Changes in Corneal Thickness in Patients With Treated and Untreated Ocular Hypertension

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Purpose: The elevated intraocular pressure (IOP) in eyes with ocular hypertension is often accompanied by increased corneal thickness. We tested the hypotheses that chronically elevated IOP causes a slow increase in corneal thickness and that lowering the IOP reverses this slow increase.

Methods: Fifty patients with ocular hypertension were randomized to medication and observation groups in the Mayo Clinic site of the Ocular Hypertension Treatment Study. Central corneal thickness was measured using an optical pachymeter at baseline and annually for 6 years. The rates of change of corneal thickness was compared between the groups. Epithelial thickness was measured by confocal microscopy 8 years after the baseline examination.

Results: Corneal thickness increased 1.5 ± 3.3 μm/yr in the observation group (n = 23) and decreased −1.3 ± 2.8 μm/yr in the medication group (n = 27, $P = 0.002$). Both rates were significantly different from zero ($P = 0.04$ and $P = 0.02$, respectively). Epithelial thickness was 46.4 ± 4.9 μm in the observation group and 41.3 ± 4.4 μm in the medication group ($P = 0.008$).

Conclusion: Results of this single-center series imply that corneal thickness increases slowly in eyes with ocular hypertension and decreases slowly if the IOP is lowered by topical medications. These phenomena could be explained by a causal relationship between elevated IOP and a slow increase in corneal thickness. A decrease in epithelial thickness accounts for a portion of the thinning that occurs with treatment. If confirmed in a larger series, these findings indicate that the effects of previous treatment on thickness should be considered if corneal thickness is to be used as a discriminant factor in the management of patients with ocular hypertension.

Key Words: ocular hypertension, corneal thickness, corneal epithelial thickness, corneal drug effects

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Ocular hypertension is diagnosed primarily from the clinical measurement of intraocular pressure (IOP). The diagnosis is made when a patient has persistently elevated IOP, open angles by gonioscopy, and no clinical signs of optic nerve damage such as pathologic cupping, disc asymmetry, or visual field abnormalities associated with glaucoma. Until recently, the only known difference between patients with ocular hypertension and normal subjects was elevated IOP in the former.[1] In recent studies, investigators found that patients with ocular hypertension have increased corneal thickness as well.[2–7] Although corneal thickness has a small effect on the IOP,[4,8–11] this effect seems unlikely to explain the increased corneal thickness in ocular hypertensives entirely. No reasons for the increased corneal thickness in this group of patients have been proposed, and it is reasonable to wonder if the elevated IOP and elevated corneal thickness are linked in some way. In particular, is the increased thickness in ocular hypertensives caused by the persistently elevated IOP? If so, reduction of IOP that has been persistently elevated may gradually reverse this increase in thickness.

The relationship between acute increases in IOP and corneal thickness has been carefully studied.[12–16] The effect of chronically elevated IOP on corneal thickness, however, has been more difficult to study, and studies have been limited to the cross-sectional studies of ocular hypertension mentioned above[2–7] and cross-sectional studies of patients with persistently elevated or decreased IOP.[14,17,18]

The Ocular Hypertension Treatment Study (OHTS) is a National Eye Institute–sponsored prospective multicenter randomized study designed to determine the safety and efficacy of pressure-lowering medication in patients with ocular hypertension.[19] Although corneal thickness was not measured in OHTS patients at most participating centers during the first 5 years of the study, it was measured annually in the OHTS patients at the Mayo Clinic study center as part of an ancillary study. This measurement was approved by the OHTS Data and Safety Monitoring Committee and the National Eye Institute to study the corneal changes, if any, associated with ocular hypertension or its treatment. These data thus constitute a 6-year longitudinal study on the relationship of corneal thickness to elevated IOP and its treatment.[20,21] In this study, we test the hypotheses that chronically elevated IOP might lead to the thicker corneas seen in patients with ocular hypertension and that reduction of persistently elevated IOP might reverse this tendency.

