Changes in Central Corneal Thickness over Time

The Ocular Hypertension Treatment Study

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Objective: To describe how much change, if any, occurs between central corneal thickness (CCT) measurements performed an average of 3.8 years apart in participants in the Ocular Hypertension Treatment Study (OHTS) and to identify clinical and demographic factors that are associated with changes in CCT, including baseline intraocular presure, duration and class of ocular hypotensive medication, medical history, and systemic medication.

Design: Secondary analysis of data from a randomized clinical trial.

Participants: Ocular Hypertension Treatment Study participants. Participants who had undergone incisional intraocular or keratorefractive surgery between CCT measurements were excluded.

Testing: The first CCT measurements were performed starting in 1999, and the second measurements were performed starting in 2002. Measurements were performed by OHTS certified technicians using an ultrasonic pachymeter under a standardized protocol.

Main Outcome Measure: Central corneal thickness measurement (micrometers).

Results: First and second CCT measurements were available from 73% (1191) of the 1636 OHTS participants randomized. Central corneal thickness decreased a mean rate of -0.74 ± 3.5 μm/year between the first and second CCT measurements. The mean medication exposure between first and second CCT measurements in participants originally randomized to observation (n = 595) was 1.1 ± 1.6 years, versus 5.0 ± 2.7 years in participants originally randomized to medication (n = 596). Central corneal thickness decreased by a mean of 1.0 ± 3.4 μm/year among participants originally randomized to observation, compared with 0.5 ± 3.5 μm/year among participants originally randomized to medication ($P<0.0001$). Subgroup analyses suggest that participants treated only with topical prostaglandin analogues (PGAs) between the two CCT measurements had a greater rate of decrease per year than participants treated only with topical β-blockers.

Conclusions: The rate of CCT decrease over 3.8 years is comparable to the cross-sectional age differences reported in the OHTS at the first measurement (0.6 μm/year) and comparable to other cross-sectional studies. Use of topical PGAs may be associated with a slightly higher rate of thinning. The modest age- and drug-related rates of thinning observed are unlikely to influence tonometry or clinical decision-making substantially in most clinical situations.

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The Ocular Hypertension Study (OHTS) is a multicenter, prospective, randomized clinical trial designed to evaluate the safety and efficacy of topical ocular hypotensive medications in delaying or preventing the onset of visual field (VF) loss and/or optic nerve damage in individuals at moderate risk for developing primary open-angle glaucoma (POAG).[1]

In 2002, the OHTS reported that central corneal thickness (CCT) was a powerful predictive factor for the development of POAG.[2] This finding has spurred great interest in CCT and new tonometry techniques. One unanswered question is whether CCT varies significantly over time in the same individual. Based on our initial cross-sectional survey of CCT among OHTS participants, we reported that mean CCT was lower in older individuals (0.63 μm/year).[3]

In the OHTS, a second measure of CCT was made 4 years after the first to investigate stability of CCT measurements. The OHTS provides a unique opportunity to obtain longitudinal CCT data from a well-studied cohort of individuals with ocular hypertension. In this report, we describe the time-dependent changes in CCT measured among OHTS participants and examine what demographic and clinical factors, including the use and class of topical ocular hypotensive medications, might influence these changes.

Materials and Methods

The remeasurement of CCT was approved by the OHTS Data and Safety Monitoring Committee and institutional review boards of participating clinics. First and second CCT measurements were

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Table 1. Mean Central Corneal Thickness (CCT) (Micrometers) for First and Second Measurements by Randomization Group and Overall

