

Elongation of the Retina and Ciliary Body in Dependence of the Sagittal Eye Diameter

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PURPOSE. To examine the elongation of the retina and ciliary body in relation to myopic axial elongation.

METHODS. Using light microscopy, we histomorphometrically measured in enucleated human globes the length of the retina from the ora serrata to the optic disc borders. The total retinal length was the mean of the retinal length measurements obtained on both sides of the optic disc. We additionally determined the length of the ciliary body between the ora serrata and the scleral spur.

RESULTS. The study included 174 eyes (mean age, 61.7 ± 14.8 years; range, 24–89 years) with a mean sagittal eye diameter of 25.9 ± 3.2 mm (range, 21.0–37.0 mm). Retinal length (beta, 0.81; nonstandardized regression coefficient B, 0.73; 95% confidence interval (CI), 0.65–0.81; $P < 0.001$) and ciliary body length elongated (beta, 0.49; nonstandardized regression coefficient B, 0.16; 95% CI, 0.12–0.20; $P < 0.001$) with a longer sagittal eye diameter. Retinal length and ciliary body length were associated with each other (beta, 0.34; nonstandardized regression coefficient B, 0.12; 95% CI, 0.07–0.17).

CONCLUSIONS. The retina elongates by 0.73 mm (95% CI, 0.65–0.81) and the ciliary body by 0.16 mm (95% CI, 0.12–0.20) for each millimeter of axial elongation. With the inner limiting membrane and retinal nerve fibers forming the only structures connecting the deeper retinal layers with the optic disc, retinal elongation may be associated with a stretching of the retinal nerve fibers, potentially leading to optic nerve damage in highly myopic eyes, and with an increased strain within the inner limiting membrane, potentially leading to an intraretinal elevation at the posterior pole with the sequel of a myopic maculoschisis.

Keywords: axial myopia, ciliary body, Bruch's membrane, choriocapillaris, myopia, myopic maculopathy, scleral staphyloma

Axial myopia is characterized by an elongation of the sagittal diameter of the eye, and to a minor degree, by an enlargement of the ocular coronal diameters.^{1–4} It leads to a change in the eye shape from a sphere in emmetropia to a prolate ellipsoid in highly myopic eyes. Except for eyes with secondary myopia owing to congenital glaucoma, the axial elongation of eyes with primary myopia is not associated with a change in the diameter or the thickness of the cornea. It implies that the axial elongation-associated enlargement of the inner ocular surface affects the ciliary body, the retina, and the optic nerve head. Numerous studies have shown that myopic axial elongation, in particular beyond a cut-off value of 26.0 to 26.5 mm of sagittal eye diameter, correlates with an enlargement of the optic nerve head canal and of the parapapillary gamma zone and delta zone.^{5–7} It has remained unclear, however, to what extent the ciliary body region and the area covered by the retina increase in size. In particular, the information about a lengthening of the retina in myopic eyes may be useful to elucidate

the etiology of high myopia-associated optic nerve damage and myopic maculoschisis, because the retinal nerve fibers and the inner limiting membrane (ILM), besides the large retinal blood vessels, are the only structures connecting the deeper retinal layers with the optic disc. Any increase in the distance to the optic disc may thus lead to a stretching of the retinal nerve fibers and an increased strain in the ILM, with both mechanisms potentially playing a role in the pathogenesis of optic nerve damage and myopic maculoschisis, respectively.⁸ We, therefore, measured in this study the length of the ciliary body and retina on histological sections of human eyes and correlated the values with sagittal eye diameter.

METHODS

This histomorphometric investigation included human eyes that had previously been enucleated owing to diseases such as malignant melanomas of the choroid and ciliary body or



owing to painful end-stage glaucoma. All patients were of European descent. None of the eyes examined in the study were hypotonic or phthitic. According to the Declaration of Helsinki guidelines, the Medical Ethics Committee II of the Medical Faculty Mannheim of the Heidelberg University approved the study and waived the necessity of an informed written consent signed by the study participants, because the enucleations had been performed up to 50 years before start of the investigation. All eyes had been fixated, measured, and prepared for the histological examination at the time of enucleation.