MATERIALS AND METHODS

One hundred sixty-one patients were evaluated for participation in the OHTS at Mayo Clinic by 1 of the authors (D.C.H.). The protocols of the OHTS and this ancillary study were reviewed and approved by the Institutional Review Board of the Mayo Clinic, and informed consent was obtained for all subjects for each study before enlistment in the study. Of these patients, 55 met the entry criteria[19] and agreed to participate. One patient was excluded because he moved to another center, and follow-up information was not available. Three patients wore contact lenses, 1 regularly and 2 occasionally; all were in the observation group. In addition to the studies performed for the OHTS, each subject had endothelial photography and central corneal pachymetry with a contact specular microscope (Keeler Instruments, Broomall, PA) by a masked examiner, usually between 10:30 AM and 12:30 PM, on enrollment in the study and annually thereafter. The average thickness at which focused images were photographed was recorded to the nearest 10 μm (0.01 mm) for each eye. A previous study reported the baseline corneal thickness characteristics of this group.[6] The mean values for both eyes for corneal thickness, IOP, and epithelial thickness was used as the values for that subject. Statistical analysis showed no difference in corneal thickness or IOP between groups. For eyes that underwent cataract extraction, all subsequent measurements were excluded. Regression lines were fitted to thickness at baseline and 12, 24, 36, 48, 60, and 72 months for each patient who had at least 5 of the 7 thickness values recorded. The slopes of these individual regression lines were used as a summary of the change in thickness over time. Corneal thickness, IOP, and the rate of change of thickness (slopes of regression lines) were compared between groups using 2-sample *t* tests.

Corneal thickness was also measured in all patients in 1999–2000 (at 60 ± 7 months; range, 48- to 84-month study visits) with an ultrasonic pachymeter (DGH-500 Pachette; DGH Technologies, Exton, PA), as mandated by the OHTS, and compared between groups by using 2-sample *t* tests. The instrument was calibrated monthly by using a calibration device provided by the manufacturer. At each session, 5 readings were taken on each eye and averaged. One value, the mean of both eyes, was used for each patient.

At 92 ± 6 months (range, 78- to 108-month study visits), the corneas of 38 patients were examined with a tandem scanning confocal microscope, as previously described.[22] The remaining 17 either declined participation in this one-time confocal microscopy portion of the study, had undergone cataract extraction in both eyes, or were unavailable. By this time, many patients in the observation group had been treated for ocular hypertension (after the OHTS had been opened to treatment). There were 19 patients in the original medication group, 10 patients in the observation group who were never treated, and 9 patients in the observation group who had started treatment with topical pressure-lowering drugs. This last group included 3 of the 4 patients cited above who were not included in the 6-year thickness data because they progressed to glaucoma and were treated during the first 4 years of the study. Drugs used to lower the pressure in the medication arm were β-blockers, topical carbonic anhydrase inhibitors, α-agonists, prostaglandins, and pilocarpine, used alone or in combination to achieve the targeted IOP reduction to less than 21 mm Hg and at least a 20% reduction of the IOP at randomization. No single drug or combination of drugs was used in a large enough sample to allow analysis of subgroups of medications.

Confocal scans with the least lateral movement and no detectable anteroposterior movement of the cornea relative to the objective were selected for analysis of total corneal thickness, which was defined as the distance between the epithelial and endothelial peaks on the intensity profile of backscattered light from each scan.[22] Epithelial thickness was determined from images of the superficial epithelium and the subbasal nerves, in scans that included images of the subbasal nerve plexus and had no detectable ocular movement in the z-axis in this region. Both epithelial and total corneal thickness were determined from the number of video frames between images of the limiting structures as described by McLaren et al.[23] The investigator who operated the confocal microscope and analyzed the video scans from this instrument was masked to the treatment status of each patient. Epithelial and total thickness were compared between the untreated members of the observation group and the medication group using 2-sample *t* tests.

RESULTS

IOP and corneal thickness (measured by specular microscopy) are given in Table 1, and the corneal thickness values are graphed in Figure 1. In the observation group, the central corneal thickness increased at a mean rate of 1.5 ± 3.3 μm/yr (range, –4.2 to +9.4 μm/yr); and in the medication group, mean thickness decreased at a rate of −1.3 ± 2.8 μm/yr (range, −7.1 to +5.6 μm/yr; $P = 0.002$). Both rates were significantly different from zero ($P = 0.04$ and $P = 0.02$, respectively). By ultrasonic pachymetry 60 ± 7 months after the baseline examinations, central corneal thickness was 588.8 μm (n = 23) in the observation group and 561.9 μm (n = 27) in the medication group ($P = 0.007$).

By confocal microscopic examination 92 ± 6 months after the baseline examinations, epithelial thickness was 46.4 ± 4.9 μm in the members of the observation group who remained untreated and 41.3 ± 4.4 μm in the medication group ($P = 0.008$). Total thickness was 565.9 ± 22.1 μm in the untreated members of the observation group and 521.0 ± 36.1 μm in the medication group ($P = 0.001$). In the members of the observation group who had been treated, because of either progression to glaucoma (n = 4) or risk-based election (n = 5), the epithelial and total thicknesses were intermediate between those of the treated and untreated groups (Table 2).

