

Effects of Central Corneal Thickness on the Efficacy of Topical Ocular Hypotensive Medications

Thomas V. Johnson, BA, Carol B. Toris, PhD, Shan Fan, MD, and Carl B. Camras, MD

Purpose: To determine the effect of central corneal thickness (CCT) on the efficacy of intraocular pressure (IOP)-reducing drugs in patients with ocular hypertension (OHT).

Methods: This retrospective study analyzed research records of 115 OHT patients and 97 ocular normotensive (ONT) volunteers. CCT was measured by slit-lamp pachymetry and IOP by pneumatonometry. The OHT patients were divided into Thick ($> 540 \mu\text{m}$, $n = 52$) and Thin ($\leq 540 \mu\text{m}$, $n = 63$) Cornea groups. Measurements in the OHT group were made after washout of all IOP-lowering drugs and at 1 week of treatment with latanoprost 0.005%, dorzolamide 2%, brimonidine 0.2%, apraclonidine 0.5%, pilocarpine 2%, or unoprostone 0.15% to 1 eye and vehicle contralaterally. ONT volunteers also were divided into Thick ($n = 34$) and Thin ($n = 63$) Cornea groups. Results were compared between groups using unpaired *t* tests or nonparametric Wilcoxon tests and within groups using linear regression analyses.

Results: Baseline IOPs were not different between CCT groups of OHT patients or of ONT volunteers. After 1 week of drug treatment, IOP was significantly ($P = 0.02$) lower in the OHT Thin Cornea group ($16.0 \pm 3.0 \text{ mm Hg}$, mean \pm SD) than the OHT Thick Cornea group ($17.4 \pm 2.8 \text{ mm Hg}$). There was a positive correlation between IOP and CCT ($R^2 = 0.06$, $P = 0.007$) in OHT drug-treated eyes, but not OHT vehicle-treated or ONT untreated eyes. The final IOP was significantly lower in the Thin than the Thick Cornea group treated with brimonidine ($P = 0.02$) but not with latanoprost ($P = 0.91$).

Conclusions: When dosed with IOP lowering drugs, eyes with thinner corneas had lower IOPs than eyes with thicker corneas. This suggests a reduced efficacy of some glaucoma medications in ocular hypertensive patients with thick corneas.

Key Words: intraocular pressure, central corneal thickness, glaucoma medication, glaucoma

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From the Department of Ophthalmology, University of Nebraska Medical Center, Omaha, Nebraska.

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Correspondence: Carol B. Toris, PhD, Department of Ophthalmology, 985840 Nebraska Medical Center, Omaha, NE 68198-5840 (e-mail: ctoris@unmc.edu).

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Widespread diagnostic and therapeutic concerns are stemming from variation in central corneal thickness (CCT) in patients with glaucoma and in those who are suspects.^{1–5} The most clinically significant of these concerns is the effect of CCT on the measurement of intraocular pressure (IOP),⁶ the most important risk factor for the development of glaucoma.^{3,7} IOP assessment is complicated because patients with thicker corneas tend to exhibit higher IOPs than patients with thinner corneas when measured by the current gold-standard, Goldmann applanation tonometry.^{6,8} Applanation tonometry assesses IOP by measuring the force necessary to flatten a fixed circular area of the cornea that is 3.06 mm in diameter. At any given IOP, the force required to flatten this fixed area is greater for thicker than thinner corneas. Therefore, in 2 eyes with equal IOPs, applanation measurement will yield a higher value in the eye with a thicker cornea.⁸ Failure to correct for CCT could result in incorrect IOP values.^{1,2,5,9}

In 1957, Goldmann and Schmidt¹⁰ first reported that CCT could affect IOP as measured by applanation tonometry. At that time, patients without corneal pathology were thought to have a narrow range of CCT values making CCT a seemingly inconsequential variable. In the 1970s, however, clinical investigators confirmed a wide population variance in CCT, which results in a significant positive correlation between CCT and IOP measured by applanation tonometry. One study demonstrated that IOP measurement by applanation tonometry may deviate by as much as 7 mm Hg from the true IOP for every 100- μm variation in CCT from a normal CCT of 520 μm for which the Goldmann tonometer is calibrated.¹¹ Another study using a Perkins applanation tonometer produced errors in IOP measurement by as much as 2.3 mm Hg per 100 μm when compared with manometric readings.² The Rotterdam Study⁸ showed a 1.9 mm Hg per 100- μm tonometric measurement error.

The problems associated with inaccurate IOP measurements may be clinically significant. Brubaker¹² suggested that tonometric error is of marginal clinical importance because the small error in IOP measurement from CCT probably would not alter the evidence by which a clinician decides to treat a patient. However, misdiagnoses do occur from erroneous IOP values. When correcting for the CCT effect on IOP measurements, one study⁵ found that 7 of 22 (31%) patients diagnosed with normal tension glaucoma (NTG) met the criteria for a diagnosis of “high tension” primary open-angle glaucoma (POAG). Conversely, 25 of 44 (56%) patients clinically

diagnosed with ocular hypertension (OHT) had “normal” IOPs.⁵ Other studies have reported that 44% of patients with NTG could be reclassified as having POAG,⁶ and that 30% to 65% of patients classified as OHT actually had ocular normotension (ONT).^{1,4,6} Johnson et al¹³ reported the diagnosis of OHT and aggressive treatment of a patient with a CCT of 900 μm and IOPs over 30 mm Hg when measured by applanation tonometry. It was later determined that the patient had a manometric IOP of 11 mm Hg, despite an applanation IOP of 35 mm Hg. Because misdiagnosis may lead to unnecessary treatment in some true ONT patients or inadequate treatment for high-tension POAG patients, accurate IOP assessment is critical.

The complications that CCT variation causes in tonometry are being recognized. In response, researchers are developing new tonometric devices that are less affected by CCT, such as the dynamic contour tonometer.^{14–17} However, CCT may have important implications for glaucoma management that extend beyond tonometry. It is possible that corneal thickness may also affect the efficacy of glaucoma medications. The Ocular Hypertension Treatment Study (OHTS) found that a thin cornea is an important, independent risk factor for glaucomatous onset and progression.³ Although the authors mostly attribute this to the effect of CCT on tonometry, other factors may be involved. Reducing IOP is the only treatment that has been proven effective in preventing the onset or progression of glaucoma.¹⁸ In an effort to reduce IOP, initial management often consists of topical application of ocular hypotensive drugs. In the OHTS,¹⁹ patients with thicker corneas demonstrated a smaller IOP response to medical treatment than patients with thinner corneas. It seems that CCT might affect the degree to which glaucoma medications lower IOP. Therefore, the current study was conducted to determine the effect of CCT on the efficacy of various topical ocular hypotensive medications in patients with OHT and to compare the baseline relationship between CCT and IOP in patients with OHT and in healthy subjects.