Immediately after enucleation, the globes had been fixated in a solution of 4% formaldehyde and 1% glutaraldehyde for 1 week at room temperature. Before fixation, the globes had not been cut open nor had the preservative agent been injected intravitreally. As also described in detail previously, the sagittal, horizontal, and vertical globe diameters had been measured.^{3,6} For most eyes, the figures had been rounded to the full millimeter. One week after fixation, the middle part with a thickness of approximately 8 mm was removed out of the fixed globes. This middle part included the optic nerve head, the pupil, and the macular region, except for eyes with a malignant melanoma, in the case of which the middle segment ran in an anterior–posterior direction through the tumor and the pupil and optic nerve head. We dehydrated the middle segment in alcohol, embedded it in paraffin, and sectioned it for light microscopy. We used the periodic acid–Schiff method or hematoxylin and eosin to stain the tissue. For further evaluation, we took one section with a thickness of approximately 5 to 8 μm and ran through the central part of the pupil and optic nerve head.

Using a millimeter scale built into the objective of the microscope, we measured histomorphometrically the length of the retina at the level of the outer nuclear layer between the ora serrata and the optic disc borders, and the length of the ciliary body between the ora serrata and the scleral spur (Fig. 1). We defined the optic disc borders either by the peripheral borders of the lamina cribrosa or, in the case of Bruch's membrane, extending into the intrapapillary compartment, we defined the optic disc border as the end of Bruch's membrane. The measurements were performed on both sides of the slide, that is, in the case of a horizontally sectioned globe, on the temporal side and on the nasal side of the optic disc. We took the mean of the retinal length measurements of both sides for further statistical analysis. In the case of a retinal detachment, we measured the length of Bruch's membrane (as a surrogate for the retinal length at the level of the outer nuclear layer) from ora serrata to ora serrata. In the region of a parapapillary gamma zone (defined as the parapapillary region without Bruch's membrane), we extrapolated the line of Bruch's membrane and measured to the optic disc border. All examinations and measurements were performed prospectively after the goal of the study had been defined.

We defined high myopic axial elongation by a sagittal eye diameter of 26.0 mm or greater.^{9–11} Inclusion criterion for the study was the light microscopical detectability of the landmarks, that is, the scleral spur, the ora serrata, and the optic disc border. If a malignant melanoma located in the pars plana region of the ciliary body prevented a clear detection of the ora serrata, that side of the histologic slide was not measured and excluded from the study.

Using a statistical software program (SPSS for Windows, version 27.0; IBM-SPSS, Chicago, IL, USA), we assessed the mean values, standard deviations, and 95% confidence inter-

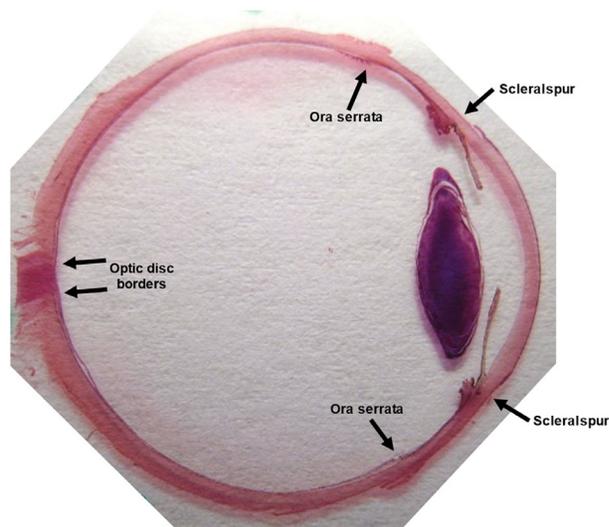


FIGURE 1. Macrophotograph of an enucleated and sectioned human globe, showing the positions of the scleral spur, ora serrata, and optic disc borders. Using a light microscope with a millimeter scale built into its objective, we measured the length of the retina at the level of the outer nuclear layer between the ora serrata and the optic disc border, and the length of the ciliary body between the ora serrata and the scleral spur. The optic disc borders were defined as the peripheral borders of the lamina cribrosa.

vals (CI) of the outcome parameters with a normal distribution, or the medians and interquartile ranges of nonparametric parameters. We assessed the normal distribution of the data of a parameter using the Kolmogorov–Smirnov test. We tested associations between the length of the retina or the length of the ciliary body with the sagittal eye diameter applying a linear regression analysis. We calculated the standardized regression coefficient beta and the nonstandardized regression coefficient B and its 95% CI. The level of significance was 0.05 (two-sided) in all statistical tests.