	Randomization Assignment								
	Medication			*Observation*			**All**		
	N	*Mean*	*SD*	*N*	*Mean*	*SD*	*N*	*Mean*	*SD*
Age at first CCT measurement	596	60.3	9.0	595	60.5	9.3	1191	60.4	9.1
Baseline intraocular pressure (mmHg)	596	24.9	2.7	595	25.1	2.7	1191	25.0	2.7
First CCT (mean of both eyes)	596	571.7	38.7	595	574.6	37.8	1191	573.1	38.3
Second CCT (mean of both eyes)	596	569.7	38.8	595	571.1	38.3	1191	570.4	38.6
Mean difference between first and second CCT measurements	596	−2.0	13.6	595	−3.5	13.1	1191	−2.7	13.4
Time between measurements (yrs)	596	3.9	0.8	595	3.8	0.7	1191	3.8	0.8
Mean decrease (μm) per year	596	−0.5	3.5	595	−1.0	3.4	1191	−0.7	3.5
Years on ocular medications between the two measurements	596	5.0	2.7	595	1.1	1.6	1191	3.0	2.9

SD = standard deviation.

made on OHTS participants using ultrasonic pachymeters (DGH-500 Pachette or Pachette II, which uses the same ultrasound transducer and software algorithm as the DGH-500, DGH Technologies, Exton, PA) under the same protocol as reported previously.[3] Five separate readings were acquired from the central cornea of each eye and averaged. Quality control measures included the requirement to retake CCT measurements when values for right and left eyes differed by ≥40 μm or when the second measurement differed ≥40 μm from the first measurement in the absence of reported intercurrent surgery. When a repeat measurement was requested by the Coordinating Center due to failure to meet these quality control standards, the repeat measurement was used for analysis.

After the OHTS reported that topical ocular hypotensive medications delay or prevent the onset of VF loss and/or optic nerve damage in patients with ocular hypertension,[4] OHTS participants who were originally assigned to the observation group were offered treatment with topical ocular hypotensive medications. It should be noted that the choice of topical ocular hypotensive treatment was at the discretion of the treating clinician and was not randomly assigned. By the time of the second CCT measurement, participants originally randomized to observation had been on topical medications for approximately 1 year.

Change in CCT was analyzed in SAS (SAS Inc., Cary, NC) with a multivariate linear model that used all data (5 readings) from right and left eyes of the participant at the first and second measurement periods. All models included eye-specific variables for right and left eyes and accounted for their intereye correlations. The statistical power of the multivariate model is increased by including all CCT readings of each eye at each period and by allowing the variances to differ by eye and by period. For the purpose of reporting results, we report the mean change in CCT in the right and left eyes in micrometers per year. Results for eye-specific continuous variables are reported as means of both eyes and are reported for levels of categorical variables.

The multivariate mixed model allowed us to test whether there was a difference between the 5 readings from the first CCT measurement and the 5 readings from the second measurement, the magnitude and direction of the change, and whether the change differed with respect to various covariates. Covariates evaluated were age at OHTS baseline; age at first CCT measurement; intraocular pressure (IOP) at OHTS baseline; gender; race; randomization group; conversion to POAG; years between CCT measurements; systemic β-blocker use; calcium channel blocker use; and self-reported history at baseline and follow-up of diabetes mellitus, high blood pressure, heart disease, and cancer. The univariate models tested if the first and second CCT measurements differed and if CCT changed with respect to a given covariate. The multivariate model included covariates that were statistically significant in the univariate models. In both univariate and multivariate models, we used baseline IOP to ascertain the influence of IOP on CCT change because of the confounding between follow-up IOP and randomization group. To capture the effect of age on change in CCT, we used age at the first CCT measurement, not age at study entry.

Because the observation group had begun hypotensive medication about 7 years after randomization, they were more likely to be prescribed prostaglandin analogues (PGAs) than β-blockers. Because of confounding between randomization group and medication class, we conducted a subanalysis to examine if the magnitude of change, if any, between the first and second CCT measurements differed by class of medication. We defined 2 different medication groups—participants who were prescribed only PGAs between the two CCT measures and participants who were prescribed only β-blockers between the two CCT measures. The multivariate model as described previously was rerun using only these 2 subgroups of participants.

Results

First and second CCT measurements were acquired in 76% (1246/1636) of OHTS participants. Participants who had undergone incisional intraocular or keratorefractive surgery between measurements were excluded, leaving 73% (1191/1636) participants for analysis.