PATIENTS AND METHODS

This was a retrospective investigation of the research study records from 115 patients with OHT and 97 ONT volunteers. All of the original studies^{20–26} were of identical design, with baseline IOPs measured between 11 AM and noon after an appropriate washout period if needed, and IOPs measured between 11 AM and noon (close to the time of the peak effect of most of the drugs) on the eighth day of treatment with an IOP-lowering drug to 1 eye and vehicle to the fellow eye. The time of IOP measurements was held constant to minimize the effect of diurnal IOP variation. Some OHT patients had participated in more than one study, but only the most recent data set for each subject is included in the multidrug analysis. Patients were considered to have OHT if they had a history of IOPs ≥ 21 mm Hg, presented at the screening examination with IOPs ≥ 21 mm Hg, and

had normal optic nerves, normal visual fields, and open angles. Control subjects had no history of ocular pathology or anatomic abnormalities and IOPs always < 21 mm Hg. The current study and the prior studies from which the data were collected were approved by the University of Nebraska Medical Center Institutional Review Board. Informed consent was obtained from all subjects before their enrollment in the studies.

The OHT group underwent 2 sets of measurements: one to establish the baseline values on no ocular medications and one to determine drug effects on day 8 of treatment. In a randomized, double-masked fashion, each patient with OHT was treated with either apraclonidine 0.5% twice daily ($n = 15$), brimonidine 0.2% twice daily ($n = 41$), dorzolamide 2% 3 times daily ($n = 16$), latanoprost 0.005% once daily ($n = 17$), pilocarpine 2% 4 times daily ($n = 15$), or unoprostone 0.15% twice daily ($n = 11$) in 1 randomly selected eye and with an appropriate vehicle in the contralateral control eye. A computer-generated randomization list was provided by a statistician or pharmacist not otherwise affiliated with the study. The ONT control group underwent one set of measurements and data from both eyes were averaged. Demographic data including the age of each subject was recorded at baseline. CCT was determined by slit-lamp pachymetry (Haag-Streit Attachment No. 1, Haag-Streit AG, Liebefeld-Berne, Switzerland) and IOP was measured by pneumatonometry (Model 30 Classic, Xomed, Jacksonville, FL). Subjects were excluded from the study if they had a history of intraocular surgery or laser treatment, had experienced ocular inflammation, or infection within 3 months before or during the collection of measurements, or had severe dry eyes.

Correlations between CCT and IOP before and after drug treatment for both the drug and vehicle-treated eyes in the OHT group were evaluated using univariate linear regression analyses. In a similar manner, correlations between mean CCT and IOP reduction for drug and vehicle-treated eyes were analyzed in an effort to account for baseline IOP. CCT was designated as the independent variable and both R^2 and P values were calculated for drug-treated eyes and vehicle-treated eyes. The difference between the regression's slope and a theoretical line of zero slope was considered statistically significant for P values < 0.05 . The correlation between CCT and IOP in ONT subjects was analyzed in a similar fashion.

All subjects were divided into 2 groups on the basis of CCT at baseline without ocular medication. The Thin Cornea group had CCTs ≤ 540 μm (OHT $n = 63$, ONT $n = 63$) and the Thick Cornea Group had CCTs > 540 μm (OHT $n = 52$, ONT $n = 34$). Five hundred forty micrometers was chosen as the CCT division point to achieve the most equal distribution of subjects with OHT between the 2 groups. CCTs and IOPs were compared between the Thick and Thin Cornea groups using unpaired, 2-tailed t tests. IOPs were compared between contralateral eyes within the cornea thickness groups before or after treatment using unpaired, 2-tailed t tests. IOP change from baseline on day eight of

treatment was compared between CCT groups using unpaired, 2-tailed *t* tests.

All data in the multidrug analysis exhibited a roughly Gaussian distribution when the subjects were grouped together. Example histograms are shown in Figure 1. Because a retrospective division was used to separate subject groups at a baseline CCT of 540 μm , the CCT group data sets were not necessarily distributed normally. However, for sufficiently large samples ($n \geq 30$ per comparison group), the Central Limit Theorem states that parametric *t* tests are applicable regardless of the underlying distribution.²⁷ Therefore, the aforementioned *t* tests were used to make comparisons in the multidrug analysis.

In 2 additional and separate analyses, the same comparisons were made for latanoprost/vehicle-treated eyes ($n = 38$) and for brimonidine/vehicle-treated eyes ($n = 49$). Pooled into the 2 separate analyses were data sets from the original, multidrug analysis (latanoprost,

$n = 17$; brimonidine, $n = 41$, respectively) and data sets that were not included in the original, multidrug analysis (latanoprost, $n = 21$; brimonidine, $n = 8$, respectively). This second set of data was derived from patients who had participated in more than one study and had not contributed their latanoprost or brimonidine data set to the original, multidrug analysis because they contributed data for one of the other ocular hypotensive medications to the multidrug analysis. As in the multidrug analysis, the CCT data sets for the brimonidine and latanoprost analyses were not distributed normally. The central limit theorem did not apply to these data sets due to their smaller sample size. Therefore, nonparametric Wilcoxon tests were used in these comparisons.

Using the statistical program GPower (Faul & Erdfelder, Bonn University, Germany), post hoc power calculations were made to determine the power of the various comparisons to recognize a clinically significant

