



Saldan Y.¹ ✉, Artemov A.²

¹ Vinnitsa National Medical University named after N. Pirogov, Vinnitsa, Ukraine

² The Filatov Institute of Eye Diseases and Tissue Therapy of NAMS of Ukraine, Odessa, Ukraine

Collagen-Elastic Eye Frame and its Role in Homeostasis and Pathology

Conflict of interest: nothing to declare.

Submitted: 09.03.2021

Accepted: 14.02.2022

Contacts: ysaldan@ukr.net

Abstract

The concept of a unified fibro-elastic eye frame, including Descemet's membrane, Dua's membrane, trabecular tissue, Bruch's membrane and the posterior borderline membrane of the optic nerve disc, makes it possible to consider a number of pathological processes affecting these structures within the framework of a single etiopathogenetic mechanism. Basement membranes are fibrous acellular structures, usually of type IV collagen, and separating the inner or outer surfaces of epithelial or endothelial formations from the underlying connective tissue. The ultrastructure organization of the basement membranes in various tissues of the body is similar: it distinguishes between the internal collagen part – the basal plate, and the underlying layer of reticular and elastic fibers.

Despite their extracellular location, the basement membranes are not part of the extracellular matrix and do not belong to connective tissue, although they have macromolecules in common with it. As you know, the most common functional role of basement membranes is manifested in the structural addition of epithelial formations histogenetically related to them and in the delimitation of the latter from the underlying connective tissue.

The basement membranes maintain the unity of the structural and functional complex, providing adhesion between the epithelial monolayer on the one hand and the underlying stroma on the other. The general plan of this organization is the unity of collagen and elastic plates, which are formed from both the epithelium and the stroma, including the adjacent vascular component, the participation of which, in particular, has long been noticed in Bruch's membrane. Violation of this unity triggers the pathogenetic mechanism of many pathological processes, which are clearly manifested in the eye. Thus, the eyeball can become part of a systemic pathological process caused by genetic defects in collagens and age-related degenerative processes.

Among such common diseases, one should first of all pay attention to open-angle glaucoma and endothelial corneal dystrophy. In these pathological processes, with all their clinical differences, one can see a unifying factor associated with the most vulnerable link that triggers the pathogenic mechanism. Despite certain molecular-biochemical nuances, collagen-elastic membranes have a universal structural design, and with a variety



of pathological conditions in which it is involved, two etiopathogenetic mechanisms can be distinguished.

These mechanisms appear as changes of a dystrophic or degenerative nature. In particular, in the trabecular tissue, the age-related decrease in the number of endothelial cells lining the trabeculae leads to a loss of the ability to retain intraocular fluid and initiates a process similar to what occurs in bullous keratopathy in the corneal stroma. Swelling of the collagen fibers of the trabecula leads to a narrowing of the lumen of the intertrabecular fissures and an increase in resistance to the outflow of intraocular fluid.

So, using the example of eye pathology, we can understand the special functional role of collagen-elastic membranes. To the same extent, this concept contributes to a deeper understanding of a number of diseases and pathological processes, in the etiopathogenesis of which Bruch's membrane plays an important role. Among these diseases is age-related macular degeneration. Thus, the hypothesis presented by us and its theoretical justification for the inner collagen capsule of the eye allows us to consider the pathogenesis of eye diseases in a new way and outline the practical steps of their treatment.

Keywords: unified fibro-elastic eye frame, Descemet's membrane, Dua's membrane, trabecular tissue

Салдан И.Р.¹ ✉, Артемов А.В.²

¹ Винницкий национальный медицинский университет имени Н.И. Пирогова, Винница, Украина

² Институт глазных болезней и тканевой терапии имени В.П. Филатова НАМН Украины, Одесса, Украина

Коллаген-эластичный каркас глаза и его роль в гомеостазе и патологии

Конфликт интересов: не заявлен.

