Macular Bruch's Membrane Defects and Axial Length: Association with Gamma Zone and Delta Zone in Peripapillary Region

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Purpose. To examine histomorphometrically the macular region of highly myopic eyes.

Methods. On horizontal anterior-posterior histological sections, we examined the posterior pole of 138 human globes (axial length: 20–35 mm). In the parapapillary region, we differentiated between the beta zone (Bruch's membrane without RPE), gamma zone (parapapillary region without Bruch's membrane), and delta zone (elongated and thinned gamma zone).

Results. In 12 (8.7%) eyes, a macular Bruch's membrane defect (MBMD) was detected. The MBMD showed a complete lack of RPE and choriocapillaris, and an almost complete lack of photoreceptors. Presence of MBMD was associated with longer axial length ($P < 0.001$), longer gamma zone ($P = 0.04$) and delta zone ($P < 0.001$), thinner peripapillary scleral flange, and thinner sclera just outside of the optic nerve meninges ($P < 0.001$) and at the posterior pole ($P < 0.001$). An MBMD was found only in eyes with an axial length of 27 mm or longer. MBMD prevalence in highly myopic eyes was 12/39 or 30.8%. MBMD presence was not significantly related to length of beta zone ($P = 0.09$). In multivariate binary regression analysis, MBMD presence was significantly ($P < 0.001$) associated only with axial length.

Conclusions. Highly myopic eyes (axial length ≥27mm) can show an MBMD associated with complete loss of RPE and choriocapillaris, and marked reduction of photoreceptors and large choroidal vessels. MBMD presence was strongly associated with axial length and indirectly with parapapillary gamma zone and delta zone. The myopia-associated secondary MBMDs may occur parallel to the myopia-associated widening of Bruch's membrane opening around the optic nerve head. (*Invest Ophthalmol Vis Sci.* 2013;54:1295–1302) DOI: 10.1167/iovs.12-11352

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Due to a profound increase in the prevalence of myopia, particularly in the young generation in East Asian metropolitan regions,[1,2] myopia has markedly gained in importance. Because high myopia is associated with an increased risk for vision-threatening diseases, such as rhegmatogenous retinal detachment, glaucomatous optic neuropathy, and myopic retinopathy, research has focused on factors associated with the development of myopia.[3,4] Recent investigations revealed that the prevalence of myopia in children was associated with older age, female sex, urban region of habitation, type of attended school, and time spent outdoors versus indoors.[5–7] Histologic studies on highly myopic eyes were focused on the optic nerve head and showed a marked thinning of the lamina cribrosa, resulting in a steepening of the translamina cribrosa pressure gradient due to the reduction of the distance between the intraocular space and the orbital cerebrospinal fluid space. These studies also revealed a stretching and thinning of the peripapillary scleral flange, which as biomechanical anchor of the lamina cribrosa is of potential importance for the increased susceptibility for glaucomatous optic neuropathy in highly myopic eyes.[8,9] Because histological studies on the macular region in highly myopic eyes have been scarce, little has been known about histological changes in the macular region of myopic eyes, in particular of highly myopic eyes. In a previous study by Grossniklaus and Green in 1992,[10] the frequency of abnormal findings in eyes with pathologic myopia was examined, with a myopic configuration of the optic nerve head, posterior staphylomata, and degenerative changes of the vitreous being the most common abnormalities. Because almost no information has been available on the pathomorphology of the macula in highly myopic eyes, we conducted this study to assess the macular region in enucleated highly myopic globes and to compare them with non–highly myopic eyes.

Methods

The study included human globes that had been enucleated either due to painful absolute glaucoma or because of a malignant choroidal melanoma. The study was approved by the ethics commission II of the Medical Faculty Mannheim of the Ruprecht-Karls-University, Heidelberg, Germany. In the glaucomatous group, vision was completely or almost completely lost, and enucleation became necessary usually due to intractable pain that could not be treated by medication. In the tumor group, the malignant choroidal melanomas did not infiltrate the trabecular meshwork, either directly or indirectly by migrating cells. The parapapillary region and the macular region were free of tumor cells. At the time when the eyes were enucleated, no other treatment modalities, such as radiologic brachytherapy, were available or were thought not to be suitable for tumor removal with respect to its location and size. The globes had already been included in previous

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histomorphometric studies.[8,9] Immediately after enucleation, the globes were fixed in a solution of 4% formaldehyde and 1% glutaraldehyde and processed for histological sectioning. The globes were prepared in a routine manner for light microscopy. A horizontally orientated, 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, sectioned for light microscopy, and stained by the periodic acid-Schiff (PAS) method or by hematoxylin-eosin. For all eyes, one section running through the central part of the optic disc was selected for further evaluation. The thickness of the sections was 8 μm.