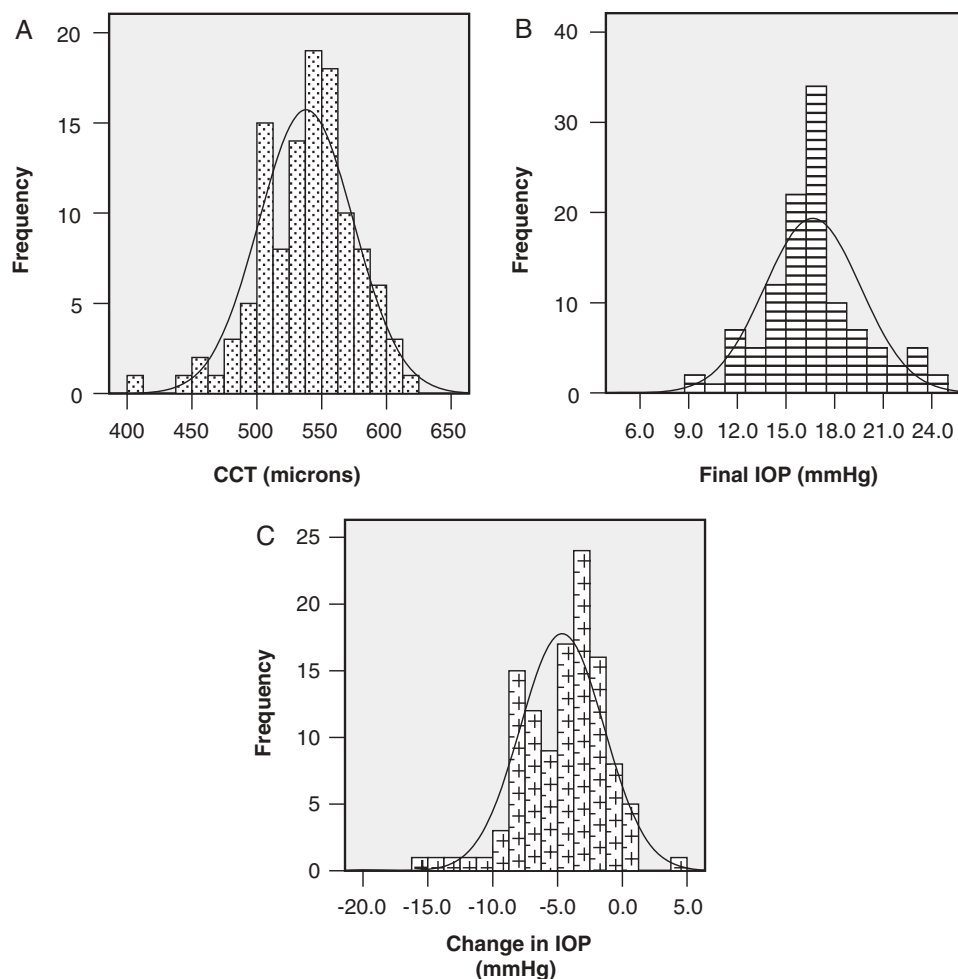


FIGURE 1. Histograms showing the distribution of data included in the multidrug analysis ($n = 115$). For each data parameter analyzed in the current study, including those pertaining to the multidrug analysis as well as the latanoprost and brimonidine analyses, a histogram was created and confirmed an approximate Gaussian distribution. Examples of such histograms are shown for mean CCT of subjects in the multidrug analysis (panel A), mean final IOP of subjects in the multidrug analysis (panel B), and mean IOP change of subjects in the multidrug analysis (panel C). An ideal normal curve is superimposed over each histogram as a solid line.

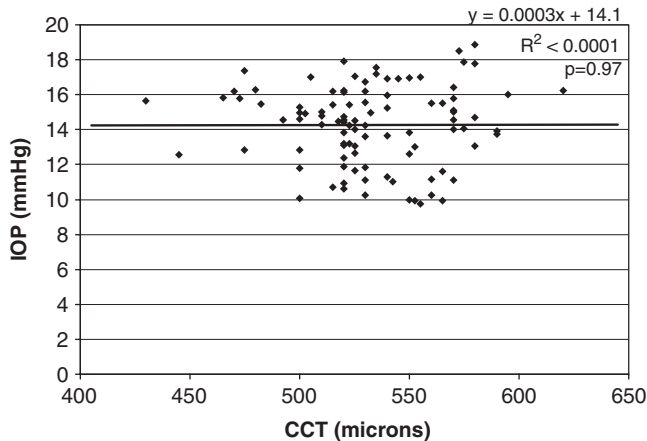


FIGURE 2. IOP as a function of CCT in ONT volunteers (n=97). Diamonds represent individual volunteers whereas the line represents a univariate linear regression. There was no correlation between IOP and CCT in eyes of ONT volunteers ($R^2 < 0.0001$).

difference in final IOP or IOP change between groups (predesignated by an effect size of $d = 0.5$) or a clinically significant correlation between baseline CCT and final IOP or IOP change (predesignated by $R = 0.30$) at the 0.05 significance level using 2-tailed means comparison or correlation tests, respectively.

Unless otherwise indicated, values are reported as means \pm SDs.

RESULTS

On the basis of the multidrug analysis data, an effect size of $d = 0.5$ (a statistically medium-sized effect) represents a difference of 1.5 mm Hg in final IOP between CCT groups and a difference of 1.6 mm Hg in IOP change between groups. Power analyses conducted for the multidrug study indicate the following power levels for discernment of group differences or correlations at the 0.05 significance level: difference in final IOP and change in IOP, power = 75%; correlation between CCT and final IOP or change in IOP, power = 92%. Analogous power calculations for the brimonidine analysis yielded: final

IOP and change in IOP, power = 39%; correlation between CCT and final IOP or change in IOP, power = 58%. For the latanoprost analysis: final IOP and change in IOP, power = 32%; correlation between CCT and final IOP or change in IOP, power = 47%.

For ONT subjects, there was no statistically significant difference between Thin and Thick Cornea groups with respect to age (47 ± 21 vs. 43 ± 22 y, respectively) or IOP (14.3 ± 2.0 vs. 14.2 ± 2.7 mm Hg, respectively). The overall mean CCT of the ONT subjects was $532 \pm 34 \mu\text{m}$. There was no correlation between CCT and IOP (Fig. 2).

For OHT patients in the multidrug analysis, there was no statistically significant difference in age between the Thin and Thick Cornea groups (57 ± 13 vs. 53 ± 13 y), but the OHT patients were significantly ($P < 0.001$) older than the healthy volunteers (55 ± 13 y vs. 46 ± 21 y, respectively). The mean baseline CCT ($538 \pm 37 \mu\text{m}$) of OHT patients was statistically similar ($P = 0.15$) to the ONT subjects. The mean baseline IOPs for eyes randomized to treatment and vehicle of OHT patients were 21.3 ± 3.5 mm Hg and 21.3 ± 3.4 mm Hg, respectively. The baseline IOPs were not different when comparing the different CCT groups or when comparing the eyes to be treated with drug versus vehicle within CCT groups (Table 1).

After 1 week of treatment with an ocular hypotensive medication, mean IOP (Table 1) in the Thin Cornea group (16.0 ± 3.0 mm Hg) was significantly ($P = 0.015$) lower than in the Thick Cornea group (17.4 ± 2.8 mm Hg). Mean IOPs of contralateral vehicle-treated control eyes were not significantly ($P = 0.36$) different between CCT groups (Thin Cornea group, 19.5 ± 2.9 mm Hg; Thick Cornea group 20.0 ± 3.2 mm Hg). The IOPs were significantly lower ($P < 0.0001$) in the OHT drug-treated eyes than in the contralateral vehicle-treated eyes within each CCT group (Table 1).

