Central Corneal Thickness and Thickness of the Lamina Cribrosa in Human Eyes

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PURPOSE. Since central corneal thickness may inversely influence the amount and rate of progression of glaucomatous optic nerve damage and because lamina cribrosa thickness may be of importance in susceptibility to glaucoma, it was the purpose of the present study to evaluate whether central corneal thickness is related to lamina cribrosa thickness.

METHODS. The histomorphometric study included 111 enucleated nonglaucomatous eyes of 111 white subjects. On anterior–posterior histologic sections through the pupil and the central optic disc region, the thickness of the cornea, lamina cribrosa, and peripapillary sclera and the shortest distance between the intraocular space and the cerebrospinal fluid space were measured. Axial length ranged between 20 and 32 mm.

RESULTS. Mean central corneal thickness (mean ± SD: 616.6 ± 108.3 µm) and mean central lamina cribrosa thickness (378.1 ± 117.8 µm) were statistically independent of each other (P = 0.15; correlation coefficient, r = 0.14). In a similar manner, lamina cribrosa thickness at the optic disc border was statistically independent of central corneal thickness (P = 0.51; r = 0.06) and peripheral corneal thickness (P = 0.34; r = 0.09). In a parallel way, peripapillary scleral thickness (P = 0.84) and the shortest distance between the prelaminar space and cerebrospinal fluid space (P = 0.10) were statistically independent of central corneal thickness.

CONCLUSIONS. In nonglaucomatous human globes, central corneal thickness may not correlate significantly with lamina cribrosa thickness, peripapillary scleral thickness, and shortest distance between intraocular space and cerebrospinal fluid space. Histologic artifact and sectioning methods could partially account for the lack of an association. The study results may suggest clinically that an assumed relationship between central corneal thickness and susceptibility to glaucoma cannot be explained by an anatomic correspondence between corneal thickness and histomorphometry of the optic nerve head. (Invest Ophthalmol Vis Sci. 2005;46:1275–1279) DOI: 10.1167/iovs.04-0851

In the Ocular Hypertension Treatment Study (OHTS), central corneal thickness has recently been recognized as a significant risk factor for progression of ocular hypertension to primary open-angle glaucoma.1 The OHTS was the first study to demonstrate prospectively that a thinner central cornea may predict the development of primary open-angle glaucoma. In a parallel manner, other investigations have reported that eyes with normal-pressure glaucoma have a thinner central cornea than normal eyes, whereas eyes with ocular hypertension can have a thicker central cornea than normal eyes.2–8 Recently, Herndon et al.9 demonstrated that central corneal thickness correlates inversely with the amount of glaucomatous optic nerve damage at the time of referral of the patient to a glaucoma center. In that study, central corneal thickness was the most consistent predictor of the degree of glaucomatous damage.

Other studies have discussed the pathogenic role as a pressure barrier between the intraocular space and the cerebrospinal fluid space that the anatomy of the lamina cribrosa may play in optic nerve diseases such as the glaucomas.10–14 Histomorphometric investigations have shown that eyes with advanced glaucomatous optic nerve damage have a markedly thinner lamina cribrosa than do normal eyes, which may explain an increased risk of further progression in patients with chronic open-angle glaucoma in an advanced stage of the disease compared with patients with an early stage of glaucoma.15–17 Another histomorphometric investigation suggested that the lamina cribrosa is significantly thinner in highly myopic eyes than in non–highly myopic eyes, which may be a reason for the presumably higher susceptibility to glaucoma of highly myopic eyes versus non–highly myopic eyes.18

Because the lamina cribrosa forms the bottom of the optic disc, and because the dimensions and shape of the cornea are correlated with the dimensions of the optic disc,19,20 we, while looking for a possible explanation of the relationship between corneal thickness and susceptibility to glaucoma, conducted the present study to evaluate whether the central thickness of the cornea is related to the thickness of the lamina cribrosa in human eyes.

METHODS

The study included 111 human globes (111 living donors, all white) in which the optic nerve was affected neither by glaucoma nor any other disease on gross inspection and microscopic examination. Mean age was 60.2 ± 15.0 years. The eyes had been enucleated because of malignant choroidal melanomas in which migrating cells did not infiltrate the trabecular meshwork, and the globes had been removed by orbital exenteration because of orbital tumors not involving the optic nerve. The peripapillary region, as well as the optic nerve head itself, were free of tumor. Visual acuity depended on the degree of cataract, vitreous opacities, and foveal involvement of the tumor. At the time when the eyes were enucleated, no other treatment modalities, such as endoresection of the tumor or radiologic brachytherapy, were available, or they were thought not to be suitable for removal of the intraocular tumor because of its location and size. The corneal endothelium was present in all eyes. There were no signs that edema of the corneal stroma or epithelium existed before the enucleation of the globe.