RESULTS

The study included 174 eyes of 174 patients with a mean age of 61.7 ± 14.8 years (range, 24–89 years) and a mean sagittal eye diameter of 25.9 ± 3.2 mm (range, 21.0–37.0 mm) (Table). The study population consisted of 83 nonhighly myopic eyes without glaucoma (47.7%) and with an intraocular malignant melanoma, 33 nonhighly myopic eyes with noncongenital glaucoma (19.0%), 15 highly myopic eyes without glaucoma (8.6%), 35 highly myopic eyes with noncongenital glaucoma (20.1%), and 8 highly myopic eyes with congenital glaucoma (4.6%) (Table).

Applying the Kolmogorov–Smirnov test revealed that the parameters of retinal length ($P < 0.001$), ciliary body length ($P = 0.004$), and sagittal globe length ($P < 0.001$) were not normally distributed. The mean length of the retina was 23.8 ± 2.9 mm and the mean length of the ciliary body was 5.6 ± 1.0 mm. In two eyes, the ora serrata could not clearly be identified on one side of the histological slide, so that for these two eyes, only the measurements of retinal length and ciliary body length taken on the other side of the histologic slide were taken for further statistical analysis.

Retinal length and ciliary body length were significantly associated with each other (equation of the regression line: Ciliary body length (mm) = $0.12 \times$ Retinal length (mm) +

TABLE. Demographic Data and Histomorphometric Measurements

Parameter	Total Study Population	Nonhighly Myopic Eyes Without Glaucoma (With Uveal Melanoma)	Nonhighly Myopic Eyes With Noncongenital Glaucoma (Without Uveal Melanoma)	Highly Myopic Eyes Without Glaucoma (Without Uveal Melanoma)	Highly Myopic Eyes With Noncongenital Glaucoma (Without Uveal Melanoma)	Highly Myopic Eyes With Congenital Glaucoma (Without Uveal Melanoma)
No. (percentage of total study population)	174 (100%)	83 (47.7%)	33 (19.0%)	15 (8.6%)	35 (20.1%)	8 (4.6%)
Age (years)	61.7 ± 14.8	60.7 ± 13.8	64.7 ± 18.6	66.2 ± 13.7	62.0 ± 16.0	48.0 ± 17.3
Sagittal eye diameter (mm)	25.0 (4.0)	24.0 (2.0)	24.0 (3.75)	29.0 (4.0)	29.0 (3.0)	32.0 (3.5)
Retinal length (mm)	23.0 (2.7)	22.4 (1.4)	22.3 (2.6)	25.9 (4.7)	26.5 (4.0)	29.6 (7.5)
Ciliary body length (mm)	5.6 (1.2)	5.2 (0.9)	5.3 (1.1)	6.1 (0.7)	6.2 (1.1)	5.9 (1.9)

Values are mean ± standard deviation or median (interquartile range) unless otherwise noted.