The time between the two measurements averaged 3.8±0.8 years (range, 1.2–6.7). We requested a repeat CCT measurement for 40 participants because either the second CCT measurement had a >40-μm difference between the eyes (n = 9) or the second measurement was >40 μm different from the first in at least one eye (n = 32; note that 1 participant violated both quality control thresholds). We received and used in the analyses repeat measures for 21 of the 40 participants. For those participants who did not receive repeat measures, the original measurement was used for analyses.

The differences between the first and second CCT measurements are reported by randomization group (Table 1); demographic factors, clinical factors, and medical history are reported in Table 2 (available at http://aaojournal.org), which pools data for all

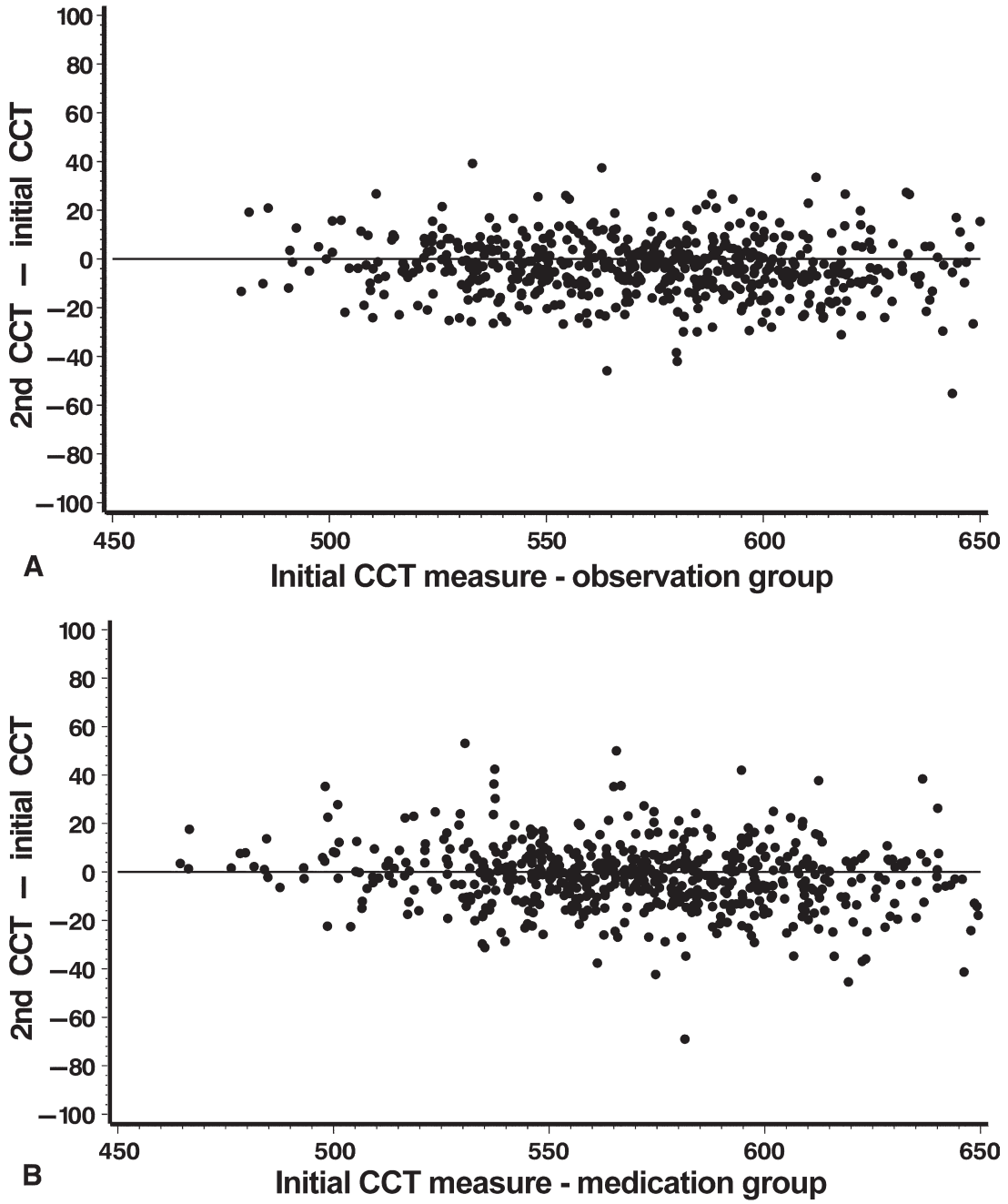

Figure 1. Bland–Altman plot comparing the difference between the first and second central corneal thickness (CCT) measurements (vertical axis) versus the range of initial CCT measurements (horizontal axis) among Ocular Hypertension Treatment Study participants originally randomly assigned to the observation group (**A**) or to the medication group (**B**).

participants without regard to the number or type of medication between the two CCT measurements. At the first measurement, the mean CCT of right and left eyes was 573.1±38.3 μm, and at the second measurement, it was 570.4±38.6 μm. There was no detectable difference in the rate of thinning between right and left eyes ($P = 0.17$). Overall, CCT decreased at a rate of −0.74±3.5 μm/year ($P<0.001$) between the two measurements (rate unadjusted for covariates). Average durations of medication exposure between first and second CCT measurements were 5.0±2.7 years in participants originally randomized to medication (n = 596) and 1.1±1.6 years in participants originally randomized to observation (n = 595) (Table 1).

In univariate models, CCT decreased at a statistically significantly greater rate among participants originally randomized to observation (−1.0±3.4 μm/year) compared with participants originally randomized to medication (−0.5±3.5 μm/year) ($P<0.0001$) (Table 2, Fig 1). Other baseline factors that were statistically significantly associated with greater thinning in univariate models included older age, "other" self-identified race, development of POAG, higher IOP, history of heart disease, history of cancer, and history of migraines. Because of the high statistical power of the models, even the small difference of 0.1 micrometers per year between males and females statistically significantly differed. The interval between the first and second measurements was not sta-

