Vietnamese descent. The white cohort included those of European-derived ancestry only.

Inclusion criteria included adult patients (18 years or older) and self-reported white, Asian, African American, or Hispanic ethnicity. Exclusion criteria included self-reported biracial ancestry; prior intracocular surgery or laser trabeculoplasty; previous ocular trauma; presence of peripheral anterior synchiae on gonioscopy; inability to conduct the necessary testing; and poor image quality preventing adequate assessment of TM anatomy. Both eyes of each participant were included except in cases in which an eye did not meet inclusion and exclusion criteria. Eyes that had undergone laser peripheral iridotomy (LPI) were included.

Data Collection

Study participants received a standardized set of examination and study procedures, including slitlamp biomicroscopy, Goldmann applanation tonometry, and anterior segment imaging by optical coherence tomography.

We conducted spectral-domain anterior segment optical coherence tomography with the Cirrus OCT (Carl Zeiss Meditec, Inc) using the anterior segment 5-line raster protocol. Study participants were instructed to fixate at an external point to center the nasal portion of the eye for the scan. We conducted the scans over the limbal area, perpendicular to the limbus and radial from the center of the cornea. Trained personnel conducted all scans (R.I.C. and D.T.B.).

A trained ophthalmologist (D.T.B.) used ImageJ software (National Institutes of Health) to measure the TM height from the spectral-domain optical coherence tomographic scans while blinded to the ethnicity of each participant. The TM height was defined as the distance from the scleral spur to the Schwalbe line (Figure). A subset of 25 randomly selected scans was reanalyzed at a later time to verify the reproducibility of TM height measurements.

Refraction, central corneal thickness (CCT), Shaffer gonioscopy grade, vertical cup-disc ratio, glaucoma medications, and glaucoma status were obtained from the participants’ medical records. Spherical equivalent was calculated from refraction data by summing the spherical power and half the cylindrical power. Gonioscopy data were interpreted as a narrow/occludable angle if there was a grade of zero or 1 in at least 2 quadrants.

Statistical Analysis

We characterized the total sample by calculating the mean, SD, and range of continuous variables, including age, vertical cup-disc ratio, CCT, number of glaucoma medications used, and spherical equivalent. We also calculated summary percentages of categorical variables, including sex, ethnicity, glau-
coma status, prostaglandin use, prior LPI, and gonioscopy. These parameters were also characterized for each of the 4 ethnic cohorts.

The mean and SD were calculated for TM height measurements for the whole sample and for each ethnic cohort. The intraclass correlation coefficient (ICC) was calculated using a 1-way random-effects model to describe the reproducibility of TM height measurements. Variation was considered to be within acceptable ranges if the ICC was greater than 0.80.

We used a linear mixed-effects regression model (clustered by person) to investigate the association of TM height with ethnicity and to correct for potential confounders; linear mixed-effects regression models adjusted for the non-independence of the 2 eyes of a given patient. Confounders included age, sex, spherical equivalent, glaucoma medications used, prostaglandin use, glaucoma status, gonioscopy, prior LPI, and the use of both eyes. Pairwise comparisons using this linear mixed model were subsequently conducted to elucidate specific relationships of TM height between ethnic cohorts. Statistical analysis was conducted using Julia (http://www.julialang.org, version 0.3 for Macintosh) and the Julia lmm package for linear mixed-effects regression.

Results

Our sample included optical coherence tomographic scans of 494 eyes from 291 participants. We excluded 34 scans owing to poor image quality, resulting in a final sample of 460 eyes. The final sample was composed of 45.1% Asian, 10.5% African American, 32.2% white, and 12.1% Hispanic participants. There were 64.2% women, and the mean age of the sample was 68.1 years.

At the level of individual eyes included in the study, 27.3% of eyes were glaucomatous, 62.1% were glaucoma suspects, and 10.1% had no glaucoma. There was a history of LPI in 24.0% of the eyes. Of the total sample, 60.6% of eyes had open angles, 32.5% had narrow/occludable angles at the time of scanning, and 6.9% did not have this data available. The mean (SD) number of glaucoma medications used was 0.58 (0.96), and 32.6% of eyes were treated with prostaglandins. The mean (SD) intraocular pressure was 16.0 (3.4) mm Hg (range, 8.0 to 29.5 mm Hg). The mean (SD) CCT was 546 (36) μm (range, 452 to 653 μm), and the mean (SD) vertical cup-disc ratio was 0.54 (1.83) (range, 0.10 to 0.90). The mean (SD) spherical equivalent was –0.9 (3.3) (range, –13.0 to 9.3). Table 1 provides the demographic and clinical characteristics of each ethnic cohort.