Подана: 09.03.2021

Принята: 14.02.2022

Контакты: ysaldan@ukr.net

Резюме

Предлагается концепция фиброзно-эластичного каркаса глаза, включающего в себя десцеметову мембрану, мембрану Дуа, трабекулярную ткань, мембрану Бруха и заднюю пограничную пластинку диска зрительного нерва. Это позволяет рассматривать ряд патологических процессов, вовлекающих эти структуры, в рамках единого этиопатогенетического механизма. Среди таких заболеваний – открытоугольная глаукома и эндотелиальная дистрофия роговицы, где при всех клинических различиях присутствует объединяющее звено, связанное с патогенетическим механизмом. Несмотря на определенные молекулярно-биохимические нюансы, коллаген-эластические мембраны имеют универсальный структурный дизайн. При различных патологических состояниях, в которые они вовлечены, выделяются два

этиопатогенетических механизма, проявляющиеся как изменения дистрофического или дегенеративного характера. Представленная концепция внутренней коллагеновой капсулы глаза позволяет по-новому взглянуть на патогенез глазных заболеваний и наметить практические этапы их лечения.

Ключевые слова: фиброзно-эластичный каркас глаза, десцеметова мембрана, мембрана Дуа, трабекулярная ткань

In previous works, we have already paid attention to the special role of membrane formations in the anterior part of the eye. Developing this idea, we would like to discuss other membrane structures of the eyeball, which, despite their topographic isolation, work in collaboration, providing homeostasis of the most important functions for the organ of vision.

The study of this issue allowed us to approach the discussion of the concept of a single fibro-elastic eye frame, including Descemet and Dua's membranes, trabecular tissue, Bruch's membrane and the posterior borderline plate of the optic nerve head. This approach makes it possible to consider a number of pathological processes affecting these structures, within the framework of a single etio-pathogenetic mechanism. Starting to consider this issue, we would like to make a short excursion on the structural organization of collagen and elastic membranes in the body.

Structural organization of fibro-elastic membranes

Basement membranes are thin (20–50 nm) fibrous acellular structures, usually represented by type IV collagen, and separating the inner or outer surfaces of epithelial or endothelial formations from the underlying connective tissue. The ultrastructural organization of the basement membranes in various tissues of the body is similar: it distinguishes between the inner collagen part – the basal plate, and the underlying layer of reticular and elastic fibers. Despite their extracellular location, the basement membranes are not part of the extracellular matrix and do not belong to connective tissue, although they have macromolecules in common with it. The adjacent connective tissue stroma connects to the basement membranes using anchor fibrils and type VII collagen microfibrils. Both of these parts are considered as building blocks of the basement membrane.

From the side of epithelial cells, communication is carried out by semi-desmosom. In the basal plate itself, light (lamina lucida) and dark (lamina densa) plates, or layers, are also distinguished. The light layer is adjacent to the epithelial lining, and the dark layer is adjacent to the connective tissue. The electron-dense dark plate has a thickness of 30–70 nm and consists of collagen-IV reticular fibrils, and also includes an internal macromolecular matrix – heparan sulfate that rich with proteoglycan perlecan. The light plate contains laminin, integrins, entactins and dystroglycans. Integrins are not part of the basement lamina; they are regarded as independent adhesion molecules (CAMs or ARs) within the basement membrane.

Through the basement membranes, nutrition of the associated cellular elements occurs; transport of gases and metabolic exchange occurs through the diffusion of substances through the basement membrane from the adjacent vessels of the microcirculatory bed.



The role of basement membranes in the body is mainly limited by this delimiting trophic function, and their participation in pathological processes is considered mainly within the framework of those epithelia that are associated with them.

Unlike other organs, the fibro-elastic membranes of the eye, having a similar macromolecular organization, are anatomical structures that play an independent role in ensuring the most important functions of the organ of vision, which we would like to dwell on in more detail.

Descemet membrane and trabecular tissue

The classical concepts of the five-layer structure of the cornea, which developed during the 19–20 centuries thanks to histological and electron microscopic studies, began to undergo correction in the last decade. Moreover, it is interesting to note that the basis for this was not discoveries in morphological studies, but clinical practice. Surgical innovations of recent decades, based on improved laser technologies, have made it possible to draw attention to the structural heterogeneity of the stroma of the inner layers of the cornea.

So, in 2013, H. Dua, a professor of ophthalmology and optics from the University of Nottingham, proposed isolating the sixth layer in the human cornea, which was named the Dua's layer. The Dua layer includes 5–8 bundles of collagen fibers, tightly packed into a thin lamina, and has an average thickness of $10.15 \pm 3.6 \mu\text{m}$ (range from 6.3 to 15.83), which is slightly larger than that of the posterior border plate, the average thickness which is from $10.97 \pm 2.36 \mu\text{m}$ (range from 7.8 to 13.98). The layer expands as it approaches the sclera, ciliary body and the root of the iris.