DISCUSSION

Both IOP and corneal thickness are elevated in ocular hypertension; therefore, we suggested a possible causative relationship between the 2 variables. The thickness data from our longitudinal ancillary study afforded a chance to test this hypothesis in the Mayo OHTS cohort. Our data support the hypothesis that persistently elevated IOP causes a gradual

TABLE 1. Corneal Thickness and Intraocular Pressure During 6 Years (Mean ± SD)

Measurement	Group	Time of Examination (mo)						
		Baseline	12	24	36	48	60	72
Corneal thickness (μm)	Observation	599 ± 31	599 ± 38	596 ± 30	604 ± 36	603 ± 35	606 ± 35	607 ± 36
	Medication	579 ± 37	582 ± 40	579 ± 41	575 ± 38†	581 ± 40	572 ± 41‡	572 ± 38‡
Intraocular pressure (mm Hg)	Observation	25.0 ± 2.7	24.0 ± 2.7	22.6 ± 2.7	25.1 ± 3.8	23.8 ± 3.6	23.3 ± 4.1	24.0 ± 3.4
	Medication	25.4 ± 2.1	20.2 ± 2.1§	19.9 ± 2.3§	18.5 ± 2.6§	18.4 ± 2.0§	18.5 ± 2.2§	18.0 ± 2.1§
Number of subjects	Observation	27	27	26*	25*	23*	23	21‖
	Medication	27	27	26¶	26¶	27	27	26‖

*Four patients in the observation group progressed to glaucoma and began treatment at 14, 26, 36, and 42 months, after which their values were excluded.
†$P = 0.05$, ‡$P = 0.02$, and §$P \leq 0.001$ vs. observation group (two-sample t test, Bonferroni-adjusted for 7 comparisons).
‖One patient in each group did not reconsent to participate after 60 months, and 1 patient in the observation group did not have measurements recorded at the 72-month examination.
¶One patient in the medication group did not have measurements recorded at these examinations.

increase in corneal thickness and that pharmacologically lowering the pressure to normal levels reduces the increased thickness. Data from the measurement at 60 months by ultrasonic pachymetry confirm the difference between groups. Clearly, more data from a larger group of subjects are needed before we can accept this hypothesis. Continued measurement of corneal thickness within OHTS could offer the opportunity to test our hypothesis in a larger group, albeit without knowing thickness before the initiation of treatment in most subjects.

Corneal thicknesses reported to date in the overall OHTS are consistent with our findings. Thickness in the observation group was 574.5 ± 37.7 μm, and thickness in the medication group was 570.5 ± 38.9 μm ($P = 0.05$, n = 699 in each group).[24] Corneal thickness was different between these groups even though the patients in the medication group had been treated for only 2 to 5 years (thickness was measured 2 years after the 3-year OHTS recruitment period), compared with 6 years in this paper. The absolute magnitude of the difference between groups was greater in this study because the groups, by chance, already differed by a nonsignificant 20 μm at baseline (Table 1). In the larger overall OHTS, the baseline thicknesses in the medication and observation groups were presumably very similar. Regardless of this baseline difference, the rate of change in each group is significantly different from zero in each group, and in opposite directions, with the treatment group corneas becoming thinner with time and the observation group corneas becoming thicker.

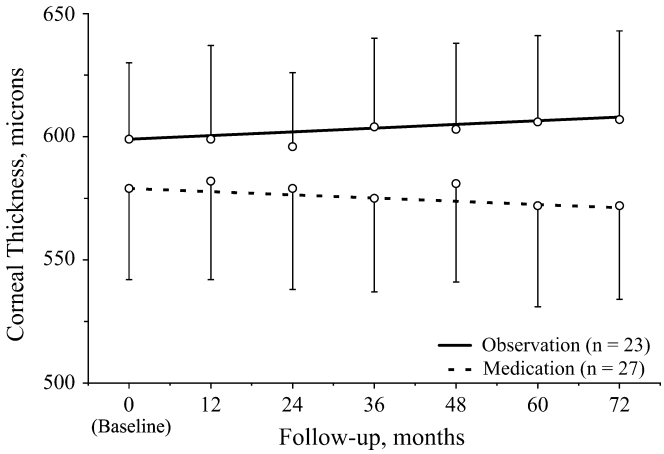

FIGURE 1. Change in corneal thickness during 6 years in observation and medication groups (mean ± SD). The 2 lines are provided as summaries of the changes with time in each group. The slope of each line is the mean of the individual slopes for that group. Each line is plotted to intersect the mean thickness at the baseline examination.