Immediately after enucleation, the globes were fixed in a solution of 4% formaldehyde and 1% glutaraldehyde. They remained in the fixation agent for ~1 week, before they were further processed for histologic sectioning. The globes were prepared in a routine manner for light microscopy. An anterior–posterior segment going through the...
pupil and the optic nerve was cut out of the fixed globes. These segments were dehydrated in alcohol, imbedded in paraffin, and sectioned for light microscopy. Most of the eyes were stained by the periodic-acid-Schiff (PAS) method, the remaining eyes were stained by hematoxylin-eosin. For all eyes, one section running through the central part of the optic disc was selected for further histomorphometric evaluation. According to the scale in the eyepiece of the microscope, the magnification at which the measurements were performed was ×100.

Axial length and horizontal and vertical diameter of the globes were measured macroscopically before sectioning of the globes. Based on axial length, the total study sample was divided into a non– highly myopic study group with an axial length of <26 mm (n = 89 globes; 80.2%) and a highly myopic study group with an axial length of ≥26 mm (n = 22; 19.8%). Histomorphometrically, we measured the following: (1) the thickness of the lamina cribrosa in the center of the optic disc; at the optic disc border, and in the intermediary positions between the center and the border of the optic disc; (2) the shortest distance between the prelaminar space and the cerebrospinal fluid space; (5) the thickness of the peripapillary sclera at the optic disc border; (4) and the thickness of the cornea in the center, at the limbus, and in the intermediary positions between the center and the limbus.

The anterior and posterior border of the lamina cribrosa were outlined on the histologic specimens. For the anterior border, care was taken to differentiate the lamina cribrosa from overlaying glial tissue. For the posterior border, care was taken to delineate the lamina cribrosa from the optic nerve. Staining of the histologic sections by the PAS method enhanced the difference between the lamina cribrosa and the surrounding tissue. The reproducibility of the technique was evaluated in a previous study in which 10 randomly selected histologic optic disc sections were reevaluated 10 times. The coefficient of variation, defined as the ratio of the mean of the standard deviations of the reevaluations divided by the mean of the means, was 0.143.

For statistical analysis, the means and standard deviations, medians, and ranges are presented. For the comparison of the study groups, statistical tests for unpaired samples were applied. The level of significance was 0.05 (two-sided) in all statistical tests. The statistical analysis was performed on computer (SPSSWIN, ver. 11.5; SPSS, Chicago, IL).

RESULTS

The mean measurements were: axial length of the globes, 24.6 ± 2.1 mm (median, 24.0; range, 20–32); horizontal globe diameter, 23.7 ± 1.5 mm (median, 23.0; range, 20–30); and vertical globe diameter 23.5 ± 1.1 mm (median, 24.0; range, 21–26).

The mean central corneal thickness measured 616.6 ± 108.3 μm (media, 612 μm). Comparison with the intravital pachymetric measurements of central corneal thickness published in the literature shows a correction factor for the histomorphometric determinations of central corneal thickness of approximately 1:1.21 The histomorphometric measurements of central corneal thickness were independent of age (P = 0.88), gender (P = 0.43), right or left eye (P = 0.40), axial length (P = 0.80), and horizontal (P = 0.06) and vertical (P = 0.80) globe diameters.

The mean central lamina cribrosa thickness was 378.1 ± 117.8 μm (median, 360 μm). The measurement was independent of age (P = 0.82), gender (P = 0.60), right or left eye (P = 0.91), and horizontal (P = 0.44) and vertical (P = 0.32) globe diameter. The mean central lamina cribrosa thickness correlated significantly and negatively with axial length (P = 0.03; correlation coefficient, r = −0.21; Fig. 1). Correspondingly, the lamina cribrosa was significantly thinner in the highly myopic group than in the non– highly myopic group (322.2 ± 144.3 μm vs. 391.9 ± 106.8 μm; P = 0.04). Within the non– highly myopic group, central lamina cribrosa thickness was statistically independent of axial length (P = 0.14, r = −0.16).

Central thickness of the lamina cribrosa and of the cornea did not show a statistically significant correlation (P = 0.15; correlation coefficient, r = 0.14; Fig. 2). This finding held true when the highly myopic subgroup (P = 0.27; r = −0.08) and the non– highly myopic subgroup (P = 0.07; r = 0.19) were analyzed separately.

Peripheral Lamina Cribrosa Thickness

As was true of the thickness of the central lamina cribrosa, the thickness of the lamina cribrosa close to the optic nerve head border showed a correlation with neither central corneal thickness (P = 0.51; correlation coefficient, r = 0.06; Fig. 5) nor peripheral corneal thickness (P = 0.34; r = 0.09).