Table 3. Mean Central Corneal Thickness (Micrometers) for First and Second CCT Measurements for Participants Prescribed Only Prostaglandin Analogues and Participants Prescribed Only β-Blockers between Measurements

	Drug Class					
	Prostaglandin Analogues			*β-Blocker*		
	N	*Mean*	*SD*	*N*	*Mean*	*SD*
Age at initial CCT	298	59.8	8.8	162	58.7	8.6
Baseline intraocular pressure (mmHg)	298	25.0	2.6	162	24.9	2.6
First CCT (mean of both eyes)	298	571.1	35.4	162	574.0	37.8
Second CCT (mean of both eyes)	298	566.0	36.7	162	572.5	38.0
Mean difference between first and second CCT measurements*	298	−5.1	11.9	162	−1.5	11.4
Time between measurements (yrs)	298	3.9	0.7	162	3.7	0.7
Mean decrease in CCT per year	298	−1.3	3.1	162	−0.5	3.2
Years on ocular medications between two measurements	298	1.4	1.3	162	2.7	1.4

CCT = central corneal thickness; SD = standard deviation.
*Multivariate model included total time on medication between CCT measurements in addition to covariates that were statistically significant in univariate analyses—older age, "other" self-identified race, development of primary open-angle glaucoma, higher baseline intraocular pressure, history of heart disease, history of cancer, and history of migraines.

tistically significantly associated with the rate of thinning in CCT partly because first and second CCT measurements were each completed in a narrow band of time.

Factors that were statistically significant in univariate models as described above were included in the multivariate model. In the multivariate model, CCT decreased with older age at time of first CCT measure ($P<0.0001$), male gender ($P = 0.040$), other self-reported race ($P<0.0001$), higher baseline IOP ($P<0.0002$), randomization to the observation group ($P<0.0001$), conversion to POAG ($P = 0.0149$), history of migraine ($P = 0.0039$), and history of heart disease ($P = 0.0386$). Factors that were statistically significantly associated with a difference between the two CCT measurements in the univariate model but not in the multivariate model included use of systemic β-adrenergic antagonists ($P = 0.86$) and a history of cancer ($P = 0.06$), reported in Table 2.

