Central Corneal Thickness in the Ocular Hypertension Treatment Study (OHTS)

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Objective: Central corneal thickness influences intraocular pressure (IOP) measurement. We examined the central corneal thickness of subjects in the Ocular Hypertension Treatment Study (OHTS) and determined if central corneal thickness is related to race.

Design: Cross-sectional study.

Participants: One thousand three hundred one OHTS subjects with central corneal thickness measurements.

Intervention: Central corneal thickness was determined with ultrasonic pachymeters of the same make and model at all clinical sites of the OHTS.

Main Outcome Measures: Correlation of mean central corneal thickness with race, baseline IOP, refraction, age, gender, systemic hypertension, and diabetes.

Results: Mean central corneal thickness was 573.0 ± 39.0 μm. Twenty-four percent of the OHTS subjects had central corneal thickness > 600 μm. Mean central corneal thickness for African American subjects (555.7 ± 40.0 μm; n = 318) was 23 μm thinner than for white subjects (579.0 ± 37.0 μm; $P < 0.0001$). Other factors associated with greater mean central corneal thickness were younger age, female gender, and diabetes.

Conclusions: OHTS subjects have thicker corneas than the general population. African American subjects have thinner corneas than white subjects in the study. The effect of central corneal thickness may influence the accuracy of applanation tonometry in the diagnosis, screening, and management of patients with glaucoma and ocular hypertension. *Ophthalmology 2001;108:1779–1788 © 2001 by the American Academy of Ophthalmology.*

The Ocular Hypertension Treatment Study (OHTS) is a multicenter, prospective, randomized clinical trial to evaluate the safety and efficacy of topical ocular hypotensive medications in preventing or delaying the onset of visual field loss and/or optic nerve damage in ocular hypertensive individuals at moderate risk of primary open-angle glaucoma developing.[1] In the OHTS, intraocular pressure (IOP) is determined by Goldmann applanation tonometry.

When Goldmann and Schmidt[2] first described the applanation tonometer, they discussed the effect of central corneal thickness on IOP as measured by this device. They assumed a corneal thickness of 500 μm and emphasized that, at least theoretically, corneal thickness might influence applanation readings. However, they believed that variations in corneal thickness occurred rarely in the absence of corneal disease.

As optical and later ultrasonic pachymeters came into widespread use, it became clear that corneal thickness does indeed have a positive correlation with IOP as measured by Goldmann applanation tonometry. In some cases the effect on measured IOP is clinically significant.[3–5] It also became apparent that central corneal thickness is more variable among clinically normal individuals than Goldmann and Schmidt recognized.

In recent years there have been a few reports of increased central corneal thickness in some patients in whom the diagnosis of ocular hypertension had been made. Argus[6] examined 36 patients with ocular hypertension and compared their central corneal thickness with that measured in 29 control subjects and 31 patients with glaucoma. He found that corneal thickness was greater in the patients with ocular hypertension compared with both the control and glaucoma patients. In a more recent study, Herndon and coworkers[7] examined 184 eyes of 109 subjects, of which 48 (74 eyes) had glaucoma, 28 (51 eyes) had ocular hypertension, and 33 (59 eyes) were normal. These investigators found that the central corneal thickness (mean ± standard deviation) of eyes of patients with ocular hypertension was significantly greater (606 ± 41 μm) than that of eyes of patients with glaucoma (554 ± 22 μm) ($P < 0.001$) or of eyes of normal

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controls (561 ± 26 μm) ($P < 0.001$). They found no significant difference in central corneal thickness between normal and glaucomatous eyes ($P = 0.40$). Herman and coworkers[8] found that central corneal thickness of 55 ocular hypertensive subjects enrolled at the Mayo OHTS clinic was significantly greater than that of 55 age-matched (± 3 years) normotensive controls ($P < 0.001$).

Other investigators have recently reported that central corneal thickness is reduced in patients with the diagnosis of "low tension glaucoma," suggesting that, in at least some of these individuals, IOP is being underestimated because of thin corneas.[9–11] Ehlers and Hansen[12] had previously reported similar findings in seven individuals in 1974.