There was a positive correlation ($R^2 = 0.062$, $P = 0.007$) between IOP and CCT in the treated eyes after 1 week of treatment (Fig. 3A). This correlation was not present in treated eyes at baseline, in contralateral control eyes at any time, or in ONT eyes (Figs. 2, 3A). There was no correlation between IOP change and mean

TABLE 1. IOP and CCT in Ocular Hypertensive Patients Treated With IOP Lowering Drugs (n = 115)*

	Thin Corneas (CCT $\leq 540 \mu\text{m}$; n = 63)		Thick Corneas (CCT $> 540 \mu\text{m}$; n = 52)		P^\dagger	
	Vehicle	Drug	Vehicle	Drug	Vehicle	Drug
Baseline						
CCT (μm)	511 \pm 26	514 \pm 29	570 \pm 18	568 \pm 21	< 0.0001	< 0.0001
IOP (mm Hg)	21.2 \pm 3.1	21.1 \pm 3.5	21.4 \pm 3.8	21.5 \pm 3.6	0.69	0.51
One week of treatment \ddagger						
CCT (μm)	524 \pm 35	522 \pm 30	554 \pm 30	559 \pm 28	< 0.0001	< 0.0001
IOP (mm Hg)	19.5 \pm 2.9	16.0 \pm 3.0 \S	20.0 \pm 3.2	17.4 \pm 2.8 \S	0.36	0.015

*Mean IOPs and CCTs are given for Thick and Thin Cornea groups of ocular hypertensive (OHT) subjects at baseline and after 1 wk of unilateral treatment with 1 of 6 topical ocular hypotensive drugs to 1 eye and an appropriate vehicle to the contralateral eye. "Drug" refers to eyes randomly selected to receive ocular hypotensive drug and "vehicle" refers to contralateral control eyes randomly selected to receive vehicle. Values in table are means \pm SD.

\dagger Unpaired, 2-tailed t test comparing Thin vs. Thick Cornea groups.

\ddagger Latanoprost 0.005%, dorzolamide 2%, brimonidine 0.2%, apraclonidine 0.5%, pilocarpine 2%, unoprostone 0.15%, or vehicle.

$\S P < 0.0001$, compared with vehicle-treated eyes within the same cornea thickness group, unpaired, 2-tailed t test.

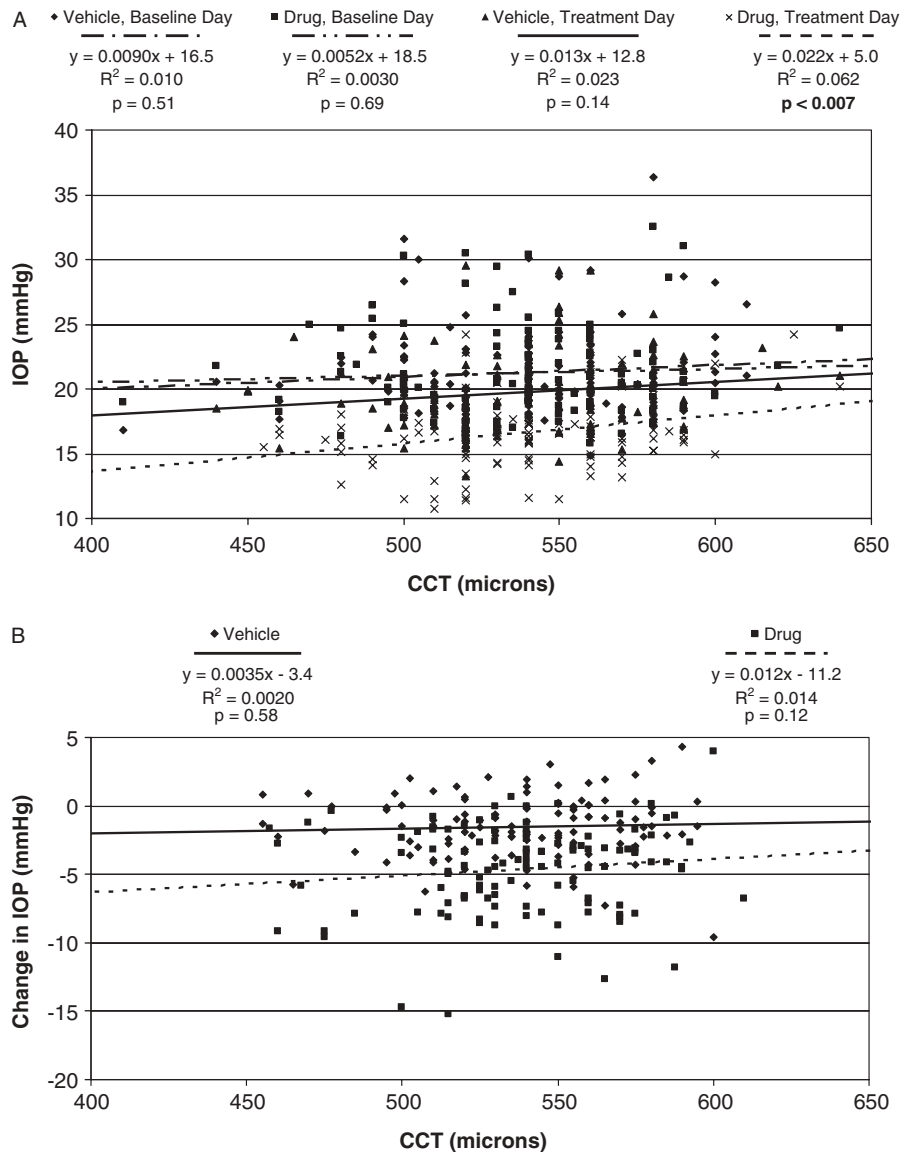


FIGURE 3. IOP or change in IOP as a function of CCT in ocular hypertensive patients before and after drug treatment (n = 115). “Drug” refers to eyes randomly selected to receive an ocular hypotensive drug and “vehicle” refers to contralateral control eyes selected to receive vehicle. In addition to the use of the respective IOPs, baseline CCTs were used for the “baseline day” data, and posttreatment CCTs were used for the “treatment day” data. The P value represents the statistical significance of the slope for each linear regression. Panel A shows that there was no correlation between IOP and CCT in vehicle-treated eyes on baseline day or after 1 week of vehicle-treatment or in the eyes selected for drug-treatment on baseline day. A positive correlation between IOP and CCT was found after 1 week of treatment with an ocular hypotensive drug (either apraclonidine 0.5%, brimonidine 0.2%, dorzolamide 2%, latanoprost 0.005%, pilocarpine 2%, or unoprostone 0.15%). In panel B, CCT values are the mean of baseline and treatment day measurements. There was no correlation between treatment-induced IOP change and CCT for the vehicle eyes of ocular hypertensive patients after 1 week of vehicle-treatment. The negative correlation between hypotensive drug-induced IOP reduction and CCT for the drug-treated eyes did not reach statistical significance.

