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Myopia: Anatomic Changes and Consequences for Its Etiology

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Abstract: The process of emmetropization is the adjustment of the length of the optical axis to the given optical properties of the cornea and lens after the end of the second year of life. Up to the end of the second year of life, the eye grows spherically. Axial elongation in the process of emmetropization after the second year of life is associated with a thinning of the retina and a reduced density of retinal pigment epithelium (RPE) cells in the equatorial and retroequatorial region, and a thinning of the choroid and sclera, starting at the equator and being most marked at the posterior pole. In contrast, retinal thickness and RPE density in the macular region and thickness of Bruch membrane (BM) in any region are independent of axial length. It led to the hypothesis that axial elongation occurs by the production of additional BM in the equatorial and retroequatorial region leading to a decreased RPE density and retinal thinning in that region and a more tube-like than spherical enlargement of the globe, without compromise in the density of the macular RPE cells and in macular retinal thickness. The increased disc-fovea distance in axially myopic eyes is caused by the development and enlargement of parapapillary, BM-free, gamma zone, whereas the length of macular BM, and indirectly macular RPE cell density, and macular retinal thickness, remain constant.

Key Words: axial elongation, Bruch membrane, high myopia, myopia, myopization, retinal pigment epithelium

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Owing to the marked rise in its prevalence, in particular, in the young generations in East and Southeast Asia, myopia has been considered to become one of the most frequent ophthalmic disorders.[1–7] As high myopia is the major risk factor for the development of myopic maculopathy and high-myopia-associated glaucomatous or glaucoma-like optic neuropathy, it is estimated that myopia may become one of the most common causes of irreversible vision impairment and blindness worldwide.[8–10] Despite its importance, the process of myopization including the underlying mechanisms leading to myopia have remained elusive so far. Myopia may be considered to be the result of a failure of emmetropization secondary to the attempt to eliminate a relative hyperopic blur in the peripheral of an elliptical eye.[11,12] A main question for understanding the process of emmetropization and myopization is which tissue or ocular coat primarily makes the eye longer. Theoretical candidates could be the retina, the retinal pigment epithelium (RPE), Bruch membrane (BM), the choroid, and/or the sclera. As anatomical findings may help elucidate the process of myopization, we examined clinically and histomorphometrically myopic human globes and compared them with emmetropic or hyperopic eyes.

CHOROID

Clinical and histological studies have convincingly shown that the subfoveal choroidal thickness decreases with longer axial length, in addition to an age-related thinning of the choroid.[13,14] If the sclera was the primary structure elongating the globe, one would assume that the distance between the inner scleral surface and BM at the posterior pole would become wider, that is, the subfoveal choroidal thickness would increase. The finding of an axial elongation-associated thinning of the choroid may therefore contradict considering the sclera as the primary globe-elongating structure. As a hypothesis, it might make sense to examine the potential role of BM in the process of axial elongation, as a posterior advancement of BM would lead to a compression and thinning of the choroid, and the sclera would secondarily relent, similar to the development of dellen in a bone after prolonged local pressure.[15] Several anatomical and clinical findings may support the notion of BM as the primary structure elongating the eye.

Histomorphometric studies have also shown that the cross-sectional area and volume of the choroid in individuals older than 18 years were not related to axial length, so that the choroidal thinning was not because of a change in volume but presumably of a re-arrangement of the available choroidal tissue.[16] It may point against the choroid having an active role in the process of emmetropization/myopization.

SCLERA

In a similar manner, other histomorphometric investigations showed that the cross-sectional area and volume of the sclera were not related to age and axial length in individuals older than 3 years. It suggested that the scleral volume was not actively

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increased during the process of emmetropization and myopization but that the available tissue was re-arranged.[17,18] In children up to the age of 2 years, the scleral cross-sectional area and volume increased with age. Other studies revealed that in primary axial myopia, the thickness of the sclera decreased only in the posterior half of the globe.[18–21] The scleral thinning was most marked at the posterior pole and least marked at the equator or at the ora serrata, whereas the scleral thickness anterior to the ora serrata and the corneal thickness and diameters were independent of axial length in eyes with primary myopia.[18–21] It indicated that the process of emmetropization and myopization took place in the posterior half of the eye, with scleral changes occurring predominantly at the posterior pole. The finding that the scleral volume was not related to axial length in individuals older than 3 years pointed against the sclera having an active role in the process of emmetropization/myopization.