It is interesting to note that the keratocytes of the Dua layer, like the cells of the trabecular tissue, are negative in relation to the membrane glycoprotein CD34, which is characteristic of the keratocytes of the corneal stroma. This immunohistochemical nuance can serve as an indirect confirmation of the histo-embryogenetic commonality of the Dua layer and trabecular tissue, and the posterior trabecular network located behind the venous sinus of the sclera, thus, can be considered an extension of the collagen fibers that form the Dua layer.

Isolation of a special collagen layer histogenetically associated with the Descemet membrane and the posterior corneal epithelium lining it is of interest not only from the point of view of histo-topography and surgical technique. So, for a long time, the posterior corneal epithelium was considered endothelium, which did not allow us to consider it as a source of collagen membranes formed during a number of pathological processes in the anterior chamber of the eye. This contradicted the concept of the histogenetic potential of endothelial cells. Only in the second half of the last century it became obvious that it is the posterior epithelium that is the source of connective tissue (retrocorneal) films formed during inflammatory and burn processes in the anterior chamber of the eyeball. The possibility of proliferation of the posterior corneal epithelium and the construction of fibrous tissue with a vitreous plate, similar to the posterior border membrane, was shown [2, 3]. It was revealed that the retrocorneal films formed by the posterior corneal epithelium include not only the elements of the posterior boundary plate, but also collagen fibers of the corneal stroma. All of these elements, including the posterior epithelium, the posterior border plate and the posterior stromal layers, are sometimes reproduced with such structural fidelity that these films can maintain transparency without impairing vision [3, 12].

It is interesting to note that the stromal component of retrocorneal films does not exceed 20–30 μm in thickness. The stroma, which the posterior epithelium reproduces under conditions of pathological regeneration, in its thickness approaches the thickness of the layer described by H. Dua et al. in the cornea. New morphological data are well projected on embryological studies, which in the middle of the last century showed the complex genesis of the corneal stroma [7]. So, in contrast to the anterior part of the cornea, the posterior epithelium begins to form later, without inductive action of the elements of the eye cup. At the same time, mesenchymal cells migrate to the posterior surface of the cornea, forming the posterior stroma, which is synchronously covered by the cells of the future posterior epithelium. The final formation of the corneal stroma (collagen plates) requires the simultaneous presence of anterior and posterior epithelium. The independent formation of the anterior and posterior parts of the cornea is also confirmed by the fact that the development of the stroma proceeds intensively from the anterior epithelium and posterior endothelium, while in the center this process is slowed down [7].

Thus, histomorphological observations of regeneration processes (the formation of retrocorneal films) and experimental embryological data indicate the existence of a stroma of the posterior boundary plate, which is a special layer that has embryogenetic and histogenetic connections that differ from the rest of the corneal stroma.

Bruch's membrane

In recent studies, it was shown that Bruch's membrane is formed with the participation of neuroglia migrating from the inner neural layer of the optic cup through the pigment layer into the stroma of the developing choroid [9]. During embryogenesis, morphologically under the pigment epithelium and its basement membrane, two types of cells are determined: light, with a large hypochromic nucleus and high nuclear-cytoplasmic ratios, and dark ones with a basophilic nucleus and low nuclear-cytoplasmic ratios. Light cells are detected at earlier stages of development and are morphologically identical to glial cells in terms of staining – their cytoplasm is chromophobic.

Bruch's membrane has a histogenetic commonality with both the choroid and the retina. Detailed light microscopy highlights the outer collagen part and the inner elastic part – lamina elastic – in Bruch's membrane. The structure of Bruch's membrane and its thickness depend on both the localization of the area under study and the age of the individual. In adults, the thickness of the membrane in the peripapillary region is 2–4 μm , and in the peripheral, it is 1–2 μm . In children, its thickness in the central areas is 2 microns. Ultrastructural studies made it possible to distinguish five layers in Bruch's membrane: the basement membrane of the pigment epithelium, the inner layer of fibers (elastic), the outer collagen layer, the basement membrane of the endothelial cells of the choriocapillaries. The innermost layer of the membrane, represented by the basement membrane of the retinal pigment epithelium, is approximately 0.3 μm thick.

