Central Corneal Thickness Correlated with Glaucoma Damage and Rate of Progression

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PURPOSE. To evaluate whether the amount of glaucomatous optic nerve damage at presentation of the patient and the rate of progression of glaucoma during follow-up are related to central corneal thickness.

METHODS. The prospective observational clinical study included 861 eyes of 454 white subjects (239 normal eyes of 121 subjects, 250 ocular hypertensive eyes of 118 patients, 372 eyes of 215 patients with chronic open-angle glaucoma). For 567 eyes (304 patients) with ocular hypertension or chronic open-angle glaucoma, follow-up examinations were performed, with a mean follow-up time of 62.7 ± 33.2 months (median, 60.8; range, 6.2–124.9). All patients underwent quantitative and morphometric evaluation of color stereo optic disc photographs and white-on-white visual field examination. Central corneal thickness was measured by corneal pachymetry.

RESULTS. Central corneal thickness correlated significantly (P < 0.001) and positively with the area of the neuroretinal rim and negatively with the loss of visual field. Development or progression of glaucomatous visual field defects detected in 119 (21.0%) eyes was statistically independent of central corneal thickness, in univariate (P = 0.99) and multivariate Cox regression analyses (P = 0.19).

CONCLUSIONS. At the time of patient referral, the amount of glaucomatous optic nerve damage correlated significantly with a thin central cornea. Progression of glaucomatous optic nerve neuropathy was independent of central corneal thickness, suggesting that central corneal thickness may not play a major role in the pathogenesis of progressive glaucomatous optic nerve damage. (Invest Ophthalmol Vis Sci. 2005;46:1269–1274) DOI:10.1167/iovs.04-0265

Based on the studies by Goldmann and Schmidt1 and Ehlers et al.2 previous studies have reemphasized the importance of central corneal thickness in applanation measurement of intraocular pressure.3 In the Ocular Hypertension Treatment Study (OHTS), central corneal thickness was found to be a powerful predictor for the development of primary open-angle glaucoma.4 In a recent investigation by Herndon et al.,5 an association of central corneal thickness and severity of primary open-angle glaucoma was reported. Patients with primary open-angle glaucoma who had thinner corneas tended to have more severe glaucomatous damage on initial examination by a glaucoma specialist. Central corneal thickness was the most consistent predictor of degree of glaucomatous damage. In other studies, the effect of central corneal thickness on ocular hypertension and normal-tension glaucoma was evaluated.6–14

Based on these preceding investigations, it was the purpose of the present study to reevaluate whether in patients with chronic open-angle glaucoma, central corneal thickness correlates with the amount of optic nerve damage and whether it influences the risk of further progression of the disease.

METHODS

The study included a total of 861 eyes of 454 white subjects, of which 622 eyes of 333 subjects had either ocular hypertension or glaucoma and 239 eyes of 121 subjects served as the normal control. Of the 622 eyes in the ocular hypertension-glaucoma group there were 250 ocular hypertensive eyes, 150 eyes with preperimetric open-angle glaucoma, 65 eyes with perimetric primary open-angle glaucoma, 24 eyes with secondary open-angle glaucoma due to reasons such as pseudoxefoliation or primary melanin pigment dispersion syndrome, and 133 eyes with normal-tension glaucoma (Table 1). Mean age was 46.8 ± 13.8 years (median, 48.4; range, 11–76), mean refractive error was −0.86 ± 2.26 D (median, 0; range, −7.78 to +7.0). All subjects and patients included in the study had an open anterior chamber angle and visual acuity of 20/25 (best corrected visual acuity) or better. On the day of examination, intraocular pressure measured by Goldmann applanation tonometry was ≤21 mm Hg in all individuals. In the group of subjects with ocular hypertension, 42.4% of eyes were receiving topical β-blockers; 5.6%, topical carbonic anhydrase inhibitors; 3.2%, latanoprost; and 6.8%, pilocarpine. The glaucoma subgroups did not vary in type of topical antiglaucoma treatment—that is, topical carbonic anhydrase inhibitors were given to a similar percentage of the patients in the various glaucoma subgroups. In the whole group of patients with glaucoma, 41.8% of eyes were receiving topical β-blockers; 8.4%, topical carbonic anhydrase inhibitors; 1.6%, latanoprost; and 7.6%, pilocarpine.