CCT in vehicle-treated eyes (Fig. 3B). In drug-treated eyes, a negative correlation between drug-induced IOP change and CCT did not reach statistical significance ($R^2 = 0.014$, $P = 0.12$). Likewise, the IOP change was greater in the Thin Cornea group (-5.0 ± 3.4 mm Hg) than in the Thick Cornea group (-4.1 ± 3.0 mm Hg) but this difference was not significant ($P = 0.13$).

In separate analyses, the mean age and baseline IOP in the brimonidine group (n = 49) was 58 ± 12 years and 20.7 ± 3.7 mm Hg, respectively, and in the latanoprost group (n = 38) was 55 ± 14 years and 20.3 ± 4.3 mm Hg, respectively. These differences were not significant. On day 8 of treatment with brimonidine, IOPs were significantly lower in the Thin Cornea group compared

TABLE 2. IOP and CCT in Ocular Hypertensive Patients Treated With Brimonidine (n = 49)*

	Thin Corneas (CCT ≤ 540 μm; n = 29)		Thick Corneas (CCT > 540 μm; n = 20)		P†	
	Vehicle	Brimonidine	Vehicle	Brimonidine	Vehicle	Brimonidine
Baseline						
CCT (μm)	512 ± 24	515 ± 27	578 ± 21	576 ± 26	< 0.0001	< 0.0001
IOP (mm Hg)	20.4 ± 2.9	19.9 ± 3.4	21.4 ± 4.8	21.8 ± 4.0	0.80	0.46
After 1 wk of treatment						
CCT (μm)	518 ± 34	520 ± 29	563 ± 25	560 ± 24	< 0.0001	< 0.0001
IOP (mm Hg)	18.8 ± 2.6	14.5 ± 2.5‡	19.9 ± 3.5	16.5 ± 2.9‡	0.43	0.02

*Mean IOPs and CCTs are given for both the Thick and Thin Cornea groups of the ocular hypertensive (OHT) subjects at baseline and after 1 wk of unilateral treatment with brimonidine 0.2% twice daily and contralateral treatment with an appropriate vehicle. "Brimonidine" refers to eyes randomly selected to receive brimonidine and "vehicle" refers to contralateral control eyes randomly selected to receive vehicle. Values in table are means ± SD.

†Nonparametric Wilcoxon test comparing Thin vs. Thick Cornea group.

‡P < 0.001, compared with vehicle-treated eyes within the same cornea thickness group, nonparametric Wilcoxon tests.

with the Thick Cornea group ($P = 0.02$, Table 2). This relationship was not found in latanoprost-treated eyes (Table 3). There were no significant correlations between IOP and CCT in either eye for either drug on baseline day or in the vehicle-treated eye on treatment day (Figs. 4A, 5A), whereas a potential positive correlation was found in the brimonidine-treated (Fig. 4A, $P < 0.06$) and latanoprost-treated eyes (Fig. 5A, $P = 0.08$) on treatment day. The mean reduction in IOP with brimonidine treatment was -5.5 ± 3.3 and -5.3 ± 3.3 mm Hg in the Thin and Thick Cornea groups, respectively. Likewise, with latanoprost treatment, corresponding values were -5.0 ± 1.5 and -4.1 ± 0.5 mm Hg in the Thin and Thick Cornea group, respectively. These differences were not significant. A nonsignificant ($P = 0.28$) negative correlation was seen between mean IOP change and CCT in brimonidine-treated eyes ($R^2 = 0.042$, Fig. 4B) but not contralateral vehicle-treated eyes. There was also no correlation between CCT and IOP change in latanoprost or contralateral vehicle-treated eyes (Fig. 5B).

DISCUSSION

Our study demonstrated that eyes with thinner corneas had significantly lower IOPs after 1 week of topical ocular hypotensive drug treatment than eyes with

thicker corneas, even though these IOPs were statistically similar before treatment. Eyes treated with brimonidine, but not latanoprost, also exhibited this difference in final IOP between CCT groups. This suggests that CCT may affect the efficacy of some ocular hypotensive medications.

It is possible that differences in mean baseline IOP between the CCT groups contributed, in part, to the differences in absolute IOP noted after 1 week of treatment. In both the multidrug and brimonidine analyses, IOP reduction was greater in treated eyes with thin than thick corneas, but these differences were not significant. Because statistical significance was lost when looking at IOP change rather than absolute final IOP, it is possible that a positive correlation between CCT and IOP that was present at baseline may have persisted after 1 week of treatment, and led to higher treatment day IOPs in the Thick Cornea group. However, we question whether baseline differences can completely account for the difference in treatment day IOPs between CCT groups, because a positive (albeit not statistically significant) correlation between IOP change and CCT seemed to exist in both the multidrug and brimonidine analyses. The power calculations demonstrated only a moderate level of power for the data sets to detect clinically significant differences between groups in the multidrug analyses, and a relatively lower power in the

TABLE 3. IOP and CCT in Ocular Hypertensive Patients Treated With Latanoprost (n = 38)*

	Thin Corneas (CCT ≤ 540 μm; n = 17)		Thick Corneas (CCT > 540 μm; n = 21)		P†	
	Vehicle	Latanoprost	Vehicle	Latanoprost	Vehicle	Latanoprost
Baseline						
CCT (μm)	514 ± 20	517 ± 18	565 ± 14	572 ± 25	< 0.0001	< 0.0001
IOP (mm Hg)	20.9 ± 4.4	20.8 ± 4.8	19.7 ± 3.1	19.9 ± 3.8	0.62	0.69
After 1 wk of treatment						
CCT (μm)	523 ± 38	519 ± 36	551 ± 24	554 ± 24	0.01	0.03
IOP (mm Hg)	19.3 ± 3.0	15.8 ± 3.1‡	19.1 ± 2.7	15.9 ± 2.4‡	0.71	0.91

*Mean IOPs and CCTs are given for both the Thick and Thin Cornea groups of the ocular hypertensive (OHT) subjects at baseline and after 1 wk of unilateral treatment with latanoprost 0.005% once daily and contralateral treatment with an appropriate vehicle. "Latanoprost" refers to eyes randomly selected to receive latanoprost and "vehicle" refers to contralateral control eyes randomly selected to receive vehicle. Values in table are means ± SD.