The inner collagen zone (1.5 μm thick) consists of tightly packed and strictly oriented collagen fibrils (fiber diameter 60 nm, striation frequency 64 nm). Collagen refers mainly to type IV collagen. The fibers are immersed in a base material consisting mainly of proteoglycans. The middle zone (elastic layer) has a thickness of about 0.8 microns, and in it elastic fibers are randomly arranged. It is in this zone that during aging and various pathological conditions, the accumulation of calcium salts and lipids is noted.



The outer collagen zone is similar in structure to the inner zone. The only difference is that it is thicker – 0.7 microns. The outer layer of Bruch's membrane, represented by the basement membrane of the endothelial cells of the capillaries of the choroid, is the thinnest (0.14 μm).

Basically, Bruch's membrane is made up of three inner layers, as the outer layers refer to the structures of the choroid. Some authors associate new therapeutic approaches with progenitor cells responsible for the morphogenesis of the Bruch membrane in early human ontogenesis. Thus, there is an idea of using neuroglial migrants from the inner wall of the optic cup for the treatment of age-related macular degeneration and diabetic retinopathy.

Lamina cribrosa of the sclera

The lamina cribrosa of the sclera is, from an anatomical point of view, a special part of the scleral membrane, which is rather uneven in thickness. Thus, according to various sources, the thickness of the lattice plate ranges from 119 to 463 μm , which is 4–5 times less than the thickness of the sclera in the region of the posterior pole of the eye; it is characterized by a large number of holes (from 200 to 400), occupying up to 2/3 of its area [4, 8].

On sagittal sections in the lamina cribrosa, from 3 to 10 perforated layers of dense fibrous connective tissue can be distinguished, which are oriented perpendicular to the axonal course. At this point, collagen fibers of types I, III, and IV are intertwined with elastin fibers, among which some authors note the presence of glial fibers [8]. This microtubule system also contains a capillary network, which generally provides structural and trophic support for the axonal bundles of the optic nerve.

The lamina cribrosa is considered by a number of authors to be the most important locus in which mechanical stresses are concentrated arising from the direct effect of intraocular pressure on the inner surface of the shell of the eyeball and the action of the cerebrospinal fluid from the outer surface [16, 17]. Thus, the ratio of forces acting in opposite directions determines the deformation profile of the lamina cribrosa, taking into account the anatomical features of the latter [6, 13, 19].

This circumstance is given special attention in connection with the study of the pathogenesis of glaucoma. In particular, based on the concepts noted above, they explain the discrepancy between the level of intraocular pressure and the degree of glaucomatous excavation of the optic nerve head. Modern diagnostic methods, in particular OCT, made it possible to establish that the progression of glaucoma and an increase in the excavation of the optic disc is combined with a decrease in the thickness of the lamina cribrosa and an increase in its displacement posteriorly [19]. In patients with intracranial hypertension, an anterior shift of the lamina cribrosa is noted. In conditions of increased IOP, a decrease in the pressure of the cerebrospinal fluid can lead to a displacement of the RPJ, which is associated with damage to the axons of the optic nerve [1, 4, 5, 17].

Collagen-elastic frame of the eye

As you know, the most common functional role of basement membranes is manifested in the structural addition of epithelial formations histogenetically related to them and the delimitation of the latter from the underlying connective tissue stroma. Along with delimitation, the basement membranes maintain the unity of the structural and functional

complex, providing adhesion between the epithelial monolayer on the one hand and the underlying stroma on the other. The general plan of this organization is the unity of collagen and elastic plates, which are formed from both the epithelium and the stroma, including the adjacent vascular component, the participation of which, in particular, has long been noted in Bruch's membrane. The violation of this unity becomes the leading pathogenetic element of many pathological processes, which acquire a clearly manifest character in the eye.

So, the eyeball can become part of a systemic pathological process caused by genetic defects in collagens, especially type IV collagen, as, for example, in hereditary Alport and Knobloch syndromes, or in mesenchymal dystrophies such as Behcet or Koyanagi syndromes, in which, in one way or another at least, individual collagen structures of the eye can be affected.

Along with this, there are a number of pathological processes in which collagen-elastic membranes of the eye become independent participants in the etiopathogenetic mechanism of eye diseases. In a number of previous works, we have already touched on the specific nature of pathological changes in membrane structures in such diseases of the anterior part of the eye as endothelial dystrophy and open-angle glaucoma [10, 11]. As part of the discussion of this topic, it is necessary to focus on the entire complex of membranes, which appear as a kind of collagen-elastic frame of the eye, maintaining homeostasis and becoming a central link, a kind of locus minoris resistentiae, in the pathogenesis of many eye diseases.