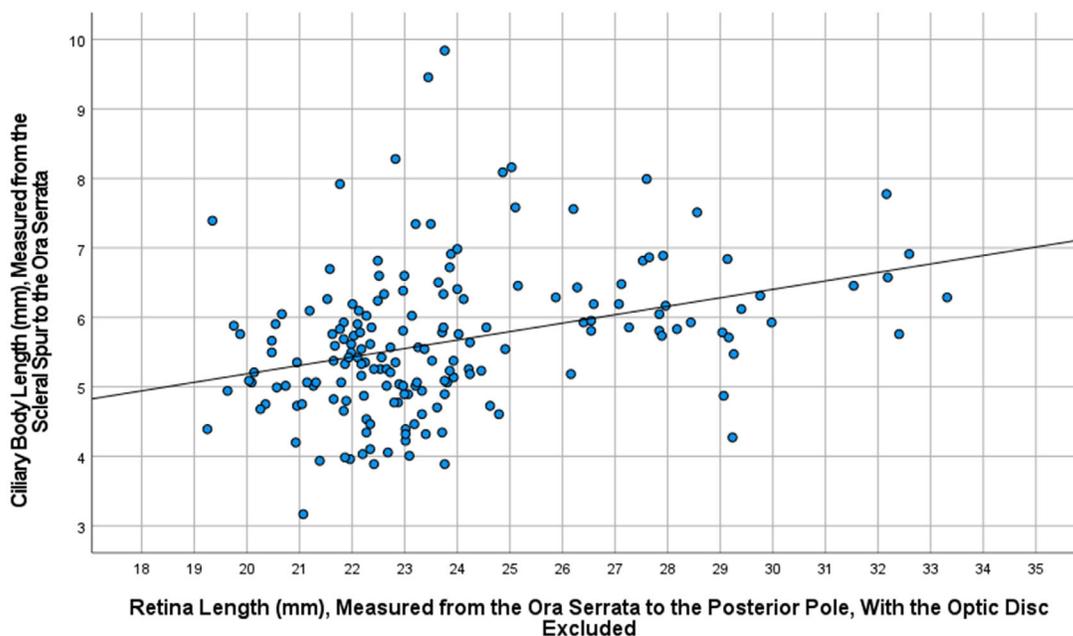


FIGURE 2. Scattergram showing the distribution of the ciliary body length (measured from the scleral spur to the ora serrata) in dependence of the length of the retina (measured from the ora serrata to the posterior pole with the exclusion of the optic disc); equation of the regression line: Ciliary body length (mm) = 0.12 × Retinal length (mm) + 2.75.

2.75) (Fig. 2). Retinal length increased ($P < 0.001$; beta, 0.81) with longer sagittal eye diameter (Retinal length [mm] = $0.73 \times$ Sagittal eye diameter [mm] + 4.95) (Fig. 3). Parallely, the ciliary body length elongated ($P < 0.001$; beta, 0.49) with a longer sagittal eye diameter (Ciliary body length [mm] = $0.16 \times$ Sagittal eye diameter [mm] + 1.54) (Fig. 4). The squared regression coefficient was slightly higher for a quadratic equation ($r^2 = 0.29$) than for the linear equation ($r^2 = 0.24$).

In multivariable analysis, the association between retinal length and sagittal eye diameter was independent of the ciliary body length ($P = 0.13$), presence of a malignant melanoma ($P = 0.24$), presence of glaucoma ($P = 0.61$), age ($P = 0.07$), and sex ($P = 0.42$). In a similar manner, the association between ciliary body length and sagittal eye diameter length was independent of the retinal length ($P = 0.13$), presence of a malignant melanoma ($P = 0.07$), presence of glaucoma ($P = 0.07$), age ($P = 0.08$), and sex ($P = 0.11$).

DISCUSSION

Our histomorphometric study revealed that eyes with longer axes have a longer retina, and to a minor degree, a longer ciliary body (Figs. 3 and 4). For each millimeter increase in sagittal globe diameter, the retinal length as measured from the ora serrata to the posterior pole (with the optic disc region excluded) increased linearly by 0.73 mm (95% CI, 0.65–0.81) (Fig. 3). The ciliary body elongated to a minor amount with longer sagittal eye diameter, and the ciliary body length was almost constant beyond a sagittal eye diameter of 30 mm (Fig. 4).

Although it has long been known that axial myopia is due to an elongation of the sagittal globe diameter in association with a deepening of the vitreous cavity, it had not been explored whether myopic axial elongation is predominantly related to an elongation of the ciliary body and/or an elongation of the retina. The results of our study, thus, cannot be compared directly with findings made in previous