The mean (SD) TM height among all eyes included in the study was 836 (131) μm. The mean (SD) TM height among white participants was 851 (131) μm; Asian, 843 (126) μm; Hispanic, 822 (147) μm; and African American, 771 (118) μm. Reproducibility of TM height measurements was verified by ICC. Comparison of the measurements from the regraded subset yielded an ICC of 0.83.

The linear mixed model showed that none of the potential confounders of age, sex, spherical equivalent, glaucoma status, number of glaucoma medications used, prostaglandin use, intraocular pressure, CCT, cup-disc ratio, previous LPI, and gonioscopy were associated with TM height (P > .05). Ethnicity overall was also not associated with TM height (P = .23).

Pairwise comparison between ethnic cohorts using the linear mixed-effects regression model demonstrated a difference between the TM heights of African American participants compared with those of white (95% CI, –119.8 to –8.1; P = .02) and Asian (95% CI, –117.4 to –10.8; P = .02) participants. A difference was not identified between the TM height of Hispanic participants compared with those of the other groups. Table 2 shows the adjusted differences, 95% CIs, and P values associated with these interethnic pairwise comparisons.

Discussion

Overall, TM height was not associated with ethnicity. However, African American individuals’ TM heights were shorter

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Asian</th>
<th>African American</th>
<th>White</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, No.</td>
<td>116</td>
<td>27</td>
<td>83</td>
<td>31</td>
</tr>
<tr>
<td>Eyes, No.</td>
<td>203</td>
<td>45</td>
<td>157</td>
<td>55</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>68.5 (11.5)</td>
<td>68.4 (10.3)</td>
<td>66.1 (10.8)</td>
<td>69.1 (13.2)</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>78/116 (67.2)</td>
<td>17/27 (63.0)</td>
<td>49/83 (59.0)</td>
<td>21/31 (67.7)</td>
</tr>
<tr>
<td>Spherical equivalent, mean (SD)</td>
<td>–1.3 (3.5)</td>
<td>–0.3 (1.6)</td>
<td>–0.9 (3.7)</td>
<td>0.5 (2.4)</td>
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<tr>
<td>Glaucoma status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>60</td>
<td>17</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Healthy</td>
<td>37</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Suspect</td>
<td>106</td>
<td>28</td>
<td>115</td>
<td>37</td>
</tr>
<tr>
<td>No. of glaucoma medications used, mean (SD)</td>
<td>0.6 (1.0)</td>
<td>0.9 (1.2)</td>
<td>0.4 (0.8)</td>
<td>0.8 (1.1)</td>
</tr>
<tr>
<td>Prostaglandin use, No. (%)</td>
<td>73/203 (36.0)</td>
<td>13/45 (28.9)</td>
<td>39/157 (24.8)</td>
<td>25/55 (45.5)</td>
</tr>
<tr>
<td>IOP, mean (SD), mm Hg</td>
<td>15.7 (2.9)</td>
<td>15.7 (3.9)</td>
<td>16.3 (3.6)</td>
<td>16.3 (3.9)</td>
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<tr>
<td>CCT, mean (SD), μm</td>
<td>546 (34)</td>
<td>526 (47)</td>
<td>549 (32)</td>
<td>560 (40)</td>
</tr>
<tr>
<td>Vertical cup-disc ratio, mean (SD)</td>
<td>0.54 (0.19)</td>
<td>0.59 (1.71)</td>
<td>0.50 (0.17)</td>
<td>0.58 (0.18)</td>
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<td>Prior LPI, No. (%)</td>
<td>41/203 (20.2)</td>
<td>20/45 (44.4)</td>
<td>27/157 (10.5)</td>
<td>22/55 (40.0)</td>
</tr>
<tr>
<td>Gonioscopy, narrow/occludable angle, No. (%)</td>
<td>73/203 (36.0)</td>
<td>13/45 (28.9)</td>
<td>39/157 (24.8)</td>
<td>25/55 (45.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CCT, central corneal thickness; IOP, intraocular pressure; LPI, laser peripheral iridotomy.
than those of white and Asian participants. To our knowledge, our study is the first to investigate TM height in an ethnically diverse sample and to characterize TM height among white, African American, Asian, and Hispanic persons.