The studies by Argus[6] and Herndon et al[7] would suggest that in at least some of the patients we currently classify as having "ocular hypertension," this classification is erroneous and is an artifact of these patients' greater central corneal thickness. If this is true in a significant number of patients, this finding would have important implications both for the OHTS and general clinical practice: patients with greater central corneal thickness may have "corrected" IOPs that fall within a statistically "normal" range that place these patients at much lower risk for glaucoma developing than previously recognized. Furthermore, a large body of evidence suggests that there is a relationship between IOP and glaucoma risk; if central corneal thickness is a significant variable in the determination of IOP, it may be found that "corrected" IOP will have a much closer risk relationship to glaucoma than "uncorrected" IOP both in the OHTS and in clinical practice.

A careful review of the corneal thickness literature reveals that there is little known about the corneal thickness in African-derived individuals. The extensive corneal thickness studies by Ehlers,[3] Ehlers et al,[4,13] and Alsbirk[14] were performed in Scandinavia and Greenland; the largest US study was performed in Iowa City on a relatively homogeneous white population.[15]

We designed this ancillary study to the OHTS to examine the distribution of corneal thickness in subjects enrolled in the OHTS; furthermore, because the OHTS cohort includes a large proportion of African Americans, we further sought to determine whether corneal thickness is related to race.

Material and Methods

The design of the OHTS and baseline description of its participants are provided in detail elsewhere.[1] The OHTS inclusion criteria included an untreated IOP ≥24 mmHg and ≤32 mmHg in at least one eye, with the untreated IOP in the fellow eye ≥21 mmHg and ≤32 mmHg, along with normal visual fields and normal optic discs. Recruitment closed on October 31, 1996, with a total of 1636 subjects enrolled at 23 clinical centers. The racial self-designation of each subject was made on entry into the OHTS. Four hundred nine (25%) enrolled subjects were African American. History of systemic hypertension and diabetes at baseline was ascertained by self-report. Baseline IOP was defined as the average of two or three IOP measurements at the baseline randomization visit. Subjects were randomly assigned to either close observation or to topical treatment aimed at lowering IOP ≥20% from the baseline IOP. Patient safety and study integrity were monitored by an Executive Committee and an independent Data Safety and Monitoring Committee; each clinical center received local institutional review board approval for the OHTS protocol. The ancillary study described here was approved as a protocol amendment by these oversight committees and by the local institutional review board for each clinical center; data acquisition began in late 1998.

Ultrasonic pachymeters were provided to each of the clinical centers (DGH-500 Pachette; DGH Technologies, Exton, PA). Study personnel were instructed and certified in the use and calibration of the instrument. Instruments were calibrated on a monthly basis using the calibration device provided by the manufacturer. Instruments or ultrasound probes failing calibration or periodic quality control tests were immediately replaced.

Operators acquired five measurements of central corneal thickness from each eye, right eye first. Measurements occurred at the time of either the annual dilated examination visit (after visual fields and tonometry and before the dilated examination) or at the midyear examination visit (after visual fields and tonometry and before direct ophthalmoscopy). Data were transmitted to the OHTS Coordinating Center in St. Louis.

We monitored data quality and reproducibility in two ways. Because the intereye difference in central corneal thickness tends to be small, we required repeat measurements of central corneal thickness when the intereye difference was ≥40 μm. A further subset of subjects at one clinic (University of California-Davis) underwent repeat measurements on separate follow-up visits to estimate the test retest reproducibility of measurements with the same instrument and protocol.

To ensure that central corneal thickness measurements were obtained from all active OHTS subjects, the Coordinating Center provided clinical centers with periodic listings of patients scheduled for upcoming visits in whom measurements had not yet been acquired. This report includes data to January 31, 2001.