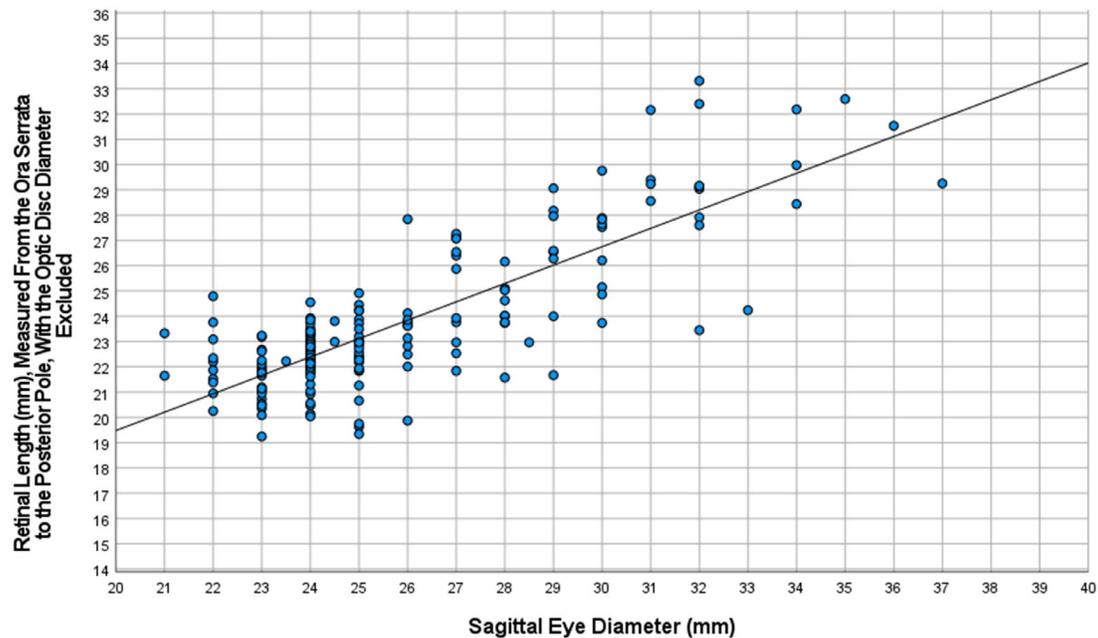


FIGURE 3. Scattergram showing the distribution of the length of the retina, measured from the ora serrata to the posterior pole with the exclusion of the optic disc, in dependence of sagittal eye diameter; equation of the regression line: Retinal length (mm) = $0.73 \times$ Sagittal eye diameter (mm) + 4.95.

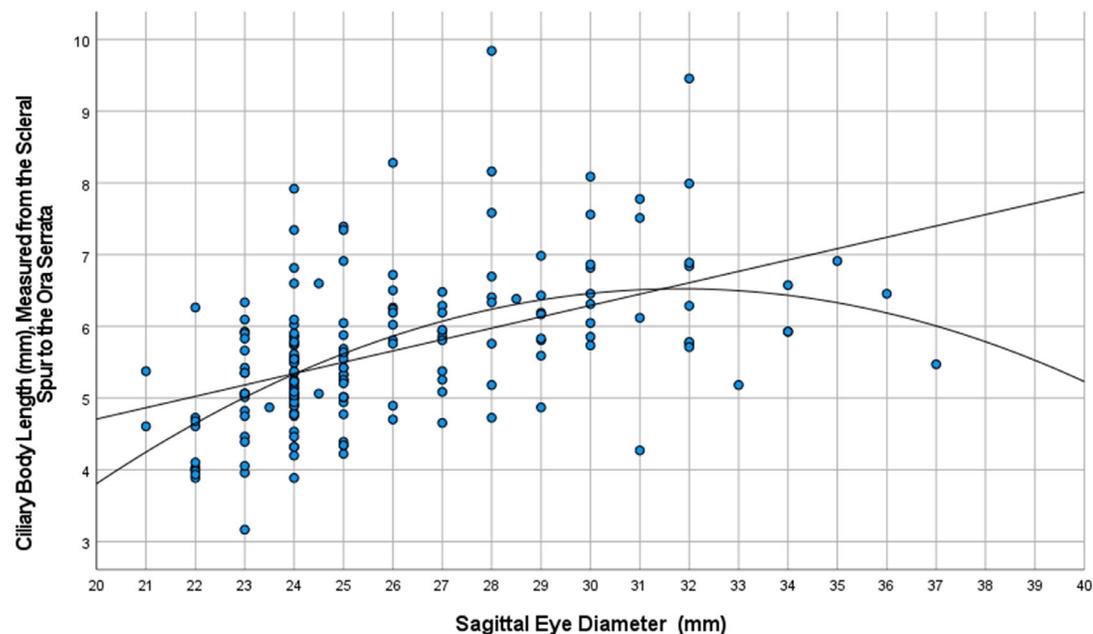


FIGURE 4. Scattergram showing the distribution of the length of the ciliary body, measured from the scleral spur to the ora serrata, in dependence of sagittal eye diameter (equation of the linear regression line: Ciliary body length (mm) = $0.16 \times$ Sagittal eye diameter (mm) + 1.54).