Among suchlike common diseases, one should first of all pay attention to open-angle glaucoma and endothelial corneal dystrophy. In these pathological processes, with all their clinical differences, one can see a unifying factor associated with the most vulnerable link that triggers the pathogenetic mechanism. Collagen-elastic membranes are such a link.

As noted above, despite certain molecular-biochemical nuances, collagen-elastic membranes have a universal structural design due to the general histogenesis of the cells involved in their formation. Therefore, despite the variety of pathological conditions in which the collagen-elastic frame of the eye is involved, two etiopathogenetic mechanisms can be distinguished here. These mechanisms appear as changes of a dystrophic or degenerative nature.

It should be noted here that there is often a mixing of these two independent pathological processes, which does not allow penetrating into the essence of specific diseases associated with them. The fact is that the term degeneration in the Latin transcription used in the English-language literature semantically coincides with the term that is widespread in our country – rebirth.

At the same time, in our medical literature, the terms degeneration and dystrophy are used synonymously, while in fact, degeneration is understood as the process of degradation, i.e. not transformation into something else, but disappearance – the loss of a structural unit. On the contrary, in the English-language literature, the concept of dystrophy is often used not as a general pathological concept, but as a characteristic of specific diseases: for example, muscular dystrophy. Thus, speaking about pathological conditions, which are based on a change in collagen-elastic structures, the concept of dystrophy can be used in situations where there is a change in the qualitative properties of an object, in this case, collagen structures.



In such cases, degenerative processes in the collagen-elastic structures of the eye, as a rule, are a local manifestation of systemic dystrophy, i.e. do not form an independent nosological unit. At the same time, such eye pathologies as open-angle glaucoma or epithelial-endothelial corneal dystrophy have long been considered independent diseases.

Moreover, within the framework of the concept considered here, the etiopathogenetic mechanism that forms the pathological symptomatic complex of these diseases is a reflection of one design. This commonality is due to the fact that the decompensation of functions that maintain homeostasis, on the one hand, with respect to IOP, and on the other, with respect to onco-osmotic pressure in the corneal stroma, is associated with one or another degree of functional deprivation of collagen-elastic membranes.

As we noted earlier, the structural organization and metabolism of collagen-elastic membranes is supported by endothelial cells, which were involved in their formation during embryogenesis. In subsequent ontogenesis, the fate of collagen-elastic membranes depends on the number of cells obtained at birth, as well as on their subsequent elimination, i.e. from age-related degeneration of endothelial cells. This process has been well studied in relation to the endothelial monolayer of the cornea, where the relationship between the density of endothelial cells and the development of one of the most severe eye diseases – endothelial dystrophy, is clearly traced. A similar degeneration of the endothelium of the trabecular meshwork of the eye drainage system may become a key link in the etiopathogenesis of primary open-angle glaucoma, although the relationship between age-related endothelial degeneration and the state of the collagen-elastic skeleton of the trabecular meshwork has not yet been sufficiently traced.

Nevertheless, the morphological, histogenetic and functional commonality of the corneal endothelium and trabecular tissue cannot but determine the general design of pathological changes. Thus, the age-related decrease in the number of endothelial cells lining the trabeculae will certainly lead to a loss of the ability to retain intraocular fluid and initiate a process similar to that which occurs with bullous keratopathy in the corneal stroma. Similarly, the swelling of the collagen fibers of the trabecula will lead to a narrowing of the lumen of the intertrabecular fissures and an increase in resistance to the outflow of intraocular fluid.

So, using the example of eye pathology, we can understand the special functional role of collagen-elastic membranes. To the same extent, this knowledge is necessary for a deeper understanding of a number of diseases and pathological processes, in the etio-pathogenesis of which Bruch's membrane plays an important role. Among them is age-related macular dystrophy. In particular, the difference between dry and wet macular degeneration [11, 12]. Thus, the hypothesis presented by us and its theoretical justification for the inner collagen capsule of the eye allows us to consider the pathogenesis of eye diseases in a new way and outline their practical steps.