Our finding of a mean TM height of 836 μm in the total sample is slightly greater than, but generally consistent with, previous reported findings by Tun et al,16 who found a mean TM height of 779 μm based on measurements taken from swept-source optical coherence tomographic scans. We interpret this slight difference to be attributable to differences in the selected clinic populations and the types of optical coherence tomographic scan from which TM height measurements were made. The robust ICC values for both studies suggest that the TM height relationships we characterized are reliable. Tun et al16 noted that the mean TM height was greater than the previously used cutoff point of 500 μm from the scleral spur, and our findings add to the growing evidence that TM height is greater than 500 μm.17−19

A novel finding in this study is that TM height is shorter in African American compared with white and Asian persons. This difference in TM height suggests genetic influences on ocular anatomy, which might contribute to ethnic differences in glaucoma risk. African American individuals are at highest risk for glaucoma diagnosis and progression. Differences in ocular anatomy in this ethnic group have already been characterized and hypothesized to play a role in glaucoma risk. African American individuals tend to have thinner CCT, which has been associated with greater glaucoma risk and disease severity.20−24

Our finding that African American individuals have shorter TM heights compared with white and Asian persons supports our hypothesis that ethnic groups at high risk of developing glaucoma have shorter TM. The TM has been implicated in the pathogenesis of glaucoma because of its central role in aqueous outflow. Impaired function of the TM is one mechanism by which outflow facility may be compromised in POAG. Various groups have demonstrated the increased formation of extracellular matrix and decreased cellularity of the TM in glaucomatous eyes, resulting in increased outflow resistance.25−28

A smaller TM may be one contributor to diminished outflow facility in POAG and may render individuals more susceptible to age-related ocular changes. With increasing age, as with glaucoma, there is increased extracellular matrix and decreased cellularity in the TM, reducing the outflow facility of the eye.29−32 Age-related narrowing of the anterior chamber may also obstruct aqueous access to the TM located at the angle of the eye.33−34 Individuals with a smaller TM may thus be more sensitive to the effects of aging on physiologic features of the eye. Future investigation of this topic will focus on elucidating the putative link between TM anatomy and glaucoma risk.

There are several limitations to this study. One is the subjective nature of identifying the scleral spur during the TM height measurement process. Previously published studies have successfully used the same manual approach to localize the scleral spur on spectral-domain optical coherence tomographic scans to measure anterior chamber parameters.35−36 Our ICC of 0.83 suggests a consistent reproducibility of TM height measurements using this method.

Another limitation of this study was the small sample size of the African American and Hispanic cohorts. Study recruitment was limited by the patient demographics of the clinics where recruitment took place. Given the limited sample size, the African American and Hispanic cohorts did not include healthy eyes, although they did include glaucoma suspects. We cannot rule out the possibility that glaucoma treatment, such as prostaglandin use, affects TM anatomy. However, there was no significant difference in glaucoma status distribution and the rate of prostaglandin use between ethnic cohorts by χ2 test (P = .34 and P = .32, respectively), and our linear mixed-effects regression corrects for glaucoma status, number of glaucoma medications used, and prostaglandin use.

One possible interpretation of the lack of association between TM height and ethnicity, despite differences in mean TM height in some pairwise comparisons between ethnic cohorts, is that the small sample size of the Hispanic and African American cohorts precluded detection of subtle differences. Increasing the size of these 2 cohorts could lend greater statistical power to our analyses and allow more sensitive detection of potential differences.

Each ethnic group included in this study also has intra-group differences. Self-identification with an ethnic group does not preclude genetic contribution from another ethnic group. To minimize intra-ethnic variation, we enforced strict inclusion and exclusion criteria, including exclusion of individuals of biracial ancestry. However, it is possible that there is still great genetic diversity within each cohort.

Conclusions

Our study characterizes the TM height among white, Asian, African American, and Hispanic individuals. Although TM height was not associated with ethnicity overall, we introduce evidence that African American individuals have a shorter TM height compared with Asian and white persons. Hispanic
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Study concept and design: Barbosa, Chen, Lin.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Chen.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Porco, Chen.

Administrative, technical, or material support: Lin.

Study supervision: Chen, Barbosa, Lin.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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REFERENCES