Peripapillary Scleral Thickness

Scleral thickness at the optic disc border measured 276.7 ± 76.1 μm (median, 278 μm; range, 120–540 μm). The measure-
ment was statistically independent of the lamina cribrosa thickness in the optic disc center ($P = 0.11$) and at the optic disc margin ($P = 0.33$) and of central corneal thickness ($P = 0.84$; Fig. 4), age ($P = 0.78$), right or left eye ($P = 0.10$), and gender ($P = 0.15$). The peripapillary sclera was significantly ($P = 0.049$) thinner in the highly myopic group than in the non–highly myopic study group (251.0 ± 89.9 µm vs. 282.9 ± 71.6 µm).

**Shortest Distance between Prelaminar Space and Cerebrospinal Fluid Space**

The shortest distance between the prelaminar space and cerebrospinal fluid space measured 420.0 ± 110.1 µm (median, 414 µm; range, 160–900 µm). This result was statistically independent of central corneal thickness ($P = 0.10$; Fig. 5), age ($P = 0.62$), right or left eye ($P = 0.47$), and gender ($P = 0.39$).

It correlated significantly with the lamina cribrosa thickness at the optic disc margin ($P = 0.032$).

**DISCUSSION**

Histomorphometric studies have suggested that the thickness of the lamina cribrosa may play a role in the pathogenesis of glaucomatous optic nerve damage.\(^{15-18}\) The lamina cribrosa at the bottom of the optic cup is a barrier between the intraocular space on its inner side and the retrobulbar cerebrospinal fluid space surrounding the optic nerve on its outer side. Since the lamina cribrosa forms the border between the intraocular space with a higher pressure and the retrobulbar cerebrospinal fluid space surrounding the optic nerve on its outer side. Since the lamina cribrosa forms the border between the intraocular space with a higher pressure and the retrobulbar cerebrospinal fluid space surrounding the optic nerve on its outer side. Because the lamina cribrosa is not indefinitely thin, the pressure reduction does not occur in an indefinitely thin layer of the lamina cribrosa, but the pressure may decrease gradually or in steps along the whole thickness of the lamina cribrosa. A recent investigation has suggested that in non–highly myopic eyes with advanced glaucomatous optic nerve damage, the lamina cribrosa is markedly thinner than in normal eyes.\(^{15}\) It has been inferred that the thinning and condensation of the lamina cribrosa in advanced glaucoma may be the histopathologic correlate of clinical studies in which an advanced stage of glaucomatous optic neuropathy, independent of the level of intraocular pressure, was shown to be a risk factor for further progression of glaucoma.\(^{27-30}\) It has been speculated that the same pressure difference between the intraocular space and the retrobulbar space across a thinner lamina cribrosa may lead to a steepening of the trans–lamina-cribrosa pressure gradient, similar to the effect of an elevated intraocular pressure with an increased trans–lamina-cribrosa pressure difference on a lamina cribrosa of normal thickness. As a
corollary, another histomorphometric investigation has suggested that highly myopic nonglaucomatous eyes have a significantly thinner lamina cribrosa than nonglaucomatous non-highly myopic eyes. The thinner lamina cribrosa in highly myopic eyes may explain the presumably increased susceptibility to glaucoma of highly myopic eyes compared with non-highly myopic eyes.

In view of the possible importance of the thickness of the lamina cribrosa at the bottom of the optic nerve head in the pathogenesis of glaucomatous optic nerve damage, considering that the dimensions of the cornea, such as horizontal and vertical diameter and anterior corneal curvature, correlate with the diameters and area of the optic nerve head, and since a thin central cornea has been described as a predictive factor for further progression of chronic open-angle glaucoma, the purpose of the present study was to evaluate whether the central corneal thickness correlates with the thickness of the lamina cribrosa. The findings showed that in nonglaucomatous human globes, the thickness of the central cornea and the lamina cribrosa do not correlate significantly (Figs. 2, 3), which suggests that an assumed relationship between central corneal thickness and susceptibility to glaucoma may not be explained by a corresponding anatomy between corneal thickness and thickness of the lamina cribrosa. This finding holds true in non-highly myopic eyes and in highly myopic eyes, since for both study subgroups, central corneal thickness was unrelated to thickness of the lamina cribrosa. The data of the present study indirectly correspond with results of the Early Manifest Glaucoma Trial (EMGT), in which the corneal thickness was unrelated to the development of visual field defects in the study population. The data of the present investigations also correspond with another study in this issue of IOVS in which central corneal thickness did not have a major impact on the rate of the progression of chronic open-angle glaucoma. Because of the loss of approximately two thirds of the originally formed retinal ganglion cell axons in the primitive optic nerve, the primitive lamina cribrosa furthermore undergoes a continuous remodeling during the embryonic stage. These differences between the cornea and lamina cribrosa in their embryonic development may contribute to the result of the present study that central corneal thickness appeared to be unrelated to the thickness of the optic nerve head structures.