For analysis purposes, the five measurements of corneal thickness taken per eye were averaged for each eye separately. For bivariate comparisons such as *t* tests and correlations and for simple descriptive statistics and graphically displayed data, one eye was randomly chosen per subject. *T* tests were used to test for differences in central corneal thickness by race, systemic hypertension, diabetes, and gender, and Pearson correlations (95% confidence intervals [CIs]) were used to describe the relationship of central corneal thickness with age at measurement, baseline IOP, and baseline refraction (spherical equivalent) using SAS (v 6.12 for Windows; SAS Inc., Cary, NC). A mixed general linear model, using data from both eyes, was used to assess the relative contributions of race, gender, age at testing, baseline IOP, baseline refraction, and patient-reported medical history (hypertension and diabetes at baseline). Because a higher percentage of African American subjects were female, were younger, and reported a history of systemic hypertension and diabetes, the mixed model adjusted for the potential influence of these factors with race was used. We also tested for an interaction of race and baseline IOP. Least squares means with 95% CIs are reported when an interaction is statistically significant ($P < 0.05$); all other reported means are unadjusted.

In the retest sample from one clinic, the mean central corneal thickness measured at the initial visit was subtracted from the value at the repeat visit. A positive value indicates that the central corneal thickness was greater at the repeat visit. Intraclass correlation coefficient was computed as an index of agreement between initial and repeat measurements.

Table 1. Mean (± Standard Deviation) Central Corneal Thickness μm in Random Eye by Self-described Race

	n	Mean ± Standard Deviation
African American*	318	555.7 ± 40.0
American Indian or Alaskan Native	2	589.4 ± 27.2
Asian or Pacific Islander	11	588.0 ± 25.4
White*	912	579.0 ± 37.0
Hispanic	43	569.7 ± 40.9
Other/Unknown	12	564.4 ± 30.3
Overall*	1298	572.9 ± 38.9
African Americans and whites*	1230	573.0 ± 39

*Excludes the three subjects (two white and one African American) who had a >40 μm difference between the eyes and had not yet completed a retest.

Results

Central corneal thickness measurements were obtained from 1301 (82%) of the living OHTS subjects as of January 31, 2001. Table 1 shows the mean central corneal thickness by race (self-described). Because of small sample sizes for American Indian, Asian, Hispanic, and Other/Unknown, these groups were excluded from further analyses, leaving a sample of 1233. The mean number of years between randomization and central corneal thickness measurement was 4.9 ± 0.7 years (range, 2.5–6.6 years).

Among the 77 subjects at one clinic in whom repeat measurements were made, the mean number of days between the initial and repeat measurements was 384.7 ± 75.2 days (range, 35–560 days). The mean difference (repeat minus initial central corneal thickness) was 12.1 ± 17.2 μm ($P < 0.0001$; range, −25.8 to 68.4 μm). The agreement between the initial and repeat measurement was 0.87 (intraclass correlation coefficient, 95% CI of 0.80–0.92). The difference between the initial and repeat measure was lower when the operator was the same (7.3 ± 12.3 μm, n = 10) than when the operator was different (12.8 ± 17.7 μm, n = 67) ($P = 0.3$).

Only 12 (0.10% of 1233) subjects had intereye differences in central corneal thickness ≥ 40 μm, suggesting that the quality of data acquisition was high. For 9 of these 12 subjects repeat measurements were completed and used for analyses; 3 subjects without a retest were excluded from analyses, making 1230 subjects available for analyses (912 white, 318 African American).

Mean central corneal thickness was 573.0 ± 39.0 μm among all OHTS subjects. Two hundred ninety-three (24%) OHTS subjects had a central corneal thickness > 600 μm (Fig 1). The mean corneal thickness of right eyes (572.5 ± 39 μm) and left eyes (573.3 ± 39 μm) was significantly different ($P = 0.02$). Multivariate analyses adjusted for differences in corneal thickness of right and left eyes.

Mean central corneal thickness among African American OHTS subjects was 555.7 ± 40 μm compared with 579.0 ± 37.0 μm among white OHTS subjects. This difference of 23 μm was statistically significant by a *t* test ($P \leq 0.001$) and confirmed in a multivariate mixed linear model that adjusted for potential confounders correlated with race in this sample ($P = 0.02$). Twenty-seven percent (249 of 912) of whites had a central corneal thickness > 600 μm compared with 14% (44 of 318) of the African American subjects. The distribution of central corneal thickness among the two groups is shown in Figure 2. The racial difference is in the same direction and of the same magnitude over the entire range of baseline IOP as shown in Figure 3. The multivariate