†Nonparametric Wilcoxon test comparing Thin vs. Thick Cornea group.

‡P < 0.001, compared with vehicle-treated eyes within the same cornea thickness group, nonparametric Wilcoxon test.

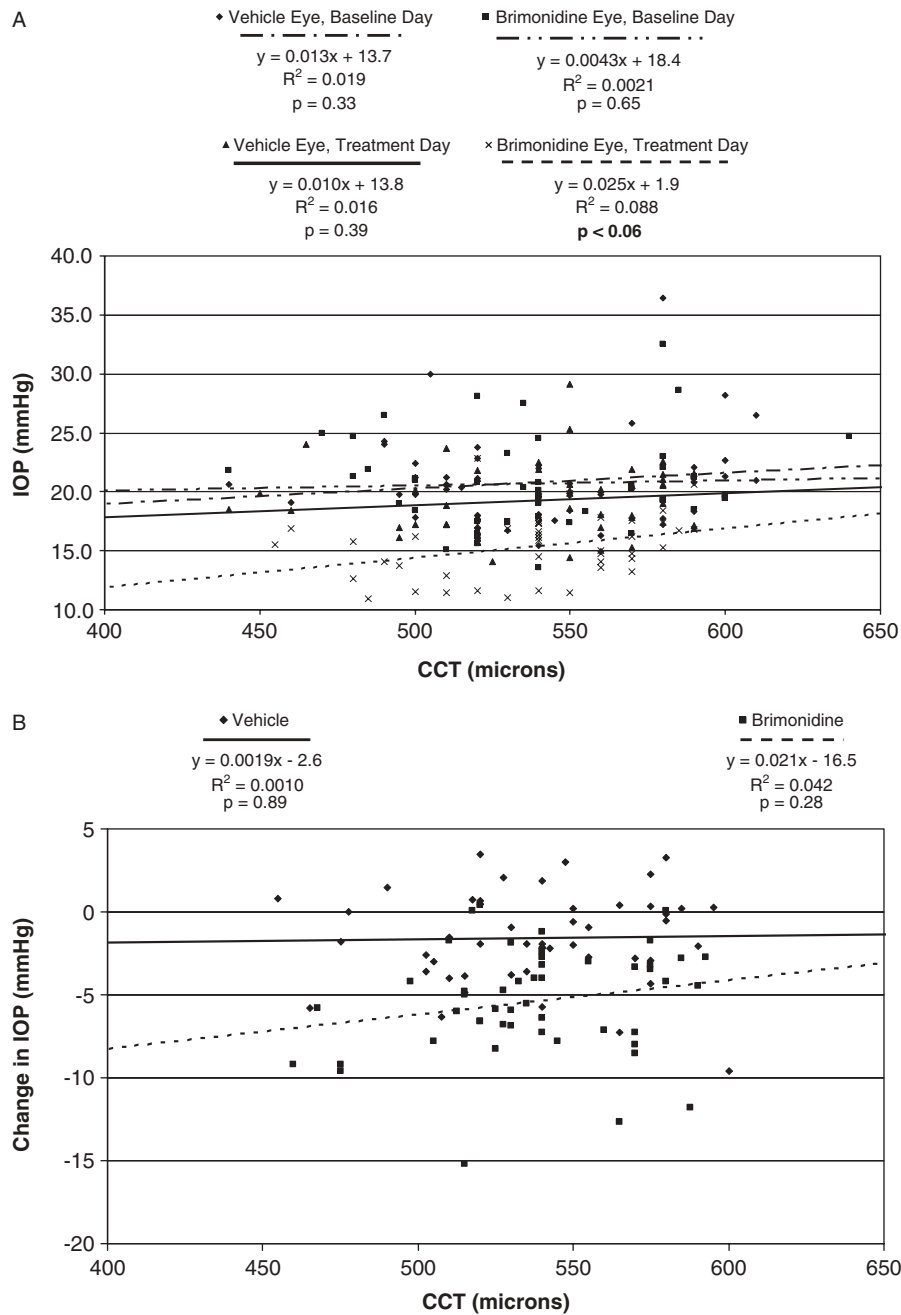


FIGURE 4. IOP or change in IOP induced by brimonidine or vehicle treatment as a function of CCT in ocular hypertensive patients (n = 49). “Brimonidine” refers to eyes randomly selected to receive brimonidine 0.2% and “vehicle” refers to contralateral control eyes selected to receive vehicle. In addition to the use of the respective IOPs, baseline CCTs were used for the “baseline day” data, and posttreatment CCTs were used for the “treatment day” data. The P value represents the statistical significance of the slope for each linear regression. Panel A shows no significant correlation between IOP and CCT with either eye before treatment or in vehicle-treated eyes posttreatment whereas a positive correlation was borderline significant in eyes treated unilaterally with brimonidine for 1 week. In panel B, CCT values are the mean of baseline and treatment day measurements. There was no correlation between IOP change and CCT for the contralateral vehicle-treated control eyes of ocular hypertensive patients treated with brimonidine. A potential correlation between the IOP reduction induced by treatment with brimonidine 0.2% twice daily for 1 week and CCT did not reach statistical significance.

secondary single drug analyses. A larger subject population would provide more power and perhaps demonstrate statistical significance in these correlations.

In the multidrug analysis, more patients received brimonidine treatment (41 out of the 115 patients) than any other treatment. Because an apparent effect of CCT