investigations. The data from our study agree with previous observations that the myopic globe enlargement affects mainly the sagittal eye diameter, whereas the horizontal and vertical eye diameters enlarge by a markedly lower amount.¹⁻⁴ In a previous study, each millimeter increase in sagittal eye diameter was associated with an increase in the coronal diameter (i.e., the horizontal and vertical diameters)

by 0.44 mm and 0.51 mm, respectively, in eyes with an sagittal eye diameter of 24 mm or less.³ In eyes with a sagittal eye diameter of more than 24 mm, the horizontal and vertical globe diameters enlarged by a smaller amount, that is, by 0.19 mm and 0.21 mm, respectively, for each millimeter increase in axial diameter.³ The markedly lower increase in the coronal globe diameters as compared with the sagittal

diameter explains the change in the shape of the eye from a sphere in emmetropia to a prolate ellipsoid in myopic eyes.

The observations made in our study may have clinical importance. The retina over its whole region from the ora serrata to the optic disc elongates by 4.3 mm, if the sagittal eye diameter increases from 24 mm in an emmetropic eye to 30 mm in a highly myopic eye. The lengthening of the retina affects those structures that extend from the retinal periphery to the optic disc. These structures are the ILM and the retinal nerve fibers. Assuming that the axons of the retinal ganglion cells are not expendable, any lengthening of the retinal nerve fibers will lead to their stretching. Such a mechanical strain may potentially lead to a damage and loss of the retinal nerve fibers, resulting in a nonglaucomatous optic neuropathy. This assumption is in agreement with clinical findings that high axial myopia can be associated with nonglaucomatous optic nerve damage.⁷ The nonglaucomatous damage of the optic nerve can occur in addition to or in parallel with an increased prevalence of a glaucomatous or glaucoma-like optic neuropathy in highly myopic eyes. The high myopia-associated glaucomatous or glaucoma-like optic neuropathy is associated with an enlargement of the optic disc and higher prevalence and larger size of parapapillary delta zone.^{12,13} The design of our study did not allow us to assess in which regions the eye walls predominantly enlarge. If one assumed that the myopic enlargement did not differ between the equatorial region, the midperipheral region, and the posterior pole, the lengthening of the retinal nerve fibers would increase with the distance to the optic disc; that is, retinal nerve fibers originating in the retinal periphery would be lengthened most. Owing to geometrical reasons, the change in the eye shape from a sphere in emmetropia to a prolate ellipsoid in high myopia suggests, however, a predominant enlargement of the eye wall in the equatorial and retroequatorial regions. This assumption is strengthened by findings that the sensory afferent part of the feedback mechanism of the process of emmetropization may be located in the midperiphery of the fundus.^{8,14-17} If axial elongation is achieved mainly by an enlargement of the eye wall in the equatorial and retroequatorial regions, the axons of the retinal ganglion cells located in the fundus midperiphery and anterior to it will be lengthened and stretched, whereas the axons of the retinal ganglion cells located posterior to the fundus midperiphery will not be affected profoundly. These assumptions fit with the clinical observation of a concentric decrease of the visual field of highly myopic eyes.¹⁸

In addition to the axial elongation-associated changes in the fundus midperiphery, an increase in the distance between the retinal ganglion cells and the optic disc occurs in the papillomacular region by the development of a temporal parapapillary gamma zone and delta zone.¹⁹ Gamma zone and delta zone, if located in the temporal parapapillary region, directly lead to an increase in the disc-fovea distance in a ratio of approximately 1:1.¹⁹ It is associated with a lengthening of the retinal nerve fibers in the papillomacular region, because these fibers run in a straight course to the optic disc already before axial elongation started. The lengthening of the fibers may lead to their stretching with secondary damage. In contrast, axons in the curved arcuate regions in the macular region may compensate for an increase in the disc-fovea distance by getting more straight-lined, without a secondary fiber stretching. Future studies may address whether the elongation and stretching of the papillomacular fibers is associated with the development

of central scotomas in highly myopic eyes without myopic macular changes in the deep retinal layers.⁷