Our hypothesis that elevated IOP causes a gradual increase in corneal thickness is the opposite of the known association between thickness and IOP (ie, that elevated thickness increases the IOP measured by applanation tonometry).[4,8–11] This measurement artifact does not affect the changes in corneal thickness that we found; it only implies that the true IOP is not quite as high as we measured in the patients with the thicker corneas. In any case, the changes in thickness that we found (1.3–1.6 μm/yr) are too small to noticeably affect the differences between true and measured IOP, which are estimated to be 2 to 7 mm Hg for each 100-μm change in thickness.[4,8–11]

Few longitudinal studies (serial measurements in the same subjects over time) in treated and untreated patients with ocular hypertension have been published. A recent randomized, double-masked prospective study by Lass et al[25] showed a small decrease in corneal thickness in patients with ocular hypertension and glaucoma treated over a 1-year period with latanoprost or a latanoprost-timolol fixed combination. A previous double-masked randomized study of dorzolamide, timolol, and betaxolol by the same authors showed no identifiable trend toward corneal thinning at 1 year.[26] The small

TABLE 2. Epithelial and Total Corneal Thickness by Confocal Microscopy After 8 Years in OHTS (Mean ± SD)

Group	Number	Epithelial Thickness (μm)	Total Thickness (μm)
Observation—untreated	10	46.4 ± 4.9	565.9 ± 22.1
Observation—treated	9	43.8 ± 4.5	543.9 ± 35.9
Medication	19	41.3 ± 4.4*	521.0 ± 36.1*

*$P < 0.01$ vs. untreated patients in observation group (2-sample t test).

decrease in thickness that we found in the treated group (1.3 μm/yr during 6 years) is unlikely to be detected in longitudinal studies limited to only 1 year. Longitudinal studies are more powerful than cross-sectional studies (each subject is measured only once), but they also require much more time and expense.

Cross-sectional studies of corneal thickness in subjects with treated and untreated ocular hypertension have shown mixed results. Korey et al[1] found no difference in corneal thickness in subjects with normal IOP, untreated ocular hypertension, treated ocular hypertension, or treated glaucoma. Subjects had been treated for an average of only 2 years, however. The results of the study by Korey et al have been contradicted by a number of subsequent studies that found increased corneal thickness in ocular hypertension. Both Argus et al[2] and Herndon et al[3] found greater corneal thickness in ocular hypertensives than in normal subjects or patients with glaucoma. Wolfs et al[4] found greater corneal thickness in 13 patients with ocular hypertension than in 352 normal subjects. Eight of the ocular hypertensives had been treated, and their thicknesses were less (548 μm) than the 5 untreated ocular hypertensives (562 μm), although the difference was not statistically significant. Copt et al[5] found thicker corneas in eyes with ocular hypertension than in normal eyes and those with glaucoma. Many of the eyes with ocular hypertension were under treatment, but their data were not presented separately. Herman et al[6] found greater corneal thickness in 55 single-center OHTS subjects than in 55 age-matched normals. Varma et al[7] also found thicker corneas in eyes with ocular hypertension than in those with glaucoma and in normal eyes.[27] Nineteen percent of the ocular hypertensives were treated, but their data were not presented separately.

Corneal pachymetry with the specular microscope measures total corneal thickness, including the epithelium (this is also true of standard ultrasonic pachymetry). The change in thickness of 8 to 10 μm over 6 years in both the medication and observation groups in this ancillary study might represent changes in epithelial thickness, stromal thickness, or both. Epithelial thickness during study years 7 to 9 measured by confocal microscopy was 5 μm (11%) thinner in the treated group than it was in the untreated patients in the observation group (Table 2). If the epithelial thickness was similar in the 2 groups at baseline, a substantial portion of the corneal thinning in the medication group could be attributed to epithelial thinning, perhaps as a direct effect of topical therapy on the epithelium and tear film. Previous studies have shown abnormalities in the ocular surface[28] and the epithelial barrier function[29] in patients taking β-blocker eye drops for glaucoma. Prostaglandin F analogs seem to leave both the ocular surface[28] and the epithelial barrier function relatively unchanged.[30] Elevated IOP is unlikely to affect epithelial thickness, because even in the observation group the epithelial thickness was no greater than 48.6[22] and 46 μm,[31] as measured by the same method in normal subjects. The total thicknesses measured by confocal microscopy were substantially less than those measured earlier by specular microscopy. Differences in thickness determined by different methods of corneal pachymetry have been discussed.[23] To eliminate this variable, we used the same contact specular microscope for all measurements of corneal thickness in our 6-year sequential study.