Exclusion criteria were all eye diseases other than glaucoma, diabetes mellitus, corneal disease, and a myopic refractive error ≥−8 D. Contact lenses were not to have been worn for at least 3 weeks before the examinations. The patients were referred by their ophthalmologists for further diagnosis and follow-up of glaucoma and were prospectively and consecutively evaluated. The normal subjects were recruited from the administrative university staff who were asked to serve as control subjects, or they were patients who attended the hospital for diseases in the contralateral eye that was not included in the study. These diseases, such as rhegmatogenous retinal detachment, did not primarily affect the optic nerve. Informed consent was obtained from each subject before enrollment. The patients were part of a prospective study on the progression of glaucoma (Erlangen Glaucoma Register). Institutional Review Board/Ethics Committee approval was obtained at the start of the study, in compliance with the Declaration of Helsinki.

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In the eyes affected by primary open-angle glaucoma, no obvious reason for the elevated intraocular pressure could be detected. Criteria for the diagnosis of normal-tension glaucoma were maximum intraocular pressure \( \leq 21 \) mm Hg in at least two 24-hour pressure profiles obtained by slit lamp applanation tonometry and containing measurements at 5 PM, 9 PM, 12 AM, 7 AM, and 12 PM. Ophthalmoscopy; medical history; and neuroradiologic, neurologic, and medical examinations did not reveal any other reason, such as intrasellar or suprasellar tumors, retinal vessel occlusions, optic disc drusen, or nonarteritic anterior ischemic optic neuropathy, for optic nerve damage than glaucoma. Ocular hypertensive eyes had intraocular pressure measurements \( >21 \) mm Hg without visual field defects and without glaucomatous abnormalities of the optic nerve head. Preperimetric glaucoma was defined by glaucomatous abnormalities of the optic nerve head and normal white-on-white visual fields. Perimetric glaucoma was defined by glaucomatous abnormalities of the optic nerve head and glaucomatous visual field defects. A glaucomatous visual field defect was defined as an Octopus G1 field (Octopus perimeter; Interzeag, Schlieren, Switzerland) with (1) at least three adjacent test points having a deviation of \( \geq 5 \) dB and one test point with a deviation \( >10 \) dB lower, (2) at least two adjacent test points with a deviation \( \leq 10 \) dB, (3) at least three adjacent test points with a deviation \( \geq 5 \) dB abutting the nasal horizontal meridian, or (4) a mean visual field defect of \( >2 \) dB.15 The rate of false-positive answers and rate of false-negative answers had to be equal to or \( <15\% \). To define the baseline of the visual field examinations, we performed two visual field tests on patients before they were included in the study. Glaucomatous changes of the optic nerve head included an unusually small neuroretinal rim area in relation to the optic disc size, an abnormal shape of the neuroretinal rim, or cup-to-disc diameter ratios vertically higher than horizontally, and localized or diffuse retinal nerve fiber layer defects.16 Because all glaucomatous eyes examined in the study had to show glaucomatous abnormalities of the optic disc, the inclusion of normotensive eyes with nonglaucomatous optic nerve damage in the normal-tension glaucoma subgroup was not likely.

For all eyes, 15° color stereo optic disc transparencies had been taken with a telecentric fundus camera (30° fundus camera, equipped with a 15° converter; Carl Zeiss Meditec, Oberkochen, Germany). The disc slides were projected in a scale of 1 to 15. The outlines of the optic cup, optic disc, peripapillary scleral ring, and alpha and beta zones of peripapillary atrophy were plotted on paper and morphometrically analyzed. To obtain values in absolute size units—that is, millimeter or square millimeter—the ocular and photographic magnification was corrected by using the Littmann method.17 The optic cup was defined on the basis of contour and not of pallor. The border of the optic disc was identical with the inner side of the peripapillary scleral ring. Peripapillary atrophy was differentiated into a peripheral alpha zone with irregular pigmentation, and a central beta zone with visible sclera and visible large choroidal vessels. To assess the configuration and the regional distribution of the neuroretinal rim and peripapillary atrophy, the optic disc and the peripapillary region were divided into four sectors. The temporal inferior sector and the temporal superior sector were right angled and were tilted 15° temporal to the vertical optic disc axis. The temporal horizontal sector and the nasal sector covered the remaining area. The diameters of the retinal arterioles were measured at the optic disc border in the inferotemporal, superotemporal, superonasal, and inferonasal region. The assessment of the optic disc slides was performed in a masked fashion so that the examiners were unaware of the diagnosis, intraocular pressure, and visual field data. The method has already been described in detail.18,19 In addition, each of the subjects and patients had to have central corneal pachymetry. Each patient’s central corneal thickness was measured 10 times with an ultrasonic pachymeter (model AL-11000; Tomey, Erlangen, Germany). The mean of the 10 measurements was not revealed for further statistical analysis. To exclude diurnal variations of the measurements, corneal pachymetry was routinely performed between 10 AM and 1 PM. Applanation tonometry was performed after corneal pachymetry. Each follow-up examination included applanation tonometry at 5 PM,
Progression of glaucomatous visual field loss was defined by point-wise regression analysis for each of the 59 locations in the visual field. Point-wise progression was assumed if a difference >1 dB/y was observed for the local defect. A point-wise improvement (learning effect or random variation) was assumed if a difference < -1 dB was observed. An eye was classified as progressive, if the number of locations with progression was significantly higher than the number of locations with improvement (binomial test, \( P = 0.05 \) two-sided). For each eye, the first follow-up measurement with progression, as defined, entered the analysis. In subsequent analyses, progression was treated as a time-to-event variable. Kaplan-Meier and simple and multiple Cox regression with forward variable selection were applied. According to the skewed distribution of some variables, for each quantitative variable, categorization according to tertiles were used.