There are several weaknesses in this study. First, postmortem tissue swelling and artifact in either the cornea or lamina cribrosa have certainly introduced some bias in the correlation between corneal thickness and measured optic disc parameters. There is little reason to believe that histologic artifacts would be related to corneal thickness, and thus this bias is probably nondifferential. However, any nondifferential bias would be toward the null, which may explain the lack of any significant associations. In addition, histologic sections were not of a consistent orientation, and lamina cribrosa thickness in each eye was characterized from a single histologic section. Considering that the lamina is remarkably variable in its three-dimensional geometry, as shown in Bellezza et al. and Burgoyne and Morrison, the lamina cribrosa may be thinnest in different regions in each eye, and anything less than a three-dimensional reconstruction or serial sectioning of each eye may fail to find the thinnest portion of the lamina that in fact correlates. From that point of view, the present investigation may be regarded as a pilot study, with findings that must be confirmed by an investigation with three-dimensional reconstruction of the anatomy of the lamina cribrosa. Another limitation of the study is the relatively small number of eyes included in the investigations. The scattergrams show, however, that there is not even a tendency toward correlation between central corneal thickness and thickness of the lamina cribrosa (Figs. 2, 3, 4, 5). This finding may suggest that an assumed relationship between central corneal thickness and susceptibility to glaucoma cannot be explained by a corresponding anatomy between corneal thickness and histomorphometry of the optic nerve head.

The finding that corneal thickness and thickness of the lamina cribrosa were not significantly associated with each other may be due to differences in embryonic development. The corneal stroma and corneal endothelium start to be formed by the fourth to sixth weeks of gestation by immigrating cells from the neural crest. The lamina cribrosa begins to develop as the lamina scleralis in the region of the primitive optic nerve head during the eighth week. Invading glial cells of the outer wall of the optic stalk form a sieve-like scaffolding around the pre-existing ganglion cell axons, followed by ingrowing of sclera-derived cells in the fourth month, which forms the mesenchymal part of the lamina cribrosa, including connective tissue fibers penetrating the glial lamina cribrosa and running between glia-covered ganglion cell axons and the centrally located hyaloid vessel. The lamina cribrosa is vascularized by the 13th to 14th weeks, and its mature structure is reached during the 7th month. It should be emphasized that, during formation of the lamina cribrosa, the ganglion cell axons and the hyaloid vessels are the first to be present. They form the contents of the future lamina cribrosa pores, followed by formation of the lamina cribrosa trabecula in two steps: In the first step, glial cells of the outer optic stalk wall create a provisional net that is stabilized and further strengthened in the second step by ingrowing sclera-derived mesenchymal cells. Consequently, the mature lamina cribrosa can be considered a result of the secondary development of vascularized scleral connective tissue penetrating the preformed glial lamina, including the ganglion cell axons and the hyaloid vessels. Because of the loss of approximately two thirds of the originally formed retinal ganglion cell axons in the primitive optic nerve, the primitive lamina cribrosa furthermore undergoes a continuous remodeling during the embryonic stage. These differences between the cornea and lamina cribrosa in their embryonic development may contribute to the result of the present study that central corneal thickness appeared to be unrelated to the thickness of the optic nerve head structures.

In conclusion, the present study suggests that in nonglaucomatous human globes, corneal thickness does not correlate significantly with lamina cribrosa thickness, thickness of the peripapillary scera, or the shortest distance between the intraocular space and the cerebrospinal fluid space. In the interpretation of the measurements, it has to be taken into account, that histologic artifact and sectioning methods led to corneal thickness measurements well over 600 to 800 μm in many eyes, which results in a nondifferential bias toward the null that may also explain the lack of any significant associations. Direct clinical–histomorphometric comparisons of enucleated eyes may answer the question of how much the histomorphometric measurements in the present study were influenced by postmortem- and preparation-induced changes. If the results of the present study are confirmed by other studies, they suggest that an assumed relationship between central corneal thickness and susceptibility to glaucoma may not be explained by a correspondence between central corneal thickness and thickness of the lamina cribrosa and peripapillary scera.
Acknowledgments

The authors thank Claude F. Burgoyne (LSU Eye Center, New Orleans, LA) for the initiation of the study and for his support and constructive criticism of the manuscript.

References