In the separate subgroup analysis, we compared first and second CCT measurements among participants prescribed only PGAs (n = 298) and participants prescribed only β-blockers (n = 162) to determine if the rate of CCT change differed between these two groups. In addition to drug class, this multivariate model also included interval between CCT measurements and time on medication. Interval between CCT measurements and time on medication were not statistically significant. Among participants prescribed only β-blockers, no differences between the first and second CCT measurements were detected ($P = 0.57$); however, among participants prescribed only PGAs the differences approached statistical significance ($P = 0.06$). Notably, CCT decreased at a rate of 1.3 ± 3.05 μm/year among the participants prescribed only PGAs, compared with a rate of 0.52 ± 3.16 μm/year among the participants prescribed only β-blockers between the two CCT measures ($P<0.0001$; Table 3, Fig 2).

Discussion

In the OHTS, the first CCT measurements were performed by ultrasonic pachymetry between 1998 and 2002, a mean of 5.0 ± 0.83 years (range, 2.5–7.6) after randomization. We have reported that, on average, OHTS participants have thicker corneas than ocular normal individuals in population-based studies and that, on average, African American OHTS participants have thinner corneas than Caucasian participants.[3]

As noted earlier, one unanswered question is whether CCT varies significantly over time in the same individual. To our knowledge, this is the first longitudinal study of the variability of CCT in a large cohort of individuals. All but one of the published studies on this question are based on cross-sectional data rather than longitudinal data.[3,5–15] In the only longitudinal study published to date, Weizer et al[16] reported on 39 patients with a variety of ocular diagnoses observed for an average of 8.2 years; they found an average thinning of 2.0 to 2.8 μm/year. Their study is limited by the varied ocular diagnoses of their participants as well as intercurrent surgery and medication use.

In those cross-sectional studies with appropriate design and sufficient power to detect a correlation with age, a modest thinning of CCT of up to 0.6 μm/year has been observed among ophthalmically normal adults (Table 4). The average rate of CCT decrease in OHTS participants over 3.8 years (0.74 ± 3.5 μm/year) was comparable to the cross-sectional age difference reported previously[3] by the OHTS after the first measurement (0.63 μm/year) and to other cross-sectional studies of ophthalmically normal individuals.

The OHTS demonstrated the importance of measuring CCT in assessing the risk of patients with ocular hypertension for the development of POAG. Given the importance of pachymetry in the clinical evaluation of the patient with ocular hypertension, 2 questions that arise are whether measurement techniques are sufficiently repeatable to accurately ascertain the true value of CCT, and whether the underlying value being measured is stable or if it changes with time or clinical intervention.

Several investigators have suggested that a single measurement of CCT is not sufficient in clinical practice. In the OHTS, we acquired 5 separate readings of each eye at the same examination and had quality control standards in place to assure reliability. Wickham et al recently compared CCT measures acquired at 2 consecutive visits in a clinical set-