We examined the macular region and searched for regions without Bruch's membrane and adjacent abnormalities in the layer of the retinal photoreceptors, retinal pigment epithelium, choriocapillaris, and middle and large choroidal vessels. We defined a macular Bruch's membrane defect (MBMD) as a dehiscence in Bruch's membrane in the macular region. As already described in detail recently,[8,9] we additionally measured the following:

- distance between the end of Bruch's membrane and the border of the optic nerve scleral canal (defined as the intraocular projection of the inner side of the pia mater) ("Gamma zone") (Fig. 1);
- distance between the end of Bruch's membrane and the beginning of retinal pigment epithelium ("Beta zone") (Fig. 2);
- length and thickness of the peripapillary scleral flange that formed the anterior border of the orbital cerebrospinal fluid space and that continued into the lamina cribrosa (Fig. 1).

We had measured the thickness of the sclera at the limbus, ora serrata, equator, midpoint between the posterior pole and the equator, posterior pole, and outside of the optic nerve head after merging of the optic nerve sheaths with the sclera. We defined "gamma zone" as the region between the border of the optic nerve scleral canal (defined as the intraocular projection of the inner side of the pia mater) and the end of Bruch's membrane, if the end of Bruch's membrane did not reach the optic nerve margin or even overhang into the region of the optic nerve head (Fig. 1). "Delta zone" was a central part of the gamma zone in which blood vessels of at least 50-μm diameter were not detected and that had a minimal length of 300 μm. The choriocapillaris was considered not to be occluded if fine open capillaries of a diameter of approximately 10 to 20 μm were detectable just beneath Bruch's membrane.

The statistical analysis was performed using a commercially available statistical software package (SPSS for Windows, version 20.0; SPSS, Inc., Chicago, IL). Means and SDs, as well as medians and ranges were presented. The prevalence was presented as mean ± SE. In binary regression analysis, the associations between the prevalence of a macular abnormality and other parameters, such as axial length, were assessed. Odds ratios were presented and their 95% confidence intervals were described. All *P* values were two sided and considered statistically significant when less than 0.05.

Results

The study included 138 human globes (138 patients) with horizontal sections running through the optic disc and macular region. Among the 138 globes, 65 eyes had been enucleated due to a malignant melanoma of the choroid, and 55 globes showed an end-stage glaucomatous optic neuropathy; 39 (28.2%) were highly myopic, defined as an axial length of 26.5 mm or longer. Mean age was 63.8 ± 12.7 years (median: 65 years; range: 33–89 years). Mean axial length was 25.3 ± 2.9 mm (median: 24.25 mm; range: 20–35 mm).

In 12 (8.7%) eyes, we detected a defect in Bruch's membrane in the macular region, associated with a complete lack of RPE cells and choriocapillaris, and an almost complete lack of photoreceptors (Figs. 3–5). In some of the eyes, the ends of Bruch's membrane at the edge of the MBMD were rolled up or folded and the RPE heaped up in some of the eyes. In univariate analysis, the presence of such an MBMD was significantly associated with longer axial length ($P < 0.001$) (Fig. 6), longer gamma zone ($P = 0.04$) and delta zone of parapapillary atrophy ($P < 0.001$) (Fig. 7), a thinner peripapillary scleral flange ($P < 0.001$), and lower thickness of the sclera just outside of the optic nerve meninges ($P < 0.001$), the posterior pole ($P < 0.001$), and in the midperiphery between the posterior pole and equator ($P < 0.001$) (Table 1). Similar results were obtained if hyperopic eyes (defined as axial length ≤23.5 mm) were excluded from the control group (Table 2). An MBMD was found only in eyes with an axial length of 27 mm or longer. The prevalence of MBMDs in highly myopic eyes, defined as an axial length of longer than 26.5 mm, was 12/39 or 30.8%. Presence of an MBMD was not significantly related to the length of beta zone of parapapillary atrophy ($P = 0.09$), with the scleral thickness at the equator ($P = 0.51$), the ora serrata ($P = 0.51$), and at the limbus ($P = 0.59$), and with the presence of glaucomatous optic nerve damage ($P = 0.56$).