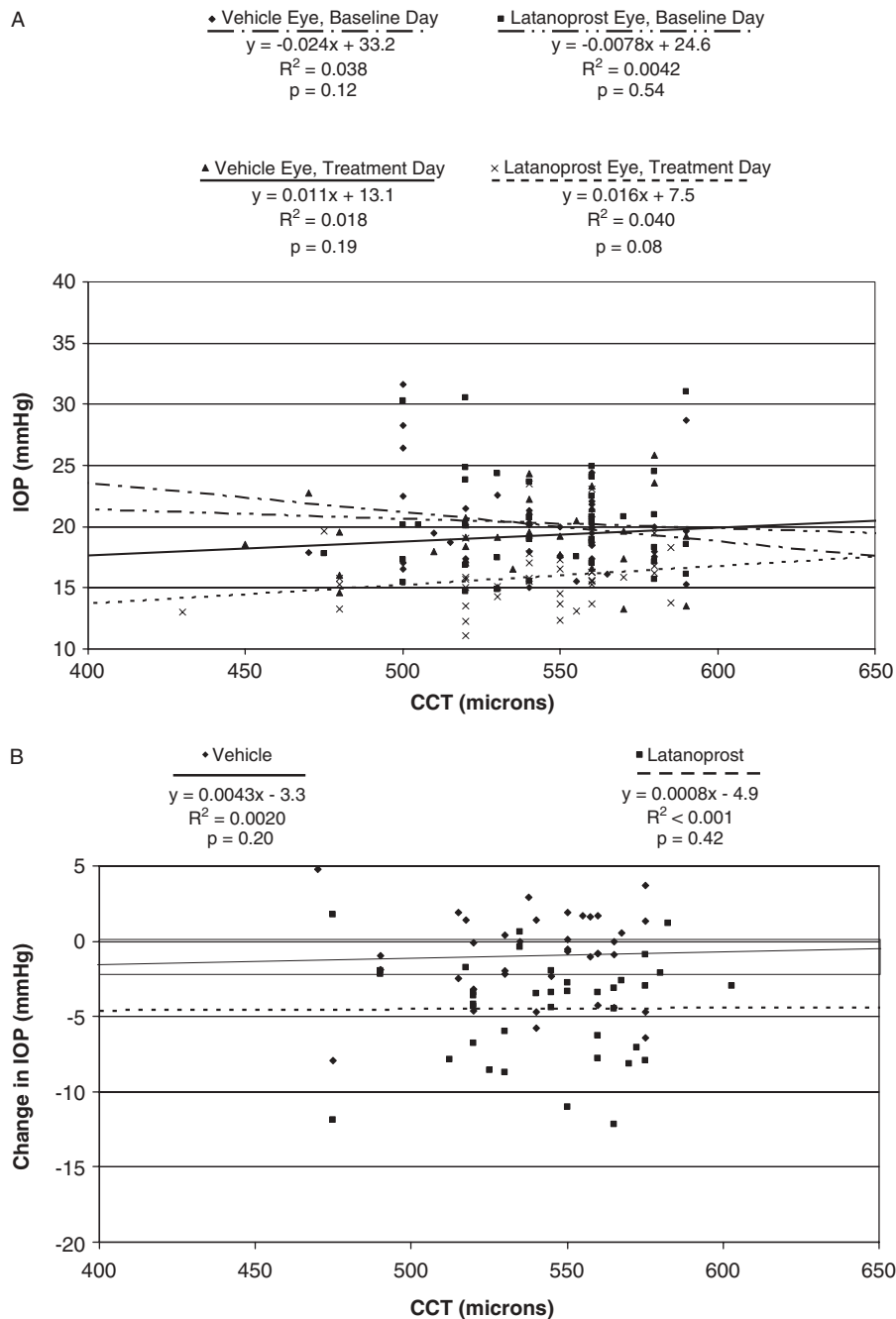


FIGURE 5. IOP or change in IOP induced by latanoprost or vehicle treatment as a function of CCT in ocular hypertensive patients (n=38). "Latanoprost" refers to eyes randomly selected to receive latanoprost 0.005% and "vehicle" refers to contralateral control eyes selected to receive vehicle. In addition to the use of the respective IOPs, baseline CCTs were used for the "baseline day" data, and posttreatment CCTs were used for the "treatment day" data. The P value represents the statistical significance of the slope for each linear regression. Panel A shows no significant relationship between IOP and CCT before treatment or in vehicle-treated eyes. A potential negative correlation between IOP and CCT in latanoprost-treated eyes did not reach significance. In panel B, CCT values are the mean of baseline and treatment day measurements. There was no correlation between IOP change and CCT for the contralateral control eyes of ocular hypertensive patients treated unilaterally with latanoprost for 1 week. Likewise, there was no correlation between IOP change and CCT for the eyes treated with latanoprost.

on the efficacy of brimonidine was found, it is possible that this effect biased the multidrug analysis to demonstrate a similar CCT-dependence. If it were the case that

only brimonidine efficacy possesses a CCT dependence, however, one would expect any correlation between CCT and IOP reduction to be diluted by the addition of data

from other glaucoma medications. The fact that the CCT-dependent effect was apparently stronger in the multidrug analysis than it was in the brimonidine analysis [as evidenced by the greater significance of the correlation between CCT and IOP as well as between CCT and IOP reduction (Figs. 3, 4)] suggests that CCT may affect the efficacy of the other drugs in the multidrug analysis as well.

Interestingly, the mean CCT of subjects in the Thin CCT group increased over the 8-day period of the current study whereas the mean CCT of subjects in the Thick CCT group decreased. This is a classic example of "regression to the mean." Because the subjects were placed into CCT groups on the basis of their baseline CCT measurements, variation and error in pachymetry resulted in a slight regression toward the CCT division point (540 μ m) for both CCT groups.

Unlike some previous studies,^{1,4,5,8,19,28-31} our study did not demonstrate a statistically significant positive correlation between baseline IOP and CCT (although a slight trend was present). The current study used pneumatonometry to measure IOP whereas these previous studies used Goldmann applanation tonometry^{1,5,8,19,28,29,31} or a historical diagnosis of OHT made on the basis of Goldmann applanation tonometry.^{4,30} Goldmann applanation tonometry seems to have a greater CCT dependence than pneumatonometry in a general population¹⁶ and in the context of Laser-Assisted in situ Keratomileusis (LASIK).³² This may explain why our baseline pneumatonometry measurements of IOP were less dependent on CCT and, therefore, more similar between CCT groups than Goldmann applanation measurements would have yielded. Additionally, our patients with OHT had a relatively narrow range of comparatively lower baseline IOPs. Because our inclusion criteria relied on clinical history of OHT and IOP on screening day, some OHT patients actually presented with an IOP < 20 mm Hg on baseline day. A lack of patients with very high IOPs, and thus the lack of a wide range of IOPs, may have contributed to our failure to find a correlation between baseline IOP and CCT.

The authors of the OHTS analyzed the effect of CCT on the reduction of IOP by ocular hypotensive medication.¹⁹ Using a multivariate analysis to correct for baseline IOP, they found that the efficacy of ocular hypotensive drug treatment after 4 to 6 weeks significantly correlated inversely with CCT, and that the effect was more pronounced for prostaglandin analogs compared with β -blockers. Additionally, IOP was positively correlated with CCT for patients treated with a variety of (and in many cases multiple simultaneous) topical ocular hypotensive medications during a follow-up period of 12 to 60 months. The authors identified 3 mechanisms to account for these findings. The idea that differential pharmacokinetics could explain limited drug penetration through thicker corneas was considered to be the least important. Trends in differences in baseline IOP and the effect of CCT on IOP measurement were presented as the most probable explanations for their results.¹⁹

On a general level, the current study presents results similar to the OHTS,¹⁹ that is, eyes with thinner corneas seem to have a greater IOP response to topical ocular hypotensive medications than eyes with thicker corneas in some analyses. Unlike the OHTS,¹⁹ we found that the effect of prostaglandin analogs on IOP response is statistically independent of CCT. Our observation that the efficacy of brimonidine seems to have some dependence on CCT is a novel finding.