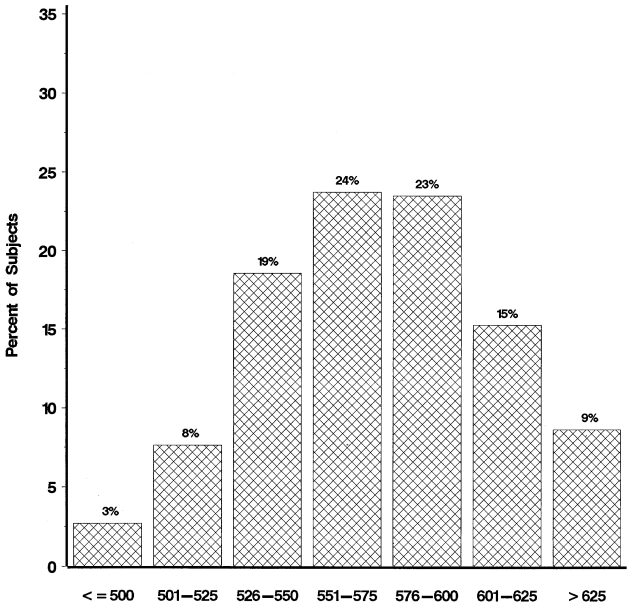

Figure 1. Distribution of central corneal thickness among Ocular Hypertension Treatment Study subjects.

model described previously found no evidence that racial differences in central corneal thickness vary over the range of baseline IOP ($P = 0.42$ for interaction of race and baseline IOP).

Baseline IOP was not significantly correlated with central corneal thickness ($r = -0.04$, 95% CI of −0.10 to 0.01; $P = 0.12$; n = 1230).

Baseline refraction (spherical equivalent) was statistically correlated with central corneal thickness ($r = -0.10$; 95% CI of −0.15 to −0.04; $P = 0.0008$; n = 1226) but not significant in the multivariate mixed model that adjusted for other factors ($P = 0.47$). Subjects who were pseudophakic at the time of baseline refraction (n = 4) were excluded from this analysis.

Older age is associated with thinner central corneal thickness ($r = -0.15$; 95% CI of −0.20 to −0.10; $P < 0.001$; n = 1230). This relationship was also statistically significant in the multivariate model ($P < 0.0001$) and did not differ by race ($P = 0.77$ for interaction of race and age). For all decades of age, African American subjects have lower median central corneal thickness compared with whites (Fig 4).

Mean central corneal thickness of females was slightly greater than males (females, n = 701; 575.0 ± 38.6 μm; males, n = 529; 570.3 ± 39.4 μm; $P = 0.03$). This relationship was also statistically significant in the multivariate model ($P = 0.01$) and did not seem to differ by race ($P = 0.86$ for interaction of race and gender).

Mean central cornea thickness of subjects reporting a history of diabetes at baseline was statistically significantly greater compared with subjects not reporting a history of diabetes (diabetics, n = 128; 580.1 ± 42.0 μm; nondiabetics, n = 1101; 572.2 ± 38.6 μm, $P = 0.02$). The relationship between self-reported diabetes and thicker central corneas was confirmed in multivariate analyses that adjusted for potentially confounding factors ($P = 0.006$) and was similar in magnitude and direction for white and African American subjects ($P = 0.34$ for interaction of race and self-reported diabetes).

Overall, the mean central corneal thickness of subjects reporting systemic hypertension at baseline (n = 455; 571 ± 40.6 μm) did not differ from subjects who did not report a history of hypertension (n = 773; 574.2 ± 38.0 μm) ($P = 0.16$). However,