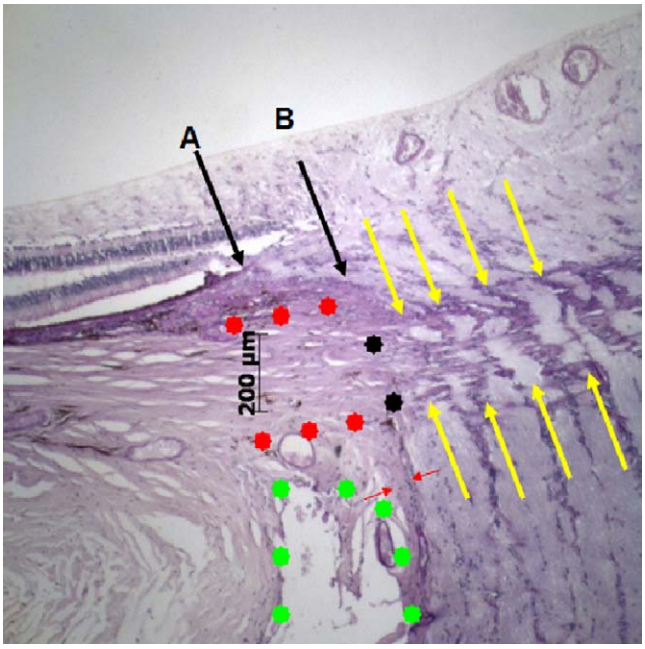

Figure 1. Histophotograph of a normal optic nerve head; between *yellow arrows*: lamina cribrosa; between *red dots*: peripapillary scleral flange; between *green dots*: orbital cerebrospinal fluid space; *arrow A*: end of Bruch's membrane; *arrow B*: border of the optic nerve head (as defined by inner margin of pia mater [*small red arrows*] and end of lamina cribrosa); between *arrow A* and *arrow B*: gamma zone of parapapillary region (PAS stain).

As the second step of the statistical analysis, a binary regression analysis was performed with the presence of an MBMD as the dependent parameter and all parameters as independent parameters, which were significantly associated with the presence of an MBMD in univariate analysis. It showed that the presence of an MBMD remained to be significantly ($P < 0.001$) associated with axial length

Discussion

In our histological study on the macular region of highly myopic eyes, we detected macular regions without Bruch's membrane and (consequently) without adjacent RPE and without chorio-

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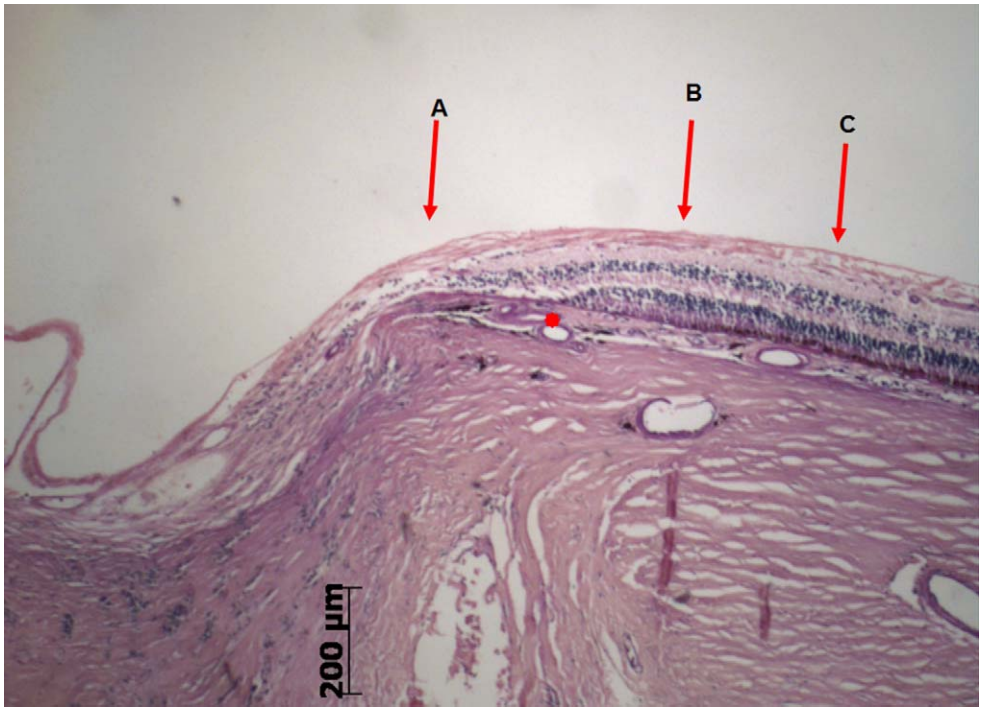