There are several differences between the current study and the OHTS, which may account for the different observations. First, the baseline IOPs in the OHTS were higher than those in the current study. The OHTS mean baseline IOP was 24.9 mm Hg overall for those undergoing medical treatment,¹⁸ and for patients on β -blockers and prostaglandin analogs was 26.0 mm Hg and 24.6 mm Hg, respectively.¹⁹ In the current study, the average baseline IOP in drug-treated eyes was 21.3 mm Hg overall, and in eyes receiving brimonidine or latanoprost was 20.7 mm Hg or 20.3 mm Hg, respectively. Because eyes with higher baseline IOPs demonstrate larger IOP reductions to ocular hypotensive medications than eyes with lower baseline IOPs, the OHTS demonstrated greater IOP responses overall. The smaller drug-induced IOP response in our study may have masked any CCT dependence in our prostaglandin group. On the other hand, we question the magnitude of this effect because the brimonidine group had similar baseline IOPs but demonstrated a trend toward a CCT dependence on IOP reduction. It is important to note the advantage of analyzing the lower baseline IOPs found in the current study. In a clinical setting, many patients with IOPs lower than 20 mm Hg (such as those diagnosed with NTG) are treated with topical ocular hypotensive medication. Thus, evaluating patients with lower IOPs provides important information that is clinically relevant. Interestingly, although only a minimal difference was found in final IOP for the 2 CCT groups of eyes treated with latanoprost, the eyes in this analysis showed a negatively correlated baseline trend—the Thick Cornea group had lower baseline IOPs than the Thin Cornea group (Table 3, Fig. 5A). Therefore, it is possible that baseline IOP trends in this analysis masked potential CCT dependence of IOP reduction by latanoprost.

Second, the OHTS^{18,19} used Goldmann applanation tonometry whereas the current study used pneumatonometry. An artificially high baseline IOP measured in patients with thicker corneas would lead to a smaller change in IOP for these patients, especially if corneal rigidity has a greater effect on IOP at lower levels.¹⁹ Because the current study used a method of tonometry that may have a smaller CCT dependence,¹⁶ this phenomenon would be minimized.

Third, the OHTS¹⁹ analyzed IOPs after patients were on medications for a period of 4 to 6 weeks whereas the current study used IOPs after 1 week of treatment. It is possible that the effect of CCT on the efficacy of prostaglandin analogs depends on the duration of treatment.

Finally, drug assignment was not randomized in the OHTS^{18,19} whereas our study included randomized, double-masked drug treatment with contralateral vehicle-treated control eyes. Prostaglandin analogs were used only in the second phase of the OHTS and older patients with poorer general health were more likely to receive prostaglandin analogs than β -blockers. If age or general health is a confounding variable affecting glaucoma drug dependence on CCT, it did not seem to contribute to the difference in results we obtained for latanoprost and brimonidine. Subjects in the latanoprost and brimonidine groups had statistically similar ages (55 y and 58 y, respectively) and were in comparable health.

Overall, the current results indicate that patients with thicker corneas exhibit significantly higher IOPs when treated with glaucoma medications for 1 week than do patients with thinner corneas. Although baseline differences in IOP may partially explain these findings, an important relationship between CCT and drug-induced IOP reduction may still be present. When taken in light of the OHTS,¹⁹ these results indicate that a negative correlation between the efficacy of topical ocular hypotensive medications and CCT may exist. The OHTS demonstrates this phenomenon for patients with very high IOPs whereas we demonstrate the correlation in patients with more modest levels of OHT. Additionally, the OHTS demonstrates this effect for patients without randomization or masking of treatment whereas the current study includes only patients who were randomized to treatment in a double-masked fashion with contralateral control eyes receiving vehicle.

The observation that the efficacy of glaucoma medications correlates inversely with CCT may be confounded by artifact from CCT-induced errors in IOP measurements. Therefore, it may be beneficial to evaluate the influence of CCT on drug-induced alterations of aqueous humor dynamics, because necessary measurements would be less influenced by CCT artifact. A correlation between thicker corneas and reduced drug effects on aqueous humor dynamics would explain the physiologic basis for the correlations found in this study. Fluorophotometric studies investigating the effects of glaucoma medications on aqueous humor dynamics in humans with varying CCTs have been conducted.^{20–26} These studies might be used retrospectively to correlate drug action with CCT, although relatively small subject populations may make it difficult to observe statistically significant correlations for these particular parameters. Further investigations are being conducted to examine this point.

Further study also is needed before concluding that the degree to which IOP response is affected by CCT may depend on the drug itself. The OHTS¹⁹ found that the effect of CCT on IOP reduction was greater for prostaglandin analogs than for β -blockers. Recently, a study reported a significant relationship between thicker corneas and smaller IOP reductions after 6 weeks of treatment with travoprost in patients with POAG but not in patients with OHT.³³ The current study suggests a CCT-dependent effect on IOP reduction for brimonidine

treatment, but questions such as an effect for latanoprost. Admittedly, the small sample size for the latanoprost analysis in the current study may have made discernment of such an effect difficult. Furthermore, the current study investigated the CCT dependence of drug efficacy after only 1 week of treatment. Because some glaucoma medication classes require multiple weeks of dosing to reach a maximal effect, it is possible that a longer study would show a stronger effect than the current 1-week study. As such, we recommend that the current results with regard to latanoprost be taken with some degree of caution and that longer-phase trials be carried out to further investigate the CCT dependence of glaucoma drug effects. If a drug-dependent effect of CCT on IOP reduction is confirmed, clinicians might consider a patient's CCT when planning a therapeutic strategy for treating glaucoma.

The importance of CCT evaluations in clinical practice has been established. Variations in CCT affect the measurement of IOP by tonometry. Furthermore, there may be an association between CCT and retinal nerve fiber layer thickness³⁴ or the microarchitecture of the trabecular meshwork.³⁵ Thus, abnormal CCT hypothetically might indicate a predisposition to optic nerve damage or impaired aqueous humor outflow, respectively. Additionally, we show that CCT may affect the efficacy of medications used to treat glaucoma. These CCT considerations might be independent of the effect of CCT on IOP measurement. Together, these findings support the recommendation that CCT measurement should be a routine part of the ocular examination in glaucoma patients and suspects.

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