Central Corneal Thickness and Measured IOP Response to Topical Ocular Hypotensive Medication in the Ocular Hypertension Treatment Study

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• PURPOSE: To determine whether central corneal thickness (CCT) correlates with measured intraocular pressure (IOP) response to topical ocular hypotensive medication in the Ocular Hypertension Treatment Study (OHTS).

• DESIGN: Prospective randomized clinical trial.

• METHODS: Intraocular pressure measurements were performed by Goldmann applanation tonometry. Central corneal thickness was measured by ultrasonic pachymetry. The following indicators of IOP response to topical ocular hypotensive medication were examined: (1) IOP after an initial four- to six-week one-eyed therapeutic trial of a nonselective β-blocker (N = 549) or a prostaglandin analog (N = 201); (2) the mean IOP response during 12 to 60 months of follow-up among medication participants (N = 689); (3) the percentage of follow-up visits at which both eyes met the treatment goal; (4). the total number of different medications prescribed to reach treatment goal; and (5) the total number of different medications prescribed multiplied by the number of months each medication was prescribed.

• RESULTS: Central corneal thickness was inversely related to the IOP response after the initial one-eyed therapeutic trial and during 12 to 60 months of follow-up ($P < .05$). Mean CCT was not correlated with the number of different medications prescribed during follow-up, the total medication-months, or the percentage of visits at which IOP target was met.

• CONCLUSIONS: Individuals with thicker corneas had smaller measured IOP responses to ocular hypotensive medication than those with normal or thin corneas. We believe that CCT measurements may be useful in patient management and in interpreting clinical trials of ocular hypotensive medication. (Am J Ophthalmol 2004; 138:717–722. © 2004 by Elsevier Inc. All rights reserved.)

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THE OCULAR HYPERTENSION TREATMENT STUDY (OHTS) is multicenter randomized clinical trial to evaluate the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of visual field loss and/or optic nerve damage in ocular hypertensive individuals at moderate risk for developing primary open-angle glaucoma.[1,2] In the OHTS, intraocular pressure (IOP) is measured by Goldmann applanation tonometry.

When Goldmann and Schmidt[3] first described the applanation tonometer, they discussed the effect of corneal thickness on the measurement of IOP. They assumed a central corneal thickness of 500 μm and emphasized that, at least theoretically, corneal thickness might influence

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applanation readings. However, they believed that variations in central corneal thickness (CCT) occurred rarely in the absence of corneal disease.

As optical and ultrasonic pachymeters came into widespread use, it became clear that CCT does indeed have a positive correlation with IOP as measured by Goldmann applanation tonometry.[4] In some cases the effect of CCT on measured IOP can be clinically significant.[5] Furthermore, it also became apparent that CCT is more variable among patients with clinically normal corneas than Goldmann and Schmidt recognized.[6–9]

In recent years there have been a number of cross-sectional studies indicating that ocular hypertensive individuals have thicker corneas than ocular normotensive individuals, suggesting that, at least in some patients, the elevated applanation measurement is the result of the thick cornea rather than truly elevated IOP.[10–16] We recently reported the results of CCT measurements in 1,301 participants of the OHTS. The OHTS participants have thicker central corneas than have been reported in cross-sectional studies of clinically "normal" individuals. Furthermore, racial differences exist among the study participants, with African American OHTS participants on average having thinner corneas than their Caucasian counterparts.[17]

The OHTS demonstrated the safety and efficacy of IOP-lowering medication in the prevention of primary open-angle glaucoma (POAG).[1] Baseline factors predictive of which OHTS participants developed POAG included CCT, cup/disk ratio, age, IOP, and pattern standard deviation.[18] Central corneal thickness was a potent predictive factor for the development of POAG, with each 40-μm reduction of CCT below the average of 572 μm conferring a 71% increased risk over a mean follow-up of 72 months. Although alternative hypotheses can be considered, we believe that much of the effect of CCT on glaucoma risk comes from its influence on Goldmann applanation tonometry.

The response to topical glaucoma medications varies widely among individuals. Although there are undoubtedly many factors responsible for this variability, we questioned whether differences in CCT might alter the *measured* IOP response to treatment. For example, we wondered if in two otherwise identical individuals with the same baseline IOP, receiving the same IOP-lowering medication, there would be a smaller drop in IOP measured in the individual with the thicker cornea than in the individual with the thinner cornea. The OHTS dataset offers a unique opportunity to test this hypothesis. Most participants had CCT measurements, and all those who were started on medication had carefully established baseline IOPs. In the present report, we examine the relationship between CCT and various indicators of IOP response to topical ocular hypotensive medication.