Figure 2. Histophotograph of the parapapillary region in a glaucomatous non–highly myopic eye. *Arrow A*: end of Bruch's membrane at the optic disc border; *arrow B*: end of irregular retinal pigment epithelium on Bruch's membrane; *arrow C*: end of normal RPE on Bruch's membrane; between *arrow A* and *arrow B*: beta zone of parapapillary region; between *arrow B* and *arrow C*: alpha zone of parapapillary region; *red dot*: end of retinal photoreceptor layer within beta zone of parapapillary region (PAS stain).

capillaris. The photoreceptor layer was markedly diminished or rudimentary, as was the remaining choroid, with only a few large choroidal vessels present. In these regions with this secondary macular opening of Bruch's membrane, the globe wall consisted of a markedly thinned sclera, some melanin-bearing cells on the inner surface of the sclera (lamina fusca sclerae), and remnants of the middle layer and inner layer of the retina, including the inner limiting membrane.

These findings have not been described in previous studies. The last major study and review on the histology of myopic

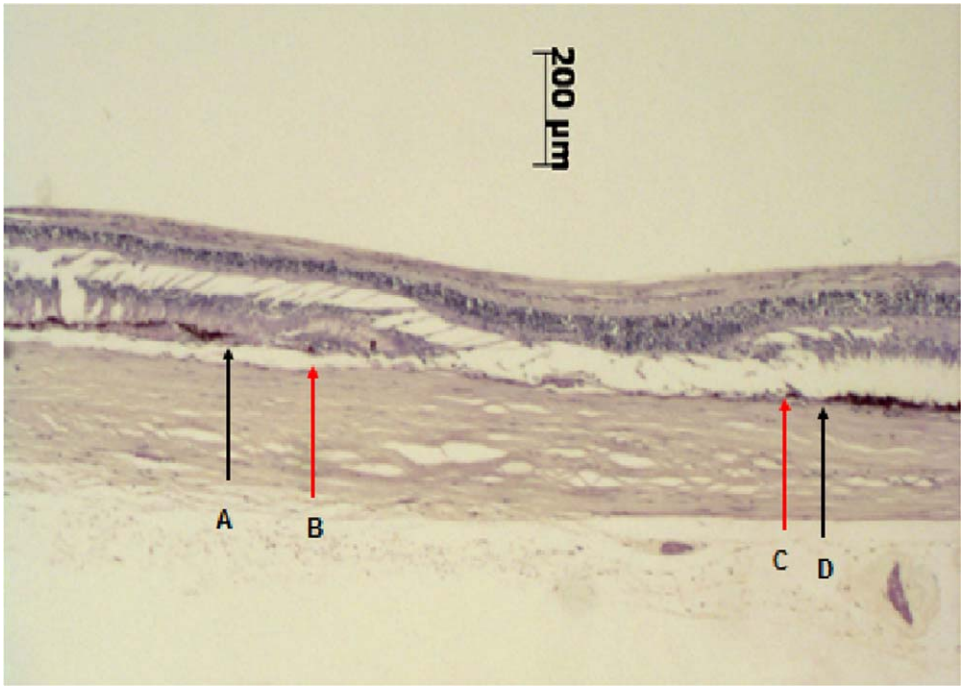

Figure 3. Histophotograph of macular Bruch's membrane defect in a highly myopic eye. *Black arrows A* and *D*: end of RPE; *red arrows B* and *C*: end of Bruch's membrane; between *B* and *C*: macular defect in Bruch's membrane without RPE and choroid (PAS stain).