In addition to the retinal nerve fibers, the ILM is the other structure directly extending from the retina to the optic disc. Any elongation of the retina leads to an elongation of the ILM. Because the ILM as basal membrane (similar to the lens capsule or Bruch's membrane) is not markedly elastic but stiff, an elongation of the ILM will increase its strain.²⁰ In particular, in eyes with a posterior staphyloma in which the distance to the optic disc has further enlarged locally, it may lead to an intraretinal detachment of the ILM owing to a washing line phenomenon. It could cause a secondary splitting of the retina into an inner part clinging to the ILM and an outer part with the retinal photoreceptors firmly attached to the retinal pigment epithelium and Bruch's membrane. It could explain the development of a myopic maculosis.

The increase in the distance to the optic disc affects, besides the ILM and retinal nerve fiber layer, also all other retinal layers since the local enlargement of their under-ground leads to a decrease in their density. This conclusion is based on the assumption that the retinal cells cannot undergo mitosis postnatally, and that the axial elongation leads to an enlargement of the ocular coats (i.e., Bruch's membrane and sclera) in that region. A decreased photoreceptor density may directly cause a decrease in spatial resolution, and in association with a decreased density of the cells of the inner nuclear layer and retinal ganglion cell layer, an enlargement of receptive fields. Correspondingly, clinical studies have revealed that the resolution acuity at peripheral retinal loci declined linearly with the magnitude of the myopic refractive error.²¹ Eyes with a myopic refractive error of -15 diopters as compared with emmetropic eyes had twice as much spacing between retinal receptive units and thus 50% of the peripheral resolution acuity.²¹ These findings also fit with the assumption that the ocular wall enlargement underlying the myopic axial elongation predominantly takes place in the equatorial region, as also discussed elsewhere in this article.

Future studies may address whether the visual field associated with myopia and high myopia are due to the enlargement of receptive fields, in particular in the midperiphery of the fundus, owing to the loss of retinal ganglion cells in association with a nonglaucomatous, glaucomatous, or glaucoma-like optic neuropathy, and/or are due to artifacts in association with an optic disc tilt.²²

Limitations of our study should be considered: First, tissue swelling owing to the ischemia occurring after enucleation and before fixation and fixation-related shrinkage of the tissue are unavoidable postenucleation changes, which may have influenced the dimensions of the ocular tissues in our study.²³ Also, mechanically induced changes during the histological processing of the globes may have altered the tissues. These changes might however have affected the globes independent of their sagittal eye diameter so that these procedure-related tissue changes may not have markedly influenced the analysis of relationships of the length of the retina and ciliary body with the sagittal eye diameter. Second, the study material of our investigation might have had a selection bias because it was based on human globes enucleated for clinical reasons. The findings of our study may therefore not directly be transferable to eyes without these diseases. Third, serial sections of the globes were not available. Fourth, the patients included in our study were of European descent. Future studies may address whether the findings obtained in our investigation

can be used to draw an inference about individuals of other ethnicities. Fifth, we performed a linear regression analysis although it was not quite appropriate to conduct a linear regression on nonparametric parameters (such as axial length in our study population sample). The distribution of the raw data points in the scattergrams showed, however, a mostly linear relationship for the association between sagittal eye diameter and retinal length (Fig. 3) and a roughly linear relationship for the association between retinal length and ciliary body length (Fig. 2). In contrast, and as also shown in the graph and discussed elsewhere in this article, the association between sagittal eye diameter and ciliary body length was more curvilinear than linear (Fig. 4).

In conclusion, the retina elongates by 0.73 mm (95% CI, 0.65–0.81) and the ciliary body by 0.16 mm (95% CI, 0.12–0.20) for each millimeter of axial elongation. With the ILM and retinal nerve fibers forming the only connecting structure between the deeper retinal layers and the optic disc, retinal elongation may be associated with a stretching of the retinal nerve fibers, potentially leading to an optic nerve damage in highly myopic eyes, and it may be associated with an increased strain within the ILM, potentially leading to an intraretinal elevation of the ILM with the sequel of a secondary myopic maculoschisis.

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