■ REFERENCES

1. Bauer S.M., Zimin B.A., Tovstik P.E. *The simplest models of the theory of shells and plates in ophthalmology*. St. Petersburg: St. Petersburg Publishing House. university; 2000. (in Russian)
2. Vojno-Yaseneckij V.V. *Growth and variability of eye tissues in its diseases and injuries*. Kiev: High school; 1979;224 p. (in Russian)
3. Vojno-Yaseneckij V.V. On the neoplasm of vitreous membranes and multilayer fibrous tissue by Descemet's endothelium. *Ophthalmological journal*. 1970;6:551–556. (in Russian)

4. Volkov V.V. *Open-angle Glaucoma*. Moscow: MIA; 2008. (in Russian)
5. Iomdina E.N., Bauer S.M., Kotlyar K.E. *Biomechanics of the eye: theoretical aspects and clinical applications*. Moscow: Real Time; 2015. (in Russian)
6. Kiseleva O.A., Iomdina E.N., Yakubova L.V., Hoziev D.D. The cribriform plate of the sclera in glaucoma: biomechanical features and possibilities of their clinical control. *Russian ophthalmological journal*. 2018;11(3):76–83. doi: 10.21516/2072-0076-2018-11-3-76-83. (in Russian)
7. Lopashov G.V. *Development of the eye in the light of experimental studies*. M.: Publishing House of the Academy of Sciences of the USSR; 1963;206 p. (in Russian)
8. Nesterov A.P., Egorov E.A. *Glaucomatous atrophy of the optic nerve*. Moscow: Medicine; 1981. (in Russian)
9. Novikov A.S., Reva I.V., Reva G.V., Yamamoto T., Abdullin E.A., Al'brandt K.F. *Ontogeny of the Bruch's membrane of the human eye*. Basic research. 2013;3:424–428. Available at: <http://www.fundamentalresearch.ru/ru/article/view?id=32367>. (in Russian)
10. Saldan I.R., Artemov A.V., Saldan Yu.I., Nazarchuk G.G., Vernigorodskij S.V. Etiopathogenesis of primary open-angle glaucoma. *Surgery news*. 2017;25(3):300–305. (in Russian)
11. Saldan I.R. Fluorescein angiography in central serous chorioretinitis. *Ophthalmol. journal*. 1972;3:447–449. (in Russian)
12. Saldan Y. *Permeability disturbance of Bruch's membrane is precondition of AMD*. Baden-Baden; 2007.
13. Saldan Y.R., Majewski O.E., Saldan Yu.Y., Artemov A.V., Korol A.P. The sixth layer of the cornea: is it fiction or real fact? *Bulletin of morphology*. 2016;2(22):198–202.
14. Puchkovskaya N.A., Vojno-Yaseneckij V.V. *Secondary dystrophic and structural changes in the anterior part of the eye*. M.: Medicine. 1986;192 p. (in Russian)
15. Downs J.C., Girkin C.A. Lamina cribrosa in glaucoma. *Curr. Opin. Ophthalmol*. 2017;28(2):113–9.
16. Anderson D.R. Ultrastructure of human and monkey lamina cribrosa and optic nerve head. *Arch. Ophthalmol*. 1969;82:800–814.
17. Mabuchi F., Lindsey J.D., Aihara M., Mackey M.R., Weinreb R.N. Optic nerve damage in mice with a targeted type I collagen mutation. *Invest. Ophthalmol. Vis. Sci*. 2004;45:1841–5.
18. Spoerl E., Boehm A.G., Pillunat L.E. The influence of various substances on the biomechanical behavior of lamina cribrosa and peripapillary sclera. *Invest. Ophthalmol. Vis. Sci*. 2005;46(4):1286–90.
19. Jonas J.B., Wang N. Cerebrospinal fluid pressure and glaucoma. *J. Ophthalmic. Vis. Res*. 2013;8(3):257–63.
20. Sigal I.A., Yang H., Roberts M.D. IOP-induced lamina cribrosa deformation and sclera canal expansion: independent or related? *Invest. Ophthalmol. Vis Sci*. 2011;52:923–32. doi: 10.1167 / iovs.11-8183.
21. Omodaka K., Takahashi S., Matsumoto A. Clinical factors associated with lamina cribrosa thickness in patients with glaucoma, as measured with Swept Source Optical Coherence Tomography. *PLoS One*. 2016;11:e0153707. doi: 10.1371/journal.pone.0153707.
22. Quigley H.A., Hohman R.M., Addicks E.M. Morphologic changes in the lamina cribrosa correlated with neural loss in open-angle glaucoma. *Am. J. Ophthalmol*. 1983;95:673–91.