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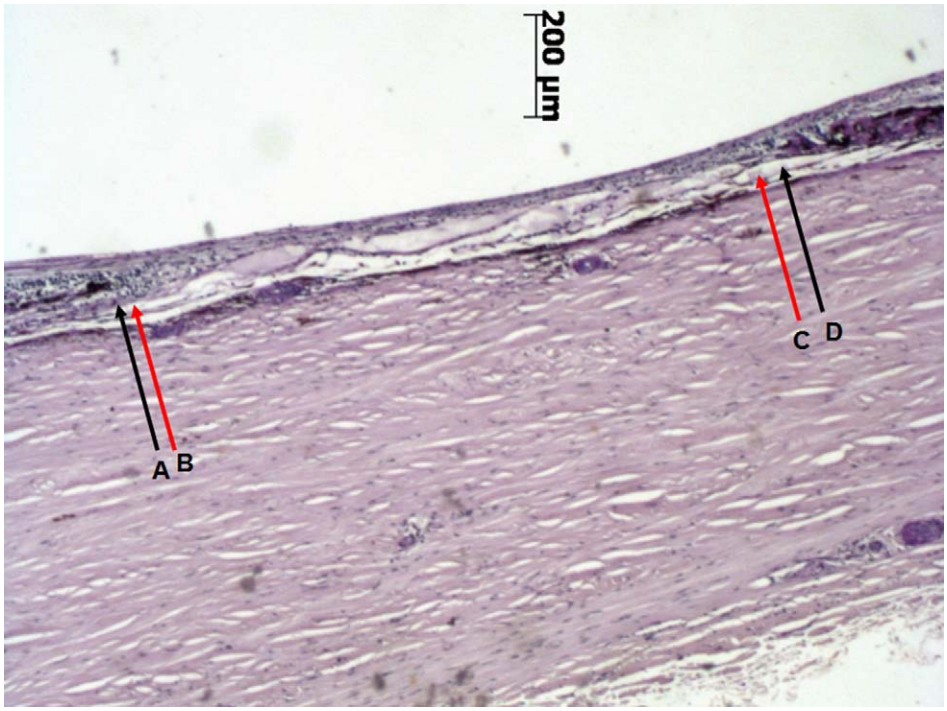

Figure 4. Histophotograph of macular Bruch's membrane defect in a highly myopic eye. *Black arrows A* and *D*: end of RPE; *red arrows B* and *C*: end of Bruch's membrane; between *B* and *C*: macular defect in Bruch's membrane without retinal pigment epithelium and with some remaining choroidal structures, including melanocytes on inner scleral surface (lamina fusca sclerae) (PAS stain).

maculopathy was performed in 1992 by Grossniklaus and Green,[10] in which 308 eyes with pathologic myopia (23 surgical eyes; 285 postmortem eyes) were examined. These eyes had been collected over a 67-year period. Grossniklaus and Green[10] assessed the frequency of histopathologic findings and described a myopic optic nerve head configuration found in 38% of the eyes to be the most common findings, followed by posterior staphylomata (35%); degenerative changes of the vitreous (35%); cobblestone degeneration (14%); myopic degeneration of the retina (11%); retinal detachment (11%); retinal pits, holes, or tears (8%); subretinal neovascularization (5%); lattice degeneration (5%); Fuchs spot (3%); and finally and lacquer cracks (1%). In Grossniklaus and Green's report,[10] a staphyloma was described as a scleral thickness reduction to approximately 0.1 mm, thin but present choroid, and intact RPE and intact photoreceptor layer. Myopic retinal degeneration was characterized by an atrophy of the RPE, atrophy of the outer layers of the overlying neurosensory retina, and loss of choroid, without described changes or lack of Bruch's membrane. These histologic descriptions of a staphyloma and myopic retinal degeneration are different from our observation, which included an absence of Bruch's membrane and thus an absence of RPE and choriocapillaris and an additional loss of the middle layer of the choroidal vessels, with some photoreceptors and a few large choroidal vessels remaining in patchy areas of the region without Bruch's membrane.

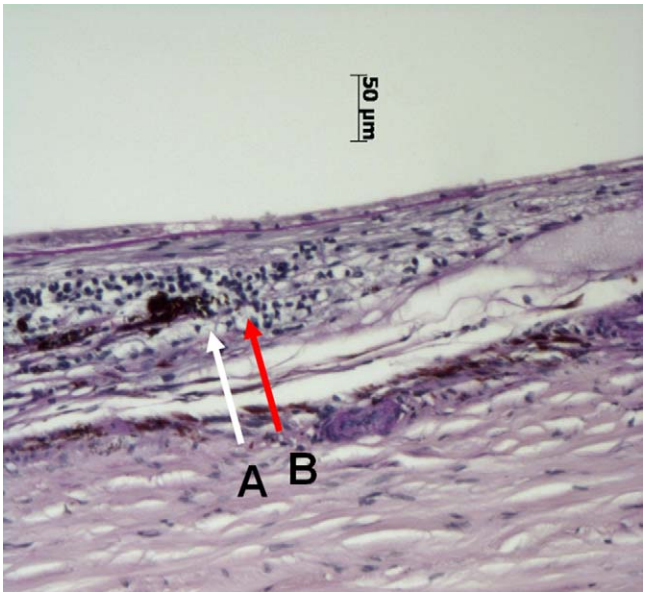

Figure 5. Histophotograph of macular Bruch's membrane defect in a highly myopic eye (detail of Fig. 4). *White arrow A*: end of RPE; *red arrow B*: end of Bruch's membrane; From *B* to the right: macular defect in Bruch's membrane (PAS stain).