METHODS

THE STUDY PROTOCOL, INCLUDING THE MEASUREMENT OF corneal thickness, was approved by local institutional review boards. All participants provided written informed consent for participation in the study. The protocol for the OHTS is described in detail elsewhere,[2] and the manual of procedures for the study is available online (https://vrcc.wustl.edu/mop/mop.htm). From February 1994 to October 1996, qualifying participants were randomly assigned to treatment with topical IOP-lowering medication or to observation. All IOP measurements were made by Goldmann applanation tonometry using separate operators and readers, with at least two measurements recorded and a third if the first two disagreed by more than 2 mm Hg. Baseline IOP was defined as the average of two or three IOP measurements performed at the randomization visit. Every attempt was made to keep subsequent IOP measurements throughout the study within a four-hour time window to minimize diurnal fluctuation. The goal of treatment with topical ocular hypotensive medication was to achieve an IOP of 24 mm Hg or less and a minimum 20% reduction from the baseline IOP, except that an IOP of less than 18 mm Hg was not required. Individually calculated target IOPs for each eye of each participant were provided to the investigators by the Coordinating Center.

Following the baseline randomization visit, participants assigned to the medication group underwent a one-eyed therapeutic trial in the higher-IOP eye, with response to medication evaluated four to six weeks later. If baseline IOP was equal in the two eyes, one eye was chosen randomly for testing. All topical ocular hypotensive drugs commercially available in the United States were included in OHTS. Among those participants originally randomized to medication, the majority (67%) were initially treated with a topical, nonselective β-blocker. As the study progressed, new medications, including prostaglandins, were added to the study formulary. Participants who were prescribed more than one medication in the initial one-eyed therapeutic trial were excluded from this report.

After the June 2002 publication of the primary outcome paper reporting that treatment was effective in delaying or preventing POAG,[1] ocular hypotensive medication was offered to participants originally randomized to the observation group. Thus, we also report data on participants who were originally randomized to the observation group and who started an initial one-eyed therapeutic trial after June 1, 2002, and completed the initial one-eyed trial by October 3, 2003. For purposes of this report, the baseline IOP of observation participants was defined as the mean of two or three IOP measurements of the treated eye at the visit initiating the one-eyed therapeutic trial. Among observation participants, we report only one-eyed therapeutic trials of prostaglandin drugs (n = 201), because

these drugs were selected for the majority of the initial therapeutic trials in this subset.

Central corneal thickness was measured at the clinical centers by calibrated ultrasonic pachymeters (Pachette 500, DGH Technologies, Exton, Pennsylvania). We began to collect CCT measurements in early 1999, about two years after randomization of the last participant. The protocol for the measurement of CCT is described in a previously published article.[17]

We investigated the relationship between CCT and measured IOP response to topical ocular hypotensive medication using the following short-term and long-term indicators:

1. Intraocular pressure in the treated eye after four to six weeks of the initial one-eyed therapeutic trial. The sample for the initial one-eyed therapeutic trials included participants originally randomized to the medication group who completed a one-eyed trial between March 14, 1994, and December 18, 1996, and participants originally randomized to the observation group who completed a one-eyed trial between June 1, 2002, and October 3, 2003.

Among participants originally randomized to the medication group the median follow-up was 96 months. We report the following long-term indicators of IOP response from 12 months of follow-up and to a maximum of 60 months:

2. Average IOP during follow-up while receiving one or more topical medications. The average follow-up IOP was the mean IOP of both eyes averaged over follow-up visits completed between 12 and 60 months. We excluded from this analysis IOP measurements obtained after POAG was diagnosed, because clinicians were likely to escalate therapy, and after surgical interventions, such as cataract surgery, which might independently affect IOP.

3. Percentage of follow-up visits at which both eyes met target IOPs. This index was defined as the percentage of completed, scheduled follow-up visits at which target IOPs were met in both eyes.

4. Total number of different medications prescribed during follow-up to reach target IOPs. Combination products were considered to be two medications.

5. The "medication-months" was calculated as the number of different medications prescribed multiplied by the months each medication was prescribed.

The primary outcome measure of IOP response in the initial one-eyed trial was the IOP in the treated eye after four to six weeks of medication. Descriptive statistics (means and standard deviations) are reported for baseline IOP, IOP after four to six weeks, change in IOP from baseline, and percentage change in IOP from baseline. Descriptive statistics for IOP response are reported for three strata of CCT of nearly equal sample size (tertiles); however, all analyses were performed using the original measurement of CCT. The relationship of IOP after four to six weeks of medication to clinical and demographic factors at baseline was examined using *t* tests and χ^2 tests. Baseline factors, in addition to CCT, that were screened for a possible relationship to IOP response included baseline IOP, days on treatment, medical history (heart disease, asthma, high blood pressure, and diabetes), and demographic characteristics (age, sex, and race). The multivariate general linear model to assess the effect of CCT on IOP response included those baseline factors found to be statistically significant in univariate analyses. We also examined whether the relationship of CCT to IOP response in the one-eyed trial differed between nonselective β-blockers and prostaglandin analogs.

We report descriptive statistics (means and standard deviations) for long-term indices of IOP response during follow-up among participants originally randomized to the medication group. A separate multivariate general linear model was run for each long-term index of IOP response (mean IOP for both eyes during follow-up, percentage of visits in which both eyes met IOP targets, total number of different medications prescribed and medication months). The multivariate model included CCT and those baseline factors found to be statistically significant in the univariate analyses described above.

RESULTS

AMONG THE 817 PARTICIPANTS ORIGINALLY RANDOMIZED to the medication group, 549 (67%) had CCT measurements and completed an initial one-eyed trial of a nonselective β-blocker. The remaining participants in the medication group received a variety of other drugs; because of the small sample sizes, separate analyses concerning these other medications were excluded from this report.

As noted above, after June 1, 2002, participants originally randomized to the observation group were offered medication. Among this group, 201 participants had CCT measurements, initiated a one-eyed therapeutic trial of a prostaglandin analog (latanoprost, bimatoprost, or travoprost), and completed a therapeutic trial by October 3, 2003. Sample sizes for other medication classes in this group were too small for analysis. Baseline demographic and clinical factors of these two groups are reported in Tables 1 and 2. Since one-eyed trials for the prostaglandin analogs were performed in the second phase of OHTS, these participants were approximately 5 years older and reported more health problems. The correlation of baseline IOP and CCT was −0.053 in the initial one-eyed trial.

Participants with thinner corneas had lower measured IOP after 4 to 6 weeks on a one-eyed trial as measured by Goldmann applanation tonometry after treatment with either nonselective β-blockers or prostaglandin analogs (Table 3). In univariate analyses as well as multivariate analyses, central corneal thickness was statistically significantly related to the measured IOP after 4 to 6 weeks of the initial one-eyed trial. The correlation of CCT to IOP after 4 to 6 weeks was 0.14 (partial correlation, $P = .0002$)

TABLE 1. Continuous Measures of Participants Prescribed Nonselective β-Blockers or Prostaglandin Analogues in Initial One-eyed Therapeutic Trials

Feature	Nonselective β-Blockers n = 549	Prostaglandin Analogues n = 201
Age in years at time of one-eyed trial		
Mean	56.3	61.8
SD	9.1	9.4
Median	55.4	60.2
Central corneal thickness (μm)		
Mean	569.6	576.6
SD	38.6	35.3
Median	567.6	573.4
Number of days on medication in the one-eyed trial		
Mean	30.8	36.2
SD	11.2	11.6
Median	29.0	35.0

TABLE 2. Categorical Measures of Participants Prescribed Nonselective β-Blockers or Prostaglandin Analogues in Initial One-eyed Therapeutic Trials

Feature	Nonselective β-Blockers N	Nonselective β-Blockers %	Prostaglandin Analogues N	Prostaglandin Analogues %
Sex				
Male	243	44.3	77	38.3
Female	306	55.7	124	61.7
Race				
Other race	423	77.0	143	71.1
African American	126	23.0	58	28.9
Diabetes prior to one-eyed trial				
No	490	89.3	158	78.6
Yes	57	10.4	43	21.4
HBP prior to one-eyed trial				
No	350	63.8	85	42.3
Yes	197	35.9	116	57.7
Asthma prior to one-eyed trial				
No	535	97.4	181	90.0
Yes	13	2.4	20	10.0
Heart disease prior to one-eyed trial				
No	524	95.4	174	86.6
Yes	25	4.6	27	13.4
Systemic β-blockers prior to one-eyed trial				
No	524	95.4	163	81.1
Yes	25	4.6	38	18.9
Calcium channel blockers prior to one-eyed trial				
No	498	90.7	133	66.2
Yes	51	9.3	68	33.8

as estimated from a multivariate model that adjusted for baseline IOP, medication class, male or female sex, asthma, and heart disease. The effect of CCT on IOP after 4 to 6 weeks of medication did not differ between the two drug classes (interaction of corneal thickness and medication class $P = .12$).

We examined several indicators of long-term IOP response in the 689 participants in the original medication group who had CCT measurements and completed follow-up of 12 to 60 months (Table 4). The average baseline IOP for these participants was 24.9 ± 2.7, and the average follow-up IOP was 19.1 ± 2.1, a 22.9% ± 9.2% mean reduction from baseline. The correlation of CCT to treated IOP averaged over 12 to 60 months of follow-up was 0.15 (partial correlation, $P = .001$) as estimated from a multivariate model that adjusted for baseline IOP, male or female sex, asthma, and heart disease. Central corneal thickness measurements were not correlated with the total number of different medications prescribed during follow-up ($P = .22$), the medication months during follow-up ($P = .86$) or the percentage of follow-up visits at which target IOP was met in both eyes ($P = .20$)

DISCUSSION

CLINICIANS HAVE LONG RECOGNIZED THAT SOME PATIENTS respond poorly, if at all, to IOP-lowering medications. In 1978, Johnson and associates[5] described a 17-year-old woman whose central corneas were 900 μm thick and in whom medical attempts to lower IOP were unsuccessful; they hypothesized that her thick corneas prevented an accurate measure of IOP and IOP response. The present study demonstrates that the effect of CCT on measured IOP response to medication extends into the range of CCTs commonly encountered in clinical practice.

We report an inverse relationship between CCT and measured IOP response to topical nonselective β-blockers and prostaglandin analogs. Correcting initial and treated IOP with formulas suggested by Ehlers and associates,[4] Doughty and Zaman,[7] and Orssengo and Pye[19] had minimal effect on this relationship (data not presented). The effect of CCT on measured IOP response appeared to be greater following administration of prostaglandin analogs than β-blockers. However, it is important to point out that the assignment to β-blockers or prostaglandin analogs was not randomized. Furthermore, participants in the observation group received prostaglandins later in the study and therefore were older and had more serious medical conditions. At the 2004 ARVO meeting, Fan and coworkers reported a substantial effect of CCT on the measured response to topical alpha 2 agonists. They also noted an effect of CCT on the measured response to latanoprost, but of smaller magnitude than we report (Fan S, Camras CB, Toris CB, unpublished data, "Effects of central corneal thickness on the efficacy of brimonidine and latanoprost,"

TABLE 3. Central Corneal Thickness (CCT) and Intraocular Pressure (IOP) in the Initial One-eyed Therapeutic Trials

Drug	CCT (μm)	CCT Mean ± SD	Baseline IOP N	Baseline IOP Mean (mm Hg)	Baseline IOP SD	IOP after 4 to 6 Weeks of One-eyed Trial Mean (mm Hg)	IOP after 4 to 6 Weeks of One-eyed Trial SD	Change in IOP Mean (mm Hg)	Change in IOP SD	% Change in IOP Mean	% Change in IOP SD
Nonselective	≤550	527.7 ± 19.1	174	26.1	3.2	19.4	3.0	−6.8	3.4	−25.3	11.4
β-blockers	>550 to ≤590	569.1 ± 11.5	215	26.0	2.7	19.7	3.1	−6.3	3.4	−23.9	12.2
	>590	615.8 ± 22.0	160	25.6	2.9	19.8	2.8	−5.8	3.3	−22.0	12.5
	All	569.6 ± 38.6	549	26.0	2.9	19.6	3.0	−6.3	3.4	−23.8	12.1
Prostaglandin	≤550	533.7 ± 12.1	51	24.9	3.6	16.8	3.2	−8.1	4.3	−31.4	14.6
analogue	>550 to ≤590	568.9 ± 11.0	78	24.8	3.8	18.2	3.7	−6.7	4.4	−25.9	14.7
	>590	615.4 ± 19.2	72	24.2	3.3	18.5	3.6	−5.8	3.6	−23.2	14.0
	All	576.6 ± 35.3	201	24.6	3.6	17.9	3.6	−6.7	4.2	−26.3	14.7

TABLE 4. Indicators of Intraocular Pressure (IOP) Response During 12 to 60 Months of Follow-up Among Participants Randomized to the Medication Group

CCT (μm)	CCT Mean ± SD	N	Mean follow-up IOP OU Mean	Mean follow-up IOP OU SD	% Visits met IOP Goal OU Mean	% Visits met IOP Goal OU SD	Number of Different Medications Prescribed Mean	Number of Different Medications Prescribed SD	Medication (months) Mean	Medication (months) SD
≤550	526.0 ± 21.9	206	18.9	2.2	89.2	19.1	2.4	1.4	64.1	28.2
>550 to ≤590	569.7 ± 11.2	271	19.0	1.9	90.6	16.8	2.3	1.4	60.8	26.6
>590	614.9 ± 21.3	212	19.4	2.3	86.0	21.3	2.5	1.4	61.2	25.9
All	570.6 ± 39.2	689	19.1	2.1	88.8	19.0	2.4	1.4	61.9	26.9

presented as a poster at the Association for Research in Vision and Ophthalmology Annual Meeting, April 2004).

Three possible mechanisms by which CCT might influence the measured IOP response to ocular hypotensive medications can be postulated:

• **DIFFERENTIAL PHARMACOKINETICS:** Thicker corneas might limit topical drug penetration to the ciliary body and outflow channels, or somehow modulate the enzymatic conversion of prodrugs to their active form. However, we question whether this explanation accounts for our results. The drugs studied penetrate the cornea and/or sclera readily and, in the case of β-blockers, the doses used clinically are two to three times that necessary to bind to all available β-adrenergic receptors.[20] The responses to treatment reported in this paper were made after weeks, months, and years of long-term dosing, long after the intraocular concentration of the drug(s) reach a steady-state. We are not aware of any specific data correlating aqueous drug levels and CCT in human or animal experiments.

• **LOWER BASELINE IOP:** Eyes with thicker corneas have lower true IOPs than measured by Goldman applanation tonometry. Eyes with lower IOPs will have smaller absolute and percentage reductions in IOP following treatment with ocular hypotensive medication. However, we question whether the magnitude of the effect of CCT noted by us and by Fan and associates (Fan S, Camras CB, Toris CB, unpublished data, "Effects of central corneal thickness on the efficacy of brimonidine and latanoprost," presented as a poster at the Association for Research in Vision and Ophthalmology Annual Meeting, April 2004) is too large to be explained solely by a lower true baseline IOP.

• **DIFFERENTIAL CORNEAL COMPLIANCE:** It is possible that thicker corneas are more rigid and less mechanically compliant than thin corneas. It is also possible that corneal rigidity has a greater effect on measured IOP at lower levels of IOP, which would tend to minimize the measured response to treatment in eyes with thick corneas.

We believe that our results are probably best explained by a combination of the latter two hypotheses. The fact that applying the various IOP correction factors for CCT to our dataset failed to fully explain our findings suggests that the relationship between CCT, Goldmann IOP, and "true" IOP is far more complex than can be modeled by a simple linear arithmetic correction.

In clinical practice and in clinical trials of topical ocular hypotensive medication, some patients are often identified as "nonresponders" to particular drugs. The "nonresponder" rate is commonly quoted as being between 10% to 30% for various drugs among patients with ocular hypertension and glaucoma. Some preferred practice guidelines recommend trying a different medication if a 20% lowering is not achieved on initial treatment.[21] We

postulate that included among these "nonresponders" are individuals with thick corneas. Conversely, the group of patients who respond very well to medications ("high responders") may include individuals with thin corneas.

The OHTS demonstrated the importance of measuring CCT in ocular hypertensive patients to help estimate an individual's risk of developing glaucoma.[18] The present study demonstrates that CCT measurements can provide clinicians and investigators with further information useful both in clinical practice and research. In clinical practice, CCT measurements can help the clinician better interpret a patient's response to therapy. In the setting of glaucoma clinical trials, CCT measurements can help investigators better understand how patients respond to IOP-lowering treatment, better define "nonresponse," and as part of the recruitment process, ensure that patients not needing treatment be properly excluded from enrollment.

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