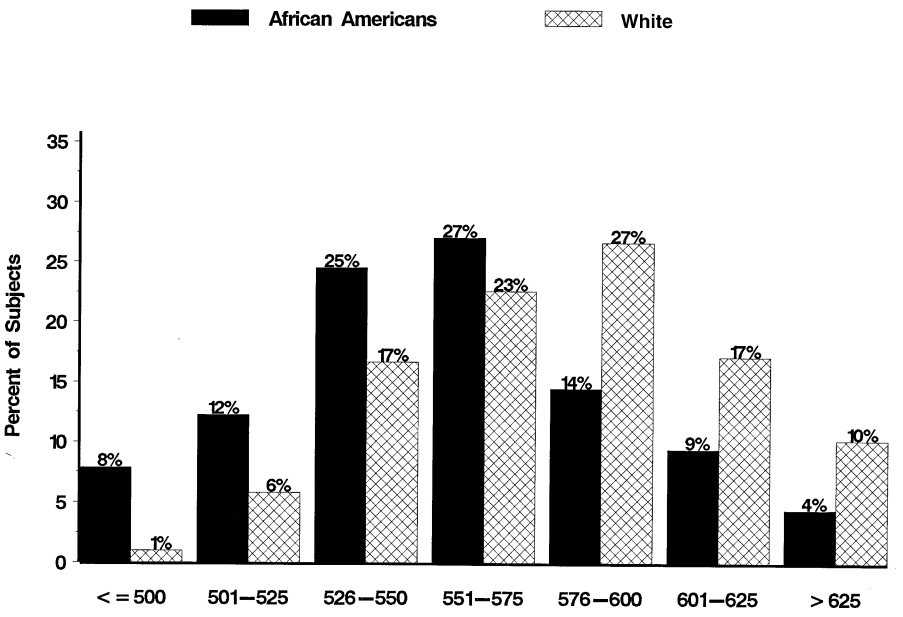

Figure 2. Distribution of central corneal thickness among Ocular Hypertension Treatment Study subjects by race.

the relationship between corneal thickness and systemic hypertension significantly differed by race. Among African American subjects, those reporting systemic hypertension had thinner central corneas (553.6 μm; 95% CI of 547.2–562.0 μm) compared with those not reporting systemic hypertension (558.2 μm; 95% CI of 550.5–565.9 μm); among white subjects, those reporting systemic hypertension had thicker central corneas (588.8 μm; 95% confidence interval of 583.5–594.1 μm) compared with those subjects not reporting systemic hypertension (582.8 μm; 95% CI of 577.9–587.6 μm) ($P = 0.03$ for interaction of race and hypertension). These corneal thickness means are least squares means, which were estimated from the multivariate mixed model.

The multivariate mixed linear model of mean corneal thickness included eye, race, gender, age at testing, baseline refraction, baseline IOP, baseline medical history (systemic hypertension and diabetes), and the interaction of race with gender, systemic hypertension, diabetes, age at testing, and baseline IOP. In the multivariate mixed model, eye ($P = 0.03$), race ($P = 0.02$), gender ($P = 0.01$), diabetes ($P = 0.006$), age at testing ($P < 0.0001$), and the interaction of race and hypertension ($P = 0.03$) were statistically significantly associated with corneal thickness. Variables that were not independently statistically significantly associated with mean corneal thickness included baseline refraction ($P = 0.47$), baseline IOP ($P = 0.53$), systemic hypertension ($P = 0.78$), and the