Because we did not have a direct clinical histological correlation, we cannot allocate the areolar defect in Bruch's membrane to an ophthalmoscopical finding. One may assume that the macular defect in Bruch's membrane may be the clinical equivalent of some patchy so-called chorioretinal atrophic regions at the posterior pole of highly myopic eyes. If that holds true, the term chorioretinal atrophy in these situations may be a misnomer, as atrophy means a whithering or shrinkage but still present tissue. Without doubt, there are other chorioretinal atrophic regions in highly myopic eyes in which Bruch's membrane is present. Future clinical studies applying optical coherence tomographic imaging of the deep retinal structures may be warranted to clinically better differentiate between these types of lesions.

Presence of an MBMD was strongly associated with axial length and indirectly with the length of the gamma zone and delta zone of the parapapillary region, whereas the beta zone was not significantly associated. Additionally, the presence of

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Figure 6. Boxplots showing the distribution of axial length in eyes with a macular Bruch's membrane defect and a control group.

an MBMD was not significantly associated with the presence of glaucomatous optic nerve damage. These findings agree with a recent histomorphometric study in which gamma zone and delta zone of the parapapillary region were significantly associated with axial length but not with glaucoma, whereas beta zone of the parapapillary region was significantly associated with glaucoma but not with axial length.[11]

The macular Bruch's membrane defect in highly myopic eyes would be second to the primary hole in Bruch's membrane as the inner layer of the optic nerve head, as the

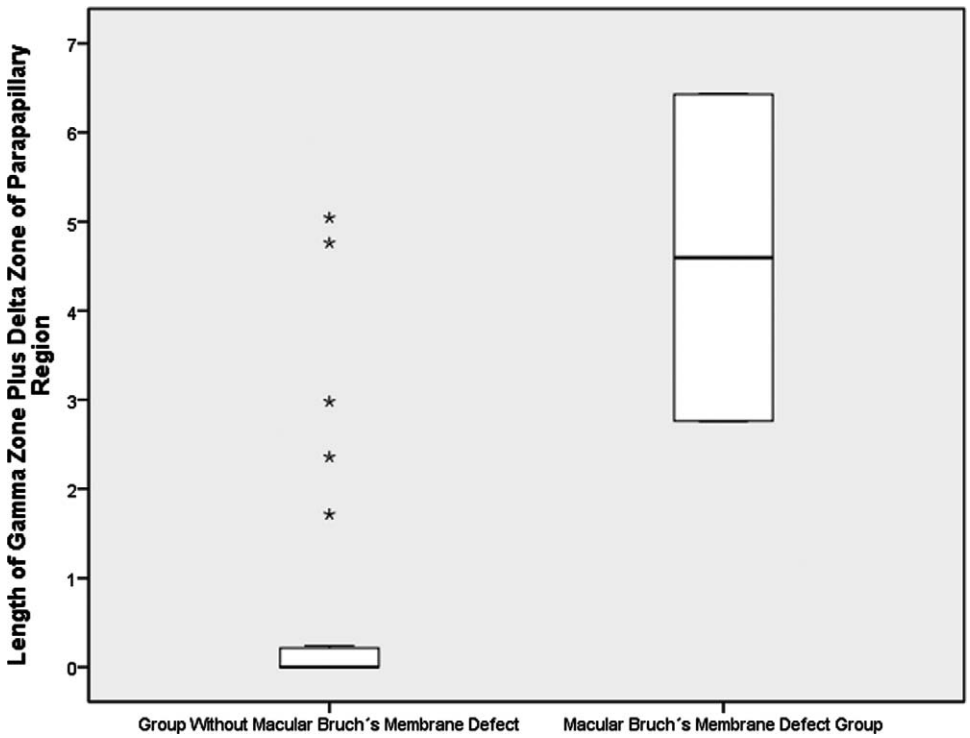

Figure 7. Boxplots showing the distribution of gamma zone plus delta zone of parapapillary region in eyes with a macular Bruch's membrane defect and a control group.