Of the 622 eyes (333 subjects) in the ocular hypertensive-glaucoma group only 567 eyes (304 subjects) with at least a 6-month follow-up were included in the statistical analysis. The mean follow-up time of these 567 eyes was 62.7 months (median, 60.8; range, 6.2–124.9 months), which consisted of a mean of 6.4 ± 2.4 examinations (median, 6.0; range, 3–12). Of the 55 eyes excluded from the analysis, 12 eyes (7 subjects) were "true" withdrawals (i.e., they withdrew from the study before the follow-up period ended). The remaining 43 eyes (22 subjects) had <6 months of follow-up. Of the total 55 eyes excluded from the statistical analysis, 47 (18.8%) of 250 eyes were in the ocular hypertensive group, 5 (2.0%) of 150 eyes in the preperimetric primary open-angle glaucoma group, 0 of 65 eyes in the perimetric primary open-angle glaucoma group, 2 (8.3%) of 24 eyes in the secondary open-angle glaucoma group, and 3 of 135 eyes (2.3%) in the normal-tension glaucoma group.

In the statistical analysis, means and standard deviations of potential predictors are given for the stable eyes and progressive eyes separately. Confirmatory analysis used Cox proportional hazard regression analysis adjusting for different follow-up of the patients. Dependency of left and right eyes from the same subject was taken into account conservatively: \( \chi^2 \) results were multiplied by the factor, number of patients divided by number of eyes. Thus, significance tests were performed with respect to the number of patients instead of the number of eyes. Except for confirmatory analyses concerning central corneal thickness, only corrected probabilities are presented, in correspondence with the rationale of the present study. With 119 eyes showing progression or new development of visual field loss, hazard rates of 1.51 were detectable (assuming a level of significance of 0.02 two-sided according to our adjustment for patients contributing two eyes, and a power of 0.8)20 statistical analysis was performed by using a commercially available statistical software package (SPSS for Windows, version 11.5; SPSS, Chicago, IL).

**RESULTS**

In the whole study group, mean central corneal thickness measured 571.1 ± 38.3 \( \mu \)m (median, 569; range, 438–692). Thickness was statistically independent of refractive error \( (P = 0.91) \), gender \( (P = 0.07) \), and right or left eye \( (P = 0.65) \). In a similar way, it was statistically independent of optic disc area \( (P = 0.10; \text{correlation coefficient, } r^2 = 0.06) \), area of the alpha \( (P = 0.11) \) and beta \( (P = 0.12) \) zones of peripapillary atrophy, and diameters of the temporal inferior \( (P = 0.58) \), temporal superior \( (P = 0.07) \), nasal superior \( (P = 0.12) \), and nasal inferior \( (P = 0.58) \) retinal arteries, determined at the optic disc border. Central corneal thickness correlated significantly and positively with the area of the neuroretinal rim as a whole \( (P < 0.001) \) and measured separately in the four optic disc sectors (temporal horizontal rim area, \( P = 0.002 \); temporal inferior rim area, \( P < 0.001 \); temporal superior rim area, \( P = 0.001 \); nasal rim area, \( P = 0.041) \). Thickness correlated negatively with mean visual field defect \( (P < 0.001; \text{Fig. 1}) \).