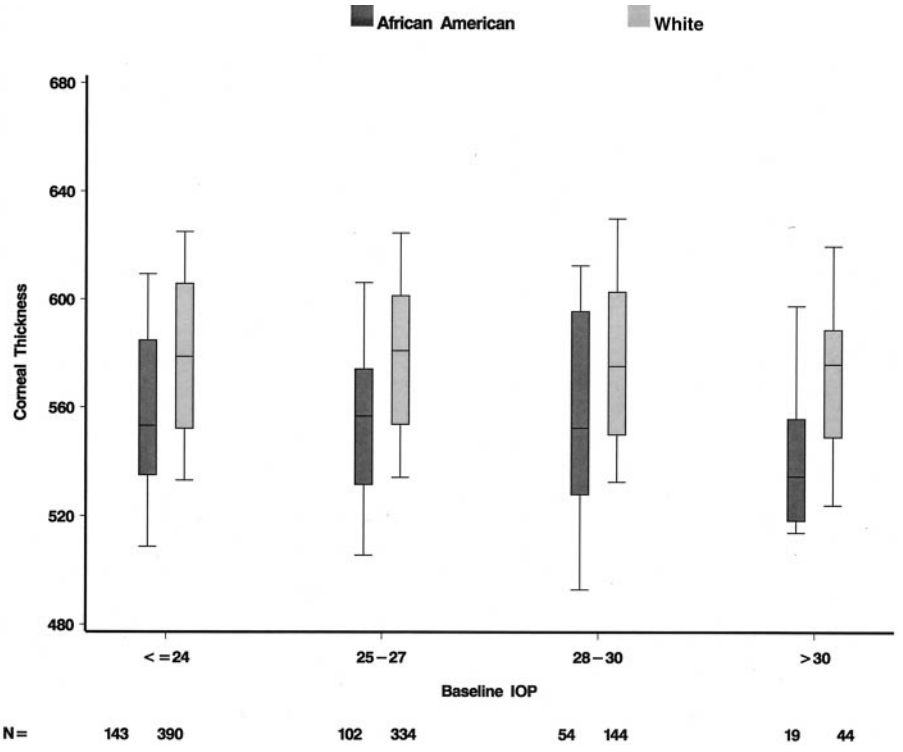

Figure 3. Central corneal thickness among Ocular Hypertension Treatment Study subjects versus baseline intraocular pressure by race. Median is the line in the center of the box. The top and bottom of the box are the 75th and 25th percentiles. The ends of the lines extend to the 90th and 10th percentiles.

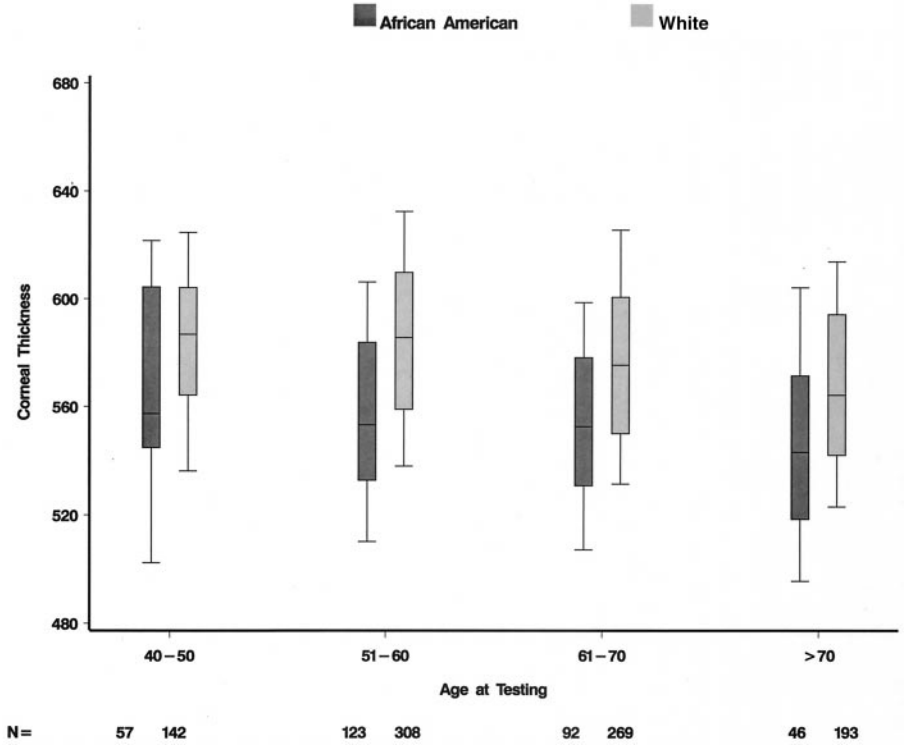

Figure 4. Central corneal thickness among Ocular Hypertension Treatment Study subjects with age at measurement by race. Median is the line in the center of the box. The top and bottom of the box are the 75th and 25th percentiles. The ends of the lines extend to the 90th and 10th percentiles.

interaction of race with the preceding variables (all $P > 0.05$) except hypertension ($P = 0.03$).

Discussion

In a recent meta-analysis of the corneal thickness literature, encompassing 300 articles from which data could be obtained, Doughty and Zaman[16] found that the mean corneal thickness of eyes reported as "normal" was 534 μm; for slit-lamp based optical pachymetry, the mean corneal thickness was 530 μm (125 data sets), and for ultrasonic pachymetry, 544 μm (80 data sets). In this study of the OHTS sample we found a central thickness of 573 μm.