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Table 1. Ocular Measurements (Mean ± SD) in Eyes with an MBMD and a Control Group

Parameter	Macular Bruch's Membrane Defect	Control Group	*P* Value
n	12	126	
Age, y	75.2 ± 9.7	63.2 ± 12.7	0.11
Axial length, mm	30.0 ± 2.8	24.8 ± 2.51	<0.001
Parapapillary region			
Beta zone, mm	0.59 ± 1.02	0.20 ± 0.20	0.09
Gamma zone, mm	1.98 ± 2.16	0.46 ± 1.03	0.04
Delta zone, mm	1.07 ± 1.06	0.06 ± 0.27	<0.001
Scleral thickness, mm			
Peripapillary flange	0.22 ± 0.13	0.37 ± 0.10	<0.001
Optic nerve outside of dura mater	0.40 ± 0.20	0.81 ± 0.23	<0.001
Posterior pole	0.43 ± 0.20	0.89 ± 0.22	<0.001
Midpoint posterior pole/equator	0.35 ± 0.14	0.61 ± 0.17	<0.001
Equator	0.35 ± 0.13	0.38 ± 0.14	0.51
Ora serrata	0.41 ± 0.12	0.39 ± 0.11	0.51
Limbus	0.48 ± 0.08	0.51 ± 0.10	0.59

optic nerve head can be considered to be a two-layered structure: an inner hole in Bruch's membrane and an outer hole in the sclera (i.e., the optic nerve scleral canal). The primary Bruch's membrane hole present in all eyes allows the passage of the retinal ganglion cell axons out of the eye, and the passage of the large retinal vessels in and out of the eye. It is usually of the same size as the scleral hole. If the primary Bruch's membrane hole is larger than the scleral optic nerve head hole, or if the primary Bruch's membrane hole in its spatial relationship to the scleral hole is slightly shifted to the temporal region, gamma zone of parapapillary region develops, leaving the temporal parapapillary region devoid of Bruch's membrane. In the eyes with a shift of the primary Bruch's membrane hole to the temporal side, the nasal edge of Bruch's membrane optic nerve head opening may extend or overhang into the region of the optic disc, as shown recently.[12]

One can thus differentiate between the primary Bruch's membrane hole forming the inner layer of the optic nerve head, and a secondary defect in Bruch's membrane, which develops due to the myopic stretching of the posterior segment of the eye in high (pathologic) myopia. The presence of a macular Bruch's membrane defect was significantly associated with presence and length of the delta zone of parapapillary atrophy. The delta zone is present only in highly myopic eyes, which explains the association. All eyes with a secondary macular Bruch's membrane defect showed a delta zone, whereas some eyes with a delta zone did not show an MBMD. Future studies may address the question of which of the two lesions may develop first.

Interestingly, the histology of the MBMDs in highly myopic eyes as described in our study may have a correlate in a recent study in which optical spectral-domain coherence tomography revealed defects in Bruch's membrane in the macular region of highly myopic eyes (Spaide RF, unpublished observation, 2012). Although we did not have sufficient clinical information on the visual function of the patients included in our study, one may infer that the region of the secondary macular Bruch's membrane defect represented psychophysically an absolute scotoma due to the complete lack of RPE cells and almost complete lack of photoreceptors. Future clinical studies may examine the posterior pole of highly myopic eyes by optical coherence tomography, and may apply retinal microperimetry to directly measure the visual functions in these areas.

A macular Bruch's membrane defect as described in our study may be added to the panoply of the features of myopic retinopathy, which includes myopic Fuchs's spot, scleral staphylomata and lacquer cracks in the macular region, gamma zone and delta zone of the parapapillary region, and a

Table 2. Ocular Measurements (Mean ± SD) in Eyes with an MBMD and a Control Group with Hyperopic Eyes (Defined as Axial Length ≤23.5 mm) Excluded

Parameter	Macular Bruch's Membrane Defect	Non-Hyperopic Control Group	*P* Value
n	12	88	
Age, y	75.2 ± 9.7	62.6 ± 12.6	0.09
Axial length, mm	30.0 ± 2.8	25.9 ± 2.2	<0.001
Parapapillary region			
Beta zone, mm	0.59 ± 1.02	0.21 ± 0.21	0.70
Gamma zone, mm	1.98 ± 2.16	0.56 ± 1.11	0.27
Delta zone, mm	1.07 ± 1.06	0.09 ± 0.32	0.04
Scleral thickness, mm			
Peripapillary flange	0.22 ± 0.13	0.37 ± 0.11	0.008
Optic nerve outside of dura mater	0.40 ± 0.20	0.79 ± 0.25	<0.001
Posterior pole	0.43 ± 0.20	0.86 ± 0.23	<0.001
Midpoint posterior pole/equator	0.35 ± 0.14	0.59 ± 0.18	<0.001
Equator	0.35 ± 0.13	0.36 ± 0.15	0.83
Ora serrata	0.41 ± 0.12	0.38 ± 0.11	0.50
Limbus	0.48 ± 0.08	0.51 ± 0.10	0.36