Differentiating the whole study population, mean central corneal thickness measured 570.8 ± 37.1 \( \mu \)m (median, 568; range, 494–682) in the normal group. Central corneal thickness was statistically independent of age \( (P = 0.71) \), refractive error \( (P = 0.94) \), and right or left eye \( (P = 0.47) \). It was positively correlated with optic disc area \( (P = 0.008 \text{ before and } P = 0.05 \text{ after correction for dependency between eyes of the same subject}) \). In the glaucoma group, mean central corneal thickness measured 571.2 ± 38.8 \( \mu \)m (median, 569; range, 458–692). It was negatively correlated with age \( (P < 0.001) \). There was no significant correlation with optic disc area \( (P = 0.77) \). As in the normal group, mean thickness was statistically independent of refractive error \( (P = 0.87) \) and right or left eye \( (P = 0.93) \). There was no significant \( (P = 0.82) \) difference in corneal thickness between the normal group and the whole glaucoma group including the patients with primary or secondary open-angle glaucoma.

Between the study groups, the central cornea was significantly thicker in the ocular hypertensive group than in the normal \( (P = 0.001) \), primary open-angle glaucoma \( (P = 0.001) \), secondary open-angle glaucoma \( (P < 0.001) \), and normal-tension glaucoma \( (P < 0.001; \text{Table 1}) \) groups. In the primary open-angle glaucoma group it was larger than in the normal-tension group \( (P < 0.001) \) and in the secondary open-angle glaucoma group \( (P = 0.043/0.14 \text{ after correction for dependency between eyes of the same subject}) \). The primary open-angle glaucoma and normal groups did not vary significantly in mean central corneal thickness \( (P = 0.96) \). Central corneal thickness was significantly \( (P < 0.001) \) thinner in the normal-tension glaucoma group than in the normal group.

In the glaucoma group and the ocular hypertensive group, 448 (79.0%) eyes remained stable and 119 (21.0%) eyes showed progression of visual field loss. In the ocular hypertensive group, 28 (13.8%) of 203 eyes showed a development of visual field defects; in the preperimetric primary open-angle glaucoma group, 13 (8.8%) of 147 eyes showed development of perimetric defects; 18 (27.7%) of the 65 eyes with perimetric primary open-angle glaucoma showed progression of glaucomatous visual field defects; and 52 (40.0%) of 130 eyes with normal-tension glaucoma and 8 (36.4%) of 22 eyes with secondary open-angle glaucoma experienced a worsening of the visual field. In the confirmatory analysis, simple and multiple Cox regression analyses were performed, with the event of...
development or progression of visual field defect as the dependent parameter. The group of eyes with progressive visual field defects was significantly ($P < 0.001$) older than the group without progression (Table 2). After adjustment for age, no differences in gender ($P = 0.08$) and refractive error were observed ($P = 0.66$). At baseline of the study, the group of eyes with eventual progression and the group of eyes without progression did not vary in size of the optic disc ($P = 0.57$) and of alpha ($P = 0.27$) or beta ($P = 0.15$) zone of peripapillary atrophy (Table 2). In the group with progressive visual field defects compared with the nonprogressive group, neuroretinal rim area was significantly ($P = 0.001$) smaller, and beta zone of peripapillary atrophy measured larger ($P = 0.056$; Table 2).

When the whole group of patients with follow-up examination—that is, 567 eyes (304 patients) of the glaucoma group and the ocular hypertensive group—was divided into three subgroups equal in size according to central corneal thickness, Kaplan-Meier analysis revealed that central corneal thickness did not have a statistically significant influence on progression ($P = 0.99$; Fig. 2).

**DISCUSSION**

For almost half a decade, applanation tonometry as introduced by Goldmann has been the gold standard for measuring intraocular pressure. It took the place of indentation tonometry as the routine method of determining intraocular pressure, because applanation tonometry compared with indentation tonometry is influenced by less parameters, such as scleral rigidity. As already discussed by Goldmann and Schmidt, central corneal thickness remains a factor with a possible impact on the intraocular pressure measurements by applanation tonometry. When optical pachymeters for measurement of corneal thickness became available, an increasing number of studies addressed the question of whether and how much applanation tonometry in the presence of glaucomatous changes of the optic nerve head and visual field) have abnormally thin corneas.

In a parallel manner, the results of the present study suggest that, when referred to hospitals, patients with chronic open-angle glaucoma have more advanced glaucomatous optic nerve damage if the cornea is relatively thin than if the cornea is relatively thick. This may be a selection artifact, since patients with thick corneas may be referred earlier because they have falsely higher intraocular pressure measurements than patients with thin corneas. The present study confirms a recent investigation by Herndon et al. who examined 350 eyes of 190 patients.
consecutive patients with primary open-angle glaucoma at the first presentation to a glaucoma specialist, and who analyzed each patient’s general data, such as age, sex, race, and family history of glaucoma, as well as ocular data such as visual acuity, refractive error, intraocular pressure, central corneal thickness, visual field indices, and vertical and horizontal cup-to-disc ratios. They found that lower central corneal thickness measurements correlated significantly and inversely with the stage of glaucomatous optic neuropathy, when measured according to the Advanced Glaucoma Intervention Study (AGIS) scale, visual field loss, and increased cup-to-disc ratios.