In eyes with secondary high myopia owing to congenital glaucoma, histomorphometrical studies showed a thinning and elongation of the sclera in all regions of the eye, fitting with the enlargement and thinning of the cornea in eyes with congenital glaucoma.[22,23]

Bruch Membrane

Histomorphometric studies of the BM revealed that BM, in contrast to the choroid and sclera, did not get thinner in axially elongated eyes, not even in eyes with an axial length of >35 mm.[24,25] It indicated that the volume of BM increased with longer axial length, pointing toward an active growth of BM and thus an active role in the process of axial elongation.[15] As the thickness of the choroid and of the sclera decreased with axial length, the ratio of posterior choroidal thickness to BM thickness and the ratio of posterior scleral thickness to BM thickness were reduced in axially elongated eyes at positions posterior to the equator.

In eyes with secondary high myopia owing to congenital glaucoma as compared with eyes with primary myopia or emmetropic eyes, the thickness of BM was significantly reduced, whereas the choroidal and scleral thickness did not vary significantly between the eyes with primary myopia and the eyes with secondary myopia.[22] One may infer that the increased intraocular pressure in congenital glaucoma was the main factor for the expansion of the eye, so that all 3 layers, the sclera, choroid, and BM, became elongated and thinned in all regions of the eyes because of the ballooning of the globe. One may also infer that the thinning of BM occurred passively in these eyes, caused by the active force of the increased intraocular pressure during the first 2 years of life during which the ocular coats have been described to be generally extensible.[26] For eyes with primary myopia not exhibiting a thinning of BM but a thinning of the choroidal and sclera, the finding supports the hypothesis of BM being actively involved in the process of axial elongation in eyes with primary myopia.

The physiological opening of BM at the optic nerve head is called the BM-opening (BMO). A larger horizontal BMO diameter and larger vertical BMO diameter were linearly associated with longer axial length beyond an axial length of 26.0 mm.[27] It explained the development of a circular parapapillary gamma zone being present also at the nasal side of the optic disc in highly myopic eyes.[28] In the same study, within the group of eyes with an the axial length of ≥28.0 mm, the BMO size was significantly smaller in eyes with macular BM defects than in eyes without macular BM defects[27,29] Macular BM defects were detected upon light microscopical histology and upon optical coherence tomography (OCT)-based histology, and the presence and number increased with axial length beyond an axial length of about 26.5 mm.[29–32] They are characterized by the lack of BM, RPE, and choriocapillaris and by the almost complete loss of the outer and middle retinal layers and of Haller's and Sattler's layer of the choroid.[29] In a cross-sectional study on highly myopic eyes, the number of BM defects increased after an enlargement of parapapillary gamma zone and delta zone.[27,32] It suggested that during the process of axial elongation, the BMO enlarged first before secondary defects in BM in the posterior region developed.

The macular BM defects corresponded to the so-called patchy chorioretinal atrophies as part of the definition of myopic maculopathy.[8] According to a recent clinical study, the region with an RPE loss was larger than the region of the BM defect.[33]

MACULAR BM LENGTH AND DISC-FOVEA DISTANCE

The distance between the foveola and the optic disc increased with longer axial length.[34,35] The elongation of the disc-fovea distance was due to the development and enlargement of parapapillary gamma zone as BM-free zone, whereas the distance between the peripheral border of gamma zone and the foveola was independent of axial length in myopic eyes with BM defects.[35,36] It suggested that the length of BM in the macular region was not related with axial elongation. By the same token, the distance between the superior temporal arterial arcade and the inferior temporal arterial arcade in eyes without macular BM defects was independent of axial length, so that one might infer that the BM in the whole macular region did not enlarge in axially elongated eyes without BM defects.[34,37] If fits with the observation that the thickness of BM did not get thinner with longer axial length.

As the disc-fovea distance increased with longer axial length and the distance between the superior and inferior temporal vascular arcade was independent of axial length, the angle between the temporal vascular arcade decreased with longer axial length.[37]

DENSITY OF RPE CELLS AND RETINAL THICKNESS IN THE MACULAR REGION AND FUNDUS PERIPHERY

A histomorphometric study showed that the density of the RPE cells and the thickness of the retina in the macular region were not significantly associated with axial length.[38,39] It corresponded to the finding that BM in the macular region was not related to axial length, and to the clinical observation that the best-corrected visual acuity was not correlated with axial length if eyes with a myopic maculopathy were excluded.[40]

In contrast to the macular region, the fundus periphery showed a decrease in the density of the RPE cells and a thinning of the retinal layers with longer axial length.[38,39]