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secondary macrodisc and a marked stretching and thinning of the lamina cribrosa in association with an increased susceptibility for glaucomatous optic neuropathy.[3,8,11,13,14] The question arises as to which reasons led to the development of an MBMD in highly myopic eyes. One may assume that the myopic enlargement of the globe mainly occurring posterior to the equator is associated with a stretching of Bruch's membrane parallel to the thinning of the sclera.[15] This is suggested by the finding that the choroidal thickness decreases with increasing axial length of the eye.[16–18] If Bruch's membrane changed its form and size by a smaller amount than the myopic change in the size and form of the sclera, the distance between the sclera and Bruch's membrane would enlarge. Future studies may thus address myopic changes in Bruch's membrane, and whether perhaps Bruch's membrane shows a thinning parallel to the scleral thinning in highly myopic eyes. Theoretically, one may then even raise the question of whether the myopic enlargement of the posterior segment of the globe is primarily due to scleral changes, or due to changes in Bruch's membrane leading secondarily to a scleral stretching and thinning. Bruch's membrane appears to be stretched in highly myopic eyes and a significant tear or dehiscence may allow for retraction of the edges of the defect. Correspondingly, the ends of Bruch's membrane at the edge of the MBMD were rolled up or folded and the RPE heaped up in some of the eyes. This feature may be due to the elastic properties of Bruch's membrane. One may also wonder whether the MBMDs may be related to the clinical condition of macular intrachoroidal cavitation, which was recently described.[19]

Limitations of our study should be mentioned. First, serial sections of the globes were not available and we had at maximum three slides per eye. It was therefore not possible to measure the defect in Bruch's membrane in all directions. It would have been markedly more precise if serial sections had been available. It may, however, be very difficult to find enough highly myopic enucleated eyes for which histological serial sections can be prepared. Although our study can therefore be regarded only as a qualitative investigation, it provides the proof of principle that highly myopic eyes can develop a defect in the macular Bruch's membrane. Additionally, our study showed some semiquantitative associations between myopia-associated changes in the parapapillary region and the presence of a macular Bruch's membrane defect. Second, we did not have fundus photographs, so that a direct clinical-histological correlation was not possible. Third, in a similar manner, it would have been advisable to take photographs of the inside of the eye cup after removal of the anterior segment during the preparation of the globes. It would have made possible a macroscopic-histologic correlation. Fourth, the study included sections of a horizontally orientated, anterior-posterior segment going through the pupil and the optic nerve. Consequently, the sections went through the macular region but not necessarily exactly through the fovea. This disadvantage of the study may, however, been outweighed by the location of the macular lesions in eyes with myopic retinopathy. Because highly myopic lesions can be found in the foveal region as well as in the perifoveal area, the chance to miss such a highly myopic lesion may not profoundly depend on the exact orientation of the histologic slide through the foveola. Fifth, it can be difficult to make out the end of Bruch's membrane by using a light microscopic examination, even if a staining method such as PAS was used to visualize basal membranes like Bruch's membrane. An alternative would have been to examine the slides using transmission electron microscopy. Unfortunately, however, the available study material was not sufficient for such a procedure. Sixth, this was a laboratory-based retrospective study with a high chance of a marked bias due to the selection of patients and eyes. It was, however, not the purpose of our study to assess the prevalence of the MBMDs in the general population but to qualitatively describe their occurrence.

In conclusion, myopic maculopathy in highly myopic eyes with an axial length of 27 mm or longer shows regions with an MBMD associated with a complete loss of RPE and choriocapillaris, and a marked reduction in outer retinal layers and large choroidal vessels. MBMD presence was strongly associated with higher axial length and indirectly with a larger gamma zone and larger delta zone of parapapillary region. Regions with MBMDs will present an absolute scotoma due to the loss RPE cells and photoreceptors. The marked stretching in high myopia may lead to the MBMDs. These secondary defects in Bruch's membrane may develop parallel to the myopia-induced widening of the primary opening in Bruch's membrane around the optic nerve head. The latter process leads to the development and enlargement of gamma zone and delta zone in the parapapillary region.

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