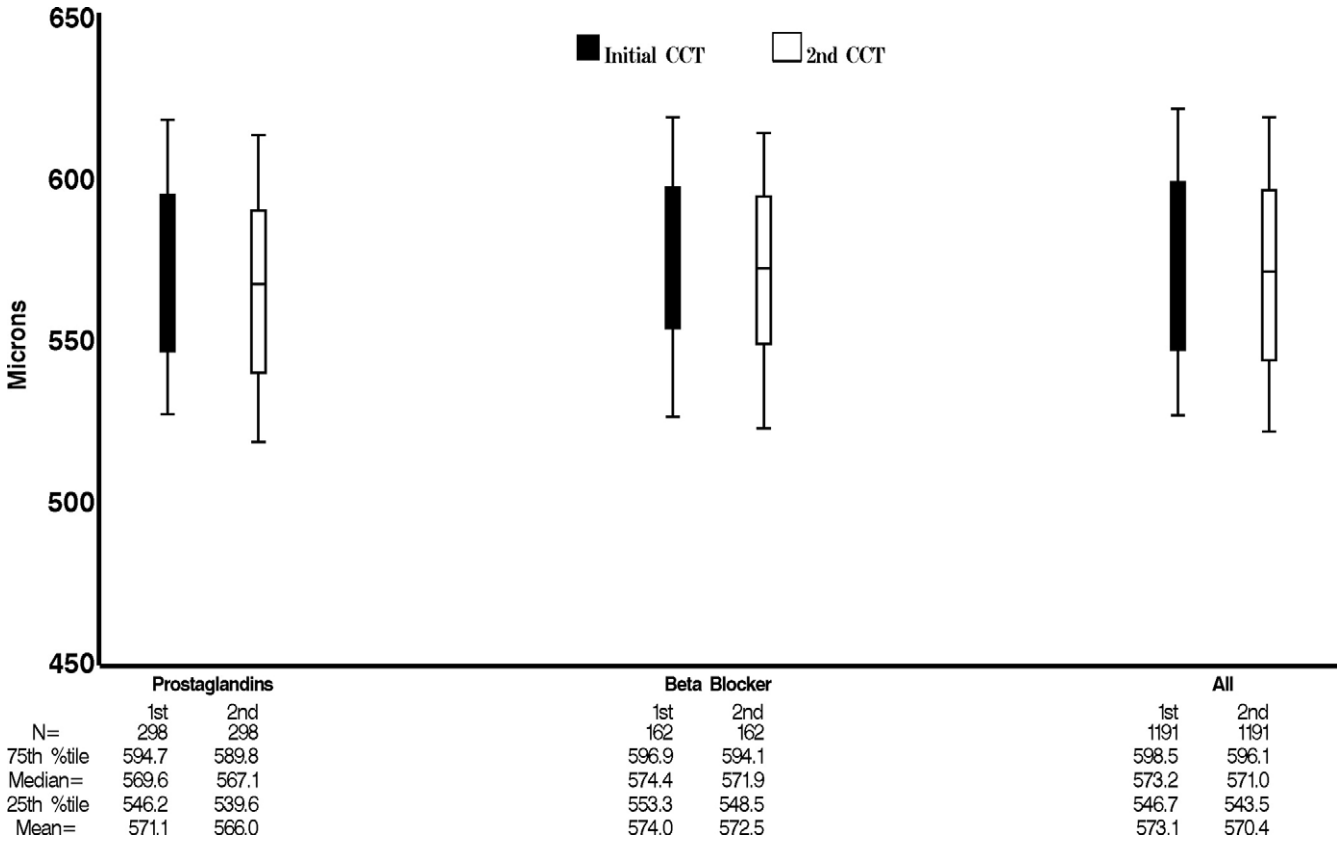

Figure 2. First and second central corneal thickness (CCT) measurements for participants in the Ocular Hypertension Treatment Study (n = 1191). Medians (line in center of box) for participants prescribed prostaglandin analogues only (n = 298) and for participants prescribed β-blockers only (n = 162). 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.

ting and found a mean difference between the visits of 9.6±26.9 μm.[17] They determined that in 32% of patients the difference in CCT values was sufficient to recategorize glaucoma risk in both eyes. Their study underscores the dictum that clinical decision-making about glaucoma risk is best made based on multiple pieces of data acquired over several visits rather than on a single data point.