OPTIC DISC SIZE AND SHAPE IN MYOPIA

With increasing axial length, the optic disc changes in shape from an almost circular one to a vertically oval structure.[41]

Parallel to the change of the optic disc form to a vertical oval shape, parapapillary gamma zone develops and enlarges at the temporal disc border.[28,29,32,41,42] A recent study showed that the width of gamma zone corresponded to the amount of overhanging of BM into the intrapapillary compartment at the nasal disc side.[27] It suggested that the development of gamma zone in medium myopic eyes was because of a shift of the BMO in the direction to the macula, whereas the choroidal optic disc layer and the scleral optic disc layer (with the lamina cribrosa) stayed behind. It might have led to the development of an oblique exit of the optic nerve fibers out of the eye, first being directed nasally anteriorly, before bending backward to the apex of the orbit. The shift of the BMO in the direction to the macula fits with the notion of a production of BM in the equatorial region during the process of myopization.

Another reason for the vertical elongation of the optic disc shape upon ophthalmoscopy may be an ophthalmoscopically perspective artefact, as during axial elongation the ophthalmoscopical view onto the optic disc changes from a mostly perpendicular angle to an oblique angle.[43] It led to a perspectively relative shortening of the horizontal optic disc diameter.

A further mechanism potentially influencing the optic disc shape in highly myopic eyes is a potential backward pull of the optic nerve (dura mater) in adduction.[44,45] The longer the axis of the eyes, the stronger may be the pull of the optic nerve dura mater on the sclera during extreme gaze position, as the optic nerve may be too short to allow a full adduction of a markedly elongated globe. As the optic nerve originates in the nasal upper part of the orbit, adduction of a highly myopic globe will lead to a backward pull more markedly on temporal optic nerve head border than on the nasal optic nerve head border. It may lead to an optic disc rotation around the vertical axis with the temporal optic disc border being drawn backward. It may also lead to a lengthening of the peripapillary scleral flange and thus enlargement of parapapillary gamma zone and delta zone. The potential optic nerve-related backward pull of the parapapillary sclera of highly myopic eyes may also explain the development of peripapillary suprachoroidal cavitations.[15,46,47]

The size of the optic disc enlarges in highly myopic eyes, approximately beyond an axial length of about 26.5 mm or a myopic refractive error of approximately −8 diopter.[48]

PROCESS OF EMMETROPIZATION

The process of emmetropization can be described as the adaptation of the length of the optical axis to the optical properties of the cornea and lens without compromise in the photoreceptor density and best corrected. It may consist of a feedback mechanism with an afferent and an efferent loop. Myopization could be regarded as an overshooting of the process of emmetropization. According to experimental investigations and clinical observations, the afferent part of the process of emmetropization may be located in the equatorial region of the globe.[11,49–51] Based on the anatomical findings described above, one may discuss that the efferent loop of the feedback mechanism may also be located in the equatorial region and consist of a new production of BM by the local RPE cells, pushing the BM at the posterior pole backward. It would explain the thinning of the choroid at the posterior pole by a compression, and the scleral thinning at the posterior pole would occur secondarily. The increase in the area of BM in the equatorial region would also explain the decrease in the density of the RPE cells and in the retinal thickness in the equatorial region. As BM in the macular region would remain untouched by the BM enlargement in the equatorial region, the notion would be consistent with the histological findings that the thickness and length of BM, the RPE cell density, and the thickness of the choriocapillaris and retina in the macular region were independent of axial length. It would go along with the condition sine qua non of the process of emmetropization not reducing the density of the macular photoreceptors, and it complies with the clinical finding that best-corrected visual acuity is independent of axial length if eyes with maculopathies are excluded.

In the case that the image on the equatorial retina is out of focus in the sense of a hyperopic defocus, the mechanism would prolong the globe by introducing new BM area in the equatorial region. There are several reasons why the image in the equatorial region can be in hyperopic defocus, whereas the central image is sharply focused onto the fovea.[11,12] These reasons include a discrepancy between the optical properties of the peripheral optical pathway as compared with the central pathway, and others.

In the case of excessive equatorial enlargement of BM, mostly in the sagittal direction and to a minor degree into the horizontal and vertical directions, the tension or stress within BM in the posterior region may increase, firstly leading to an enlargement of the BMO in the optic nerve head region, and secondarily to the development of macular BM defects (as category III of the definition of myopic maculopathy).