In the present study, the rate of eventual progression of glaucomatous visual field loss was statistically independent of central corneal thickness (Table 2; Fig. 2). Central corneal thickness measurements did not differ significantly between eyes with progression and eyes with stable visual fields. Correspondingly, the rate of progression did not vary between subgroups of eyes with different central corneal thickness (Fig. 2). This result is in contrast to the OHTS, in which central corneal thickness was a significant risk factor for progression of ocular hypertension to primary open-angle glaucoma. The OHTS is the first study to document prospectively that a thinner central corneal measurement may predict the development of primary open-angle glaucoma. Corneal thickness was a strong predictive factor for the development of primary open-angle glaucoma, even after adjusting for the effects of baseline age, intraocular pressure, vertical cup-to-disc ratio, and visual field indices. Participants with a corneal thickness of 555 μm or less had a threefold risk for developing primary open-angle glaucoma than did participants who had a corneal thickness of more than 588 μm. This inverse relationship was found across the ranges of baseline intraocular pressure and baseline vertical cup-to-disc ratios. One of the reasons for the discrepancies in the results between the OHTS and the present study may be differences in the protocol. For example, the OHTS measured only central corneal thickness for 3 years, made five measurements once a year, did not control for diurnal variation, made measurements after tonometry, and began measuring central thickness 2 years after randomization of the last participant. In the present study, central corneal thickness was measured before tonometry was performed, corneal pachymetry was performed at the same time of day, 10 measurements were taken, and the mean of these 10 measurements was used for further statistical analysis. Another, perhaps even more important question may be whether and how the OHTS corrected the intraocular pressure measurement values for their dependence on central corneal thickness and whether after that correction, the central corneal thickness measurements remained significantly associated with the rate of progression.

The possible effect of the topical medications used by the patients in this study on corneal thickness was statistically evaluated. Mean central corneal thickness did not vary significantly (P > 0.80) between the normal and glaucoma groups. We performed a univariate analysis revealing no significant association between the use of topical β-blockers or topical carbonic anhydrase inhibitors and central corneal thickness. Central corneal thickness tended to be greater in the group of eyes that received latanoprost (P = 0.007 before and P = 0.048 after correction for dependency between eyes of the same subject) and to be smaller in the group of eyes receiving pilocarpine (P = 0.033/0.119). After adjustment for topical medication in simple and multiple Cox regression analysis, all results concerning influencing factors on glaucoma progression, as presented in Table 2, remained unchanged.

We were interested to note that central corneal thickness significantly (P = 0.008/0.05 after correction for dependency between eyes of the same subject) and positively correlated with optic disc area in the present study. This finding may correspond with those in a previous study, in which the horizontal and vertical corneal diameters and the anterior corneal curvature radius correlated significantly and positively with the optic disc area, suggesting that eyes with a large optic disc have a large and thick cornea. One may infer, that if a thin cornea were a risk factor for progression of chronic open-angle glaucoma, a small optic disc would also be a risk factor. A small optic disc area has not been identified yet, however, as a risk factor for progression of chronic open-angle glaucoma, which may therefore support the conclusion of the present study that central corneal thickness may not play a major role in the progression of chronic open-angle glaucoma.

In summary, the present study showed a highly significant association between a thin central cornea and more pronounced glaucomatous optic nerve damage in patients at the time of first referral to a glaucoma center, confirming results in a recent study by Herndon et al. One of the reasons that may explain the relationship between central corneal thickness and the amount of glaucomatous optic nerve damage at the time of presentation to a glaucoma specialist, may be a selection artifact by the referring ophthalmologists. In the present study, central corneal thickness did not have a statistically significant influence on the rate of progression of glaucoma, contradicting the OHTS. Histomorphometric studies suggesting a pathogenic role of a thinned lamina cribrosa for an increased glaucoma susceptibility have not shown a relationship between a thin lamina cribrosa and a thin cornea, and may thus not support the clinical observation of a relationship between a thin cornea and an increased susceptibility to glaucoma. In view of the data of the present study, patients with thin corneas are at a higher risk for delayed detection of glaucoma; however, they are not at a higher risk for progression of glaucoma.

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