We examined whether the second CCT measurement would change a patient's 5-year risk of developing glaucoma and thereby change a decision to withhold or initiate

Table 4. Representative Sample of Previous Cross-sectional Studies Comparing Central Corneal Thickness (CCT) and Age

Study	Design	Sample Size	Age Range	Pachymetry Technique	Age-Related Δ in CCT (μm/yr)
von Bahr[5]	Convenience sample	224	15–74	Optical	NS
Martola and Baum[6]	Convenience sample	121	<90	Optical	NS
Hansen[7]	Convenience sample	76	>10	Optical	NS
Rotterdam Study[8]	Cross-sectional study in a defined population	395		Optical	NS
Mongolian Eye Study[9]	Cross-sectional study in a defined population	1129	≥40	Optical	−0.5 in males, −0.6 in females
Ocular Hypertension Treatment Study[3]	Cross-sectional data from participants in a prospective controlled clinical trial	1301	≥40–80	Ultrasound	−0.63
Reykjavik Eye Study[11]	Cross-sectional study in a defined population	925	≥50	Optical	NS
Los Angeles Latino Eye Study[12]	Cross-sectional study in a defined population	2060	≥40	Ultrasound	−0.29
Tanjong Pagar Survey[10]	Cross-sectional study in a defined population	1232	40–79	Optical	−0.5 in males, −0.6 in females
Barbados Eye Studies[13]	Cross-sectional study in a defined population	1142	50–84	Ultrasound	−0.4
Aghaian et al[14]	Retrospective chart review of patients in a glaucoma clinic	801	≥18	Ultrasound	−0.3
Tajimi Study[15]	Cross-sectional study in a defined population	2623	≥40	Optical	NS

NS = not significant.

treatment. We calculated the 5-year risk of developing glaucoma changing only whether the first or second CCT measurement was used while holding all other predictive factors constant.[18] If the 5-year risk of developing glaucoma was ≥10%, we assumed it would be cost-effective to initiate treatment as indicated by economic analyses of OHTS data.[19] The treatment decision using the first or second CCT measurement did not change for 92% to 93% of the participants. For 8% of participants, the decision changed from withholding to initiating treatment; for 7%, the decision changed from initiating to withholding treatment. It is not clear how acquired changes in CCT affect the patient's underlying risk of developing POAG.

Our data confirm, in a cohort of individuals with ocular hypertension, previous cross-sectional studies that have indicated an age-related thinning of CCT among otherwise normal individuals throughout adult life (age 18–mid-80s). The underlying pathophysiology of the modest age-related corneal thinning we observed among OHTS participants remains unknown. One candidate is drying of the ocular surface; Dayanir et al recently reported that CCT thinned by 3% within 30 seconds in individuals prevented from blinking between measurements.[20] Altered tear film and increased symptoms of dry eye are commonly observed in older individuals,[21] but the Blue Mountains Eye Study did not confirm a strong association of dry eye with age.[22]

What about the impact of topical medications? Despite the fact that participants randomized to medical treatment had been on topical medications for almost 5 years before the first measurement of CCT,[3] we found no difference in CCT between the two randomization groups at time of the first measurement (Table 1; $P = 0.19$). Similarly, the European Glaucoma Prevention Study, in which CCT also was measured several years after randomization, found no difference in CCT between patients randomly assigned to a placebo or dorzolamide 2%.[23]

The impact of topical medications on the rate of corneal thinning is complex, and longitudinal data provide a more nuanced view. The rate of corneal thinning was higher in the observation group than in the medication group, suggesting a protective effect of hypotensive medication. Furthermore, a higher baseline IOP was associated with a higher rate of corneal thinning in both the observation and medication groups. In addition, our longitudinal data suggest that certain classes of topical ocular hypertensive medications used by the OHTS participants may underlie some of the thinning over time. Although the topical ocular hypotensive medication prescribed to participants in OHTS was not randomly assigned, a slightly higher rate of thinning appears to be associated with the use of topical PGAs. Viestenz et al performed a nonrandomized controlled cross-sectional study of CCT among patients using topical PGAs and found thinner CCTs among patients using PGAs (529±35 μm) than among controls (542±35 μm) ($P \leq 0.01$).[24] More recently, Harasymowycz et al prospectively evaluated CCT in individuals treated with the topical PGA travoprost, and found a mean decrease in CCT of 6.9 μm after 6 weeks of treatment ($P < 0.001$).[25] With only 2 CCT measurements separated by approximately 4 years, our data cannot determine whether the accelerated rate of thinning rate we observed in individuals treated with PGAs was the result of an acute (weeks to months) thinning after initiating treatment, as observed by Harasymowycz et al, or a longer-term effect on time-dependent thinning.