The finding of recent experimental study agrees with the notion of BM playing a biomechanical role for size and shape of the eye. The average elastic moduli of BM at 0% and 5% strain were 1.60 ± 0.81 and 2.44 ± 1.02 MPa, respectively, and BM could withstand an intraocular pressure of 82 mm Hg before rupture.[52] The notion of BM as a biomechanically important structure may also give hints to the etiology of dome-shaped maculas and ridge-shaped maculas in highly myopic eyes.[53,54] As described by Spaide and Jonas,[55] macular BM defects can occur also in nonhighly myopic eyes, such as in globes with Stargardt disease, in eyes with a toxoplasmotic retinochoroidal scar or in patients with pseudoxanthoma elasticum and peripapillary atrophy.[55–59] Future studies may assess the effect of such BM defects on the occurrence of local collateral scleral staphylomas.

Recent experimental studies did not contradict the notion of BM as a potentially driven structure in the process of axial elongation. In a study performed by Dong et al,[60] a study group of young guinea pigs underwent lens-induced axial elongation, whereas a control group of young guinea pigs did not have any intervention. It revealed that the experimental axial elongation was associated with a thinning of the retina, choroid, and sclera and a decrease in density of the RPE cells, with the changes most marked at the posterior pole. In contrast, BM thickness was not related to axial elongation. It agreed with the findings obtained in aforementioned histomorphometric examination of human globes.[24,25] In another investigation conducted by Dong et al,[61] amphiregulin antibody applied intravitreally was associated with a reduction in lens-induced axial elongation and with a reduction of the physiological eye growth, whereas amphiregulin itself increased the axial elongation in young guinea pigs with and without lens-induced axial elongation. Eyes with lens-induced axial elongation as compared with eyes without lens-induced axial elongation revealed an increased visualization of amphiregulin

upon immunohistochemistry and higher expression of mRNA of endogenous amphiregulin and epidermal growth factor (EGF) receptor, in particular in the outer part of the retinal inner nuclear layer and in the RPE.[61] Amphiregulin is a member of the EGF family, and the RPE possesses receptors for EGF including amphiregulin. In particular, EGF increases the proliferation of RPE cells in cell culture. The RPE produces BM, the inner layer of which is formed by the basal membrane of the RPE.

When discussing the findings presented above, one should take into account the limitations of this review. First, it has to be emphasized that this review is focused on the potential role of BM in the process of emmetropization and myopization and that it was not balanced with respect to other or complementing theories of the process of axial elongation. Neglecting in this review other hypotheses, such as those on the role of the choroid and sclera in myopization, does not indicate that these hypotheses are not valid.[58,59,62–65] Second, it has remained unclear whether anatomical differences between normal eyes and myopic eyes were the cause or the effect of the process of emmetropization and the process of axial elongation. The changes in the ocular structure may be just related to the mechanism of expansion, not to the causes of the phenomenon of axial elongation. Third, in particular, it has to be stressed that there may be many counter-arguments against the hypothesis of BM as a driving structure in the process of axial elongation. It could be that the choroid has a tendency to mould itself to the supporting sclera, so that there would be no reason for the development of a suprachoroidal cavitation in the case the sclera were the primary structure moving backward. It would even more hold true if in the process of axial elongation, BM followed the choroid and brought the retina with it. It has also been acknowledged that a proliferation of BM in the process of axial elongation has not directly been shown yet. Indeed, one of the characteristic features of myopia is the development of BM defects in the macular region, a finding what primarily may speak against a proliferation of BM. The notion is, however, that BM proliferates in the equatorial region leading to an increase in diameters of the globe, to a major part in the sagittal axis and to a minor part in the horizontal and vertical directions. The globe enlargement in the coronal direction may lead to a tension within BM at the posterior pole, resulting first in an enlargement of the BM opening of the optic nerve head, and in a second step to the development of new BM defects in the macular region. From that point of view, a proliferation of BM in the equatorial region may indeed be in agreement with BM defects at the posterior pole. Lastly, it should also be noted that although it may now generally be accepted that the peripheral retina has a regulatory role in the process of emmetropization, it may not mean that the central retina has no role, as has also been expressed in a recent report on animal models and myopia.[66]

In conclusion, BM as a composite of 5 layers, that is, the basal membrane of the RPE, a collagenous layer, an elastic layer, a collagenous layer, and the basal membrane of the choriocapillaris, may potentially play a biomechanical role in influencing size and shape of the eye and may thus involve in the process of emmetropization and myopization.

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