Previous studies have revealed that central corneal thickness tends to decrease with increasing age.[14,17] In our study, we found a statistically significant negative correlation between age and central corneal thickness that corresponds to an age-related thinning of 6.3 μm per decade. This is similar to the 10 μm/decade thinning reported by Foster et al.[17] Other investigators have shown a modest effect of gender on central corneal thickness, with females having slightly thicker corneas than their male counterparts. Similarly, in our study we also found a modest effect of gender on corneal thickness, with females having corneas approximately 5 μm thicker than males. We believe that the small differences in central corneal thickness induced by age or gender measured among the OHTS subjects are not clinically significant in the determination of IOP. Subjects reporting a history of diabetes at baseline had slightly thicker corneas than those without diabetes. The difference was small (less than 10 μm) but is consistent with the subtle alterations in the corneal endothelium described in patients with early diabetes by Keoleian and coworkers.[18]

We found virtually no correlation between baseline IOP and central corneal thickness in the OHTS subjects. The absence of such a correlation is not likely to be due to the lack of statistical power, because the statistical power of the OHTS sample is at least 0.89 for detecting correlations of approximately 0.10 and greater. We attribute the lack of correlation to the limited range of IOP represented in OHTS because of the exclusion of subjects with IOP $<$24 mmHg or $>$32 mmHg in the higher eye. In previous studies reporting a relationship between IOP and corneal thickness, the study samples included a larger range of IOPs, particularly normotensive subjects.

As noted previously, most of the corneal thickness studies to date have examined racially homogeneous populations. Foster and coworkers[17] recently studied a Mongolian population and found a strong positive correlation between central corneal thickness and IOP, with the average central corneal thickness being 495 $\pm$ 32 μm. This average central corneal thickness is thinner than that reported in the literature for the predominantly white populations studied previously, suggesting that racial differences in corneal thickness do indeed exist.

It is well established that African Americans have a higher prevalence and incidence of glaucoma, that the disease presents earlier in life, and that the disease is more aggressive in its clinical course than in Caucasian Americans.[19–22] We wondered whether one explanation for this might be a racial difference in central corneal thickness. If African Americans have thinner corneas than their white counterparts, perhaps this might explain some of the poor

performance of glaucoma screening by tonometry alone in this population. On average, African American ocular hypertensives in OHTS had central corneas 23 μm thinner than their counterparts. Our statistical analyses suggest that the difference between African Americans and whites cannot be attributed to differences in age, IOP, gender, refractive error, systemic hypertension, or diabetes, which our analyses adjusted for. We conclude that the differences in corneal thickness are attributable to race (self-designated) and other factors that may be associated with race that we did not measure. Whether this racial difference holds for the normal population or is unique to ocular hypertensive patients or to OHTS subjects remains to be seen. A recent study by LaRosa and colleagues[23] of a racially diverse population of male veterans in Texas suggests that this racial difference is present among clinically normal patients, as well as those with glaucoma. Our results also suggest that the direction and magnitude of the relationship between central corneal thickness and factors such as age, IOP, refractive error, gender, and diabetes is similar among African American subjects and white subjects.

How to "correct" IOP on the basis of central corneal thickness remains an open question. Ehlers et al[4] cannulated 29 "normal" eyes at the time of cataract surgery and determined that a 70 μm change in central corneal thickness corresponded to approximately 5 mmHg of IOP difference. In their recent meta-analysis, Doughty and Zaman[16] derived a correction of 2.5 mmHg for each 50 μm change in central corneal thickness. Whitacre et al[24] have described the smallest correction factor, approximately 2.0 mmHg for each 100-μm difference in central corneal thickness, a correction factor similar to that described in the Rotterdam Study.[25]

The implication that IOP can be "corrected" with an arithmetic, linear "correction" factor of some mmHg/μm clearly represents an oversimplification of what is undoubtedly a complex and nonlinear relationship between corneal thickness and "true" IOP. For example, simply applying the Ehlers correction of 5 mmHg/70 μm to patients with low IOPs and very thin corneas could lead to negative values for IOP! Nonetheless, these correction factors, derived as they are from actual patients, provide clinicians with an estimate of the range of effects that corneal thickness may have on IOP measurements in some of the patients.