The corneal thinning in excess of epithelial thinning in the medication group suggests that the stroma became thinner. Likewise, corneal thickening in the observation group during 6 years of this study suggests stromal thickening, because epithelial thickness was not greater than normal in this group. If chronic increases in IOP indeed increase stromal thickness and chronic normalization of IOP reverses this trend, this response to chronic pressure changes is different from that found after acute changes in IOP. Ehlers[14] found that short-term decreases in IOP after treatment increased corneal thickness in glaucomatous eyes with original pressures above 30 mm Hg but did not change thickness in normal eyes, although the reduction in IOP in normal eyes was much less.[14] Other studies found that short-term increases in IOP decreased the thickness of a cornea that was swollen[13,15] and did not change[12,13] or increased[16] thickness in corneas that were of normal thickness.

Changes in corneal thickness in response to a long-term change in IOP, however, may be quite different, and conflicting results have appeared in the few cross-sectional studies that address this topic. With respect to persistently elevated IOP, both Ytteborg and Dohlman[17] and Ehlers[14] found no difference in the corneal thickness between hypertensive and normotensive eyes in patients with unilateral glaucoma and IOP above 30 mm Hg in 1 eye and normal IOP in the other eye. Ytteborg and Dohlman did not mention if their patients were under treatment. Ehlers, however, included patients under treatment who stopped their medications 2 days before the measurement. With respect to persistently lowered IOP, Ytteborg and Dohlman found no difference in corneal thickness between the right and left eyes of 8 patients with unilateral retinal detachments and IOP 7 mm Hg or less in the eye with the detachment and at least 6 mm Hg lower than the opposite normal eye.[17] In patients with unilateral retinal detachments for 1 week to several months, however, Ehlers found thicker corneas in the eye with the detachment if the IOP was reduced compared with the other eye.[18]

How might long-term increases in IOP gradually increase stromal thickness? In the context of our current understanding of corneal physiology, we do not have evidence for a specific mechanism. However, to account for the chronic changes in thickness that we found, only extremely small changes in endothelial barrier or pump function or in the corneal thickness-hydration-swelling pressure relationship[32] would be needed in response to elevated IOP and its treatment. In most studies, the corneal thickness of ocular hypertensive patients was about 30 μm greater than that of normal subjects.[2–7] A constant swelling rate of 1.6 μm/yr, as we measured, could thicken corneas by this amount in 19 years, so the hypothesis is at least plausible. On the other hand, if swelling is in fact constant throughout ocular hypertension, one might expect that older individuals who have been hypertensive longer would have thicker corneas. Thickness was unrelated to age, however, in our subjects at baseline.[6] In the OHTS, older subjects had thinner rather than thicker corneas, although the majority of the patients were under treatment by the time the thickness was measured.[33] Corneal swelling may not be constant but may change more dramatically at the onset of ocular hypertension

and more moderately during the chronic phase that we measured. No difference in endothelial cell density between the observation and medication groups was found at any time during the study.[20]

Corneal thickness in patients with ocular hypertension is likely determined by a complex relationship between age, IOP, corneal endothelial function, and the possible effects of hypotensive medications. Because of this complex myriad of factors, we cannot discern a single physiologic explanation for the changes in corneal thickness over time in treated and untreated ocular hypertensive subjects. The magnitude of the changes, however, seems to be small and therefore unlikely to lead to functional changes in vision or corneal clarity. Because treatment is now provided to nearly all subjects enrolled in the OHTS, investigators will have the opportunity to observe this phenomenon in a larger population of treated subjects with ocular hypertension. If the larger population behaves in a similar way as our sample, corneal thickness may not be an independent variable in the OHTS. The small changes in thickness over time that we found, however, are unlikely to decrease the power of corneal thickness as a predictor of the development of primary open angle glaucoma in patients with ocular hypertension.[34] The effect of IOP and its treatment on corneal thickness may be another piece in the glaucoma puzzle.[35]

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