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Hydrostatic Pressure Gradients and a New Membrane-glymphatic Theory of Primary Glaucoma

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Abstract: The paper describes a novel theory of primary glaucoma etiopathogenesis based on a new understanding of the glymphatic system of the eye. Glymphatic flow routes of the eye include the vitreous body, uveal tract, paravascular spaces, and the retina. There are different pressure gradients of the intraocular fluid flow within the divided central channel of the vitreous body. In normal conditions above the foveola there is highly positive pressure gradient whereas above the optic disc it is 3 times lower. The retinal pigment epithelium is responsible for water and metabolic exchanges between choroid and the vitreous, therefore may contribute to intra-ocular fluid accumulation. Impairment of the outer blood-ocular and/or blood-aqueous barriers is the key pathogenic element of glaucoma including secondary forms due to uveitis. A disbalance of the pressure gradients above the macula and above the optic disc leads to fluid accumulation above the latter. An abundant intra-retinal fluid flow through the glymphatic pathways in the outer and inner plexiform layers, formed by Muller cell processes, contributes to accumulation of the interstitial fluid before the lamina cribrosa. Excessive interstitial fluid from the retina passes not only through the retinal pigment epithelium to choroid but also through paravascular spaces to the optic disc cup and discharges partly back to the vitreous body through the prevascular vitreous fissures. There is an interstitial fluid flow existing through paravascular spaces, the plexiform layers of retina and along the axons of ganglion cells to the optic nerve and its sheath where excessive fluid is absorbed into the subarachnoid space. The RPE plays a major role in glaucoma etiopahogenesis, probably acting as a regulator of fluid transport in the eye.

Keywords: Glaucoma, Optic Nerve, Glymphatic Flow, Hydrostatic Pressure Gradient, Retina, Neuroglia, Cerebrospinal Fluid, Intraocular Pressure

1. Introduction

Glaucoma is one of the leading causes of irreversible blindness in the world [1]. A glymphatic system of the brain was suggested by M. Nedergaard laboratory in 2012 [2]. Presence of glymphatic routes in the brain [3] and along the visual pathways in vivo [4] was confirmed in humans by MRI. The involvement of glymphatic system was suggested in the pathogenesis of neurodegenerative [5, 6] and eye diseases such as glaucoma and age-related macular degeneration [7-9]. The inner nuclear layer of the retina is supposed to take part in retinal glymphatic fluid flow [10]. There are controversies about functioning of the glymphatic system in the brain [5, 11]. Nevertheless the outflow pathways of the eye including lymphatic [12-14] and glymphatic routes, mainly within the optic nerve, are widely investigated nowadays [15-17]. Damage to the ganglion cells' axons at the scleral edge and lamina cribrosa is an important part of the pathogenesis of glaucoma but its key element is the disturbance of hydrodynamic and metabolic processes which affects all structures of the eye. Flow routes of intraocular fluid in the posterior segment of the eye have scarcely been investigated to this day.

Aim of this work is to calculate hydrostatic pressure

gradients in the posterior segment of the eye and to propose a new theory of etiopathogenesis of primary glaucoma.

Methods: literature review, mathematical calculations using Laplace' law and its analysis.

2. Results

The human eye is a derivate of the brain. All sheaths of the optic nerve are direct continuation of the brain's meningeal sheaths. In early stages of embryogenesis an intra-retinal space between outer pigmented and inner neurosensory layers of the eye vesicle is connected through the ocular stalk, future optic nerve, to the cavity that becomes the third ventricle within the rudiment of the diencephalon. Thus, the eye can be compared to the brain: sclera corresponds to dura mater, choroid to the Arachnoid with vessels underneath it, internal and outer limiting membranes of the retina correspond to pia mater, inner retina corresponds to the brain cortex, outer retina to white matter of the brain, and the vitreous body with its bursas and tracts could be compared to the ventricular and cistern system of the brain. Of course, this comparison is simplistic, but it