The effect of applying each of these "correction factors" to the baseline IOPs of the OHTS cohort is shown in Figure 5, with a shift to lower IOPs once a "correction factor" is applied. Uncorrected, only 10% of the OHTS subjects had an IOP $\leq$21 mmHg in a randomly chosen eye at their baseline visit; with the Ehlers correction factor applied, as many as 52% of subjects had an IOP $\leq$21 mmHg at entry. The racial differences are particularly notable with the Ehlers correction factor applied—only 37% of African Americans had a "corrected" IOP $\leq$21 mmHg compared with 57% of whites.

With the increasing recognition that central corneal thickness is an important variable in the measurement of IOP has come the realization that many ocular hypertensive

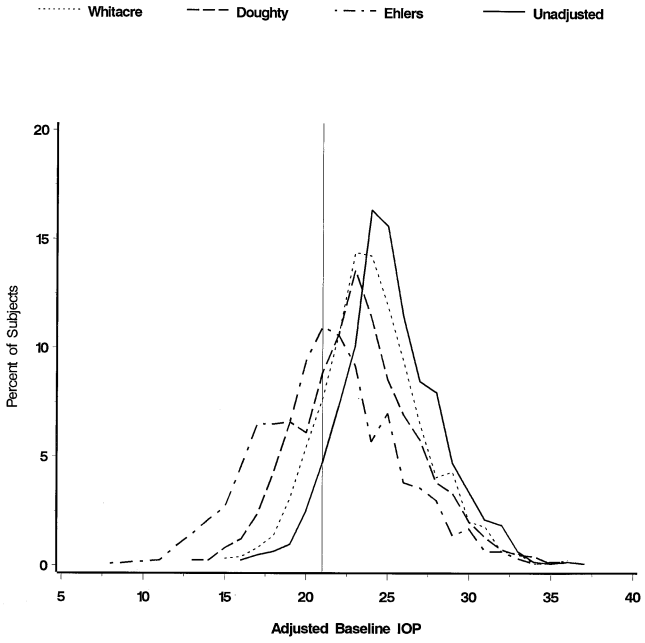

Figure 5. Distribution of baseline intraocular pressures (IOPs) determined by Goldmann applanation tonometry compared with baseline IOPs "corrected" by a variety of published correction factors. These correction factors represent an oversimplification of the relationship between corneal thickness and "true" IOP, yet provide an estimate of the effect corneal thickness might have on IOP measurement in a large clinical trial like Ocular Hypertension Treatment Study.

patients may have little more than thickened corneas leading to erroneous IOP measurements. By use of even the most conservative of the "correction factors" described previously, the IOP of patients with central corneal thickness $>$600 μm will be overestimated by at least 2 mmHg. This error may be clinically significant, particularly in a screening setting. If we choose an arbitrary cutoff of 600 μm, above which greater central corneal thickness likely influences IOP measurement to a clinically significant degree, the racial differences among the OHTS subjects are striking. Among whites, 27% had a central corneal thickness $>$600 μm compared with only 14% of the African American subjects.

This study was not designed to validate or derive a "correction factor" for IOP but, rather, was intended to describe the central corneal thickness characteristics of the OHTS subjects and to determine whether central corneal thickness differed by race among OHTS subjects. It is now evident that central corneal thickness plays an important role in the measurement of intraocular pressure. One of the major goals of the OHTS is to better define a risk model for the development of primary open-angle glaucoma among ocular hypertensives; the data collected and presented here will ensure that central corneal thickness will be integrated into this risk model.

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Appendix

Participating Clinics, Committees, and Resource Centers in the Ocular Hypertension Treatment Study. Current to 10/1/00

Study Centers and Groups	Investigators	Coordinators and Staff
Clinical Centers		
Bascom Palmer Eye Institute, University of Miami, Miami, Florida	*Richard K. Parrish II, MD Donald L. Budenz, MD Francisco E. Fantes, MD Steven J. Gedde, MD	Madeline L. Del Calvo, BS
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