The OHTS previously reported a significant inverse relationship between CCT and the measured IOP-lowering response to topical agents.[26] It is interesting to speculate that this observation might result from drug-induced thinning in CCT, extracellular matrix, endothelial function, or other effects of medication on the cornea not yet understood, and these possible explanations are worth investigating.

In summary, we report that in longitudinal data from the OHTS, CCT decreased in the same direction and magnitude as observed in previous cross-sectional studies of normal populations; furthermore, we identified a possible treatment-related effect on thinning rate, particularly among participants receiving PGAs. It is important to emphasize; however, that the modest age- and drug-related rates of thinning we report here are unlikely to influence tonometry or clinical decision-making over the short to intermediate term.

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Footnotes and Financial Disclosures

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Table 2. Average Change in Central Corneal Thickness per Year Adjusted for Covariates*

	Univariate *P* Value	Multivariate *P* Value	Average Change (μm) per Year		
			N	*Mean*	*SD*
Randomization assignment	<0.0001	<0.0001			
Medication			596	−0.5	3.5
Observation			595	−1.0	3.4
Race	<0.0001	<0.0001			
Other			883	−0.8	3.5
African American			308	−0.4	3.2
Gender	0.001	0.04			
Male			506	−0.8	3.5
Female			685	−0.7	3.4
POAG in either eye?	0.0002	0.015			
No			1034	−0.7	3.5
Yes			157	−1.2	3.5
Systemic β-blocker use ever reported?	0.039	0.87			
No			772	−0.7	3.4
Yes			419	−0.8	3.6
Calcium channel blocker ever reported?	0.08				
No			761	−0.7	3.5
Yes			430	−0.8	3.5
Diabetes ever reported?	0.21				
No			888	−0.7	3.4
Yes			303	−0.8	3.5
High blood pressure ever reported?	0.51				
No			749	−0.7	3.5
Yes			442	−0.7	3.4
Heart disease ever reported?	<0.0001	0.04			
No			962	−0.7	3.5
Yes			229	−1.0	3.2
Cancer ever reported?	0.0002	0.06			
No			1029	−0.7	3.4
Yes			162	−1.2	3.5
Migraine ever reported	0.02	0.004			
No			1024	−0.7	3.5
Yes			167	−1.0	3.1
Baseline intraocular pressure (mmHg)	0.006	0.0002			
≤23			282	−0.6	3.5
>23–25			382	−1.0	3.4
>25–27			292	−1.0	3.2
>27			235	−0.2	3.7
All			1191	−0.7	3.5
Age at initial CCT	<0.0001	<0.0001			
≤53			299	−0.2	3.5
>53–60			318	−0.6	3.2
>60–67			266	−1.2	3.3
>67			308	−1.0	3.7
All			1191	−0.7	3.5
Years between CCT measurements	0.864				
≤3.47			317	−1.0	3.7
3.47–3.79			277	−0.8	3.3
3.79–4.27			299	−0.8	3.2
>4.27			298	−0.3	3.5
Medication prescribed between CCT measurements†	<0.0001	<0.0001			
Prostaglandin analogue only			298	−1.3	3.1
β-blocker only			162	−0.5	3.2
Other topical medications			592	−0.7	3.5
No medications			139	0.2	4.2

CCT = central corneal thickness; POAG = primary open-angle glaucoma; SD = standard deviation.
*Multivariate model included covariates that were statistically significant in univariate analyses—older age, "other" self-identified race, development of POAG, higher baseline intraocular pressure, history of heart disease, history of cancer and history of migraines.
†Multivariate model with medication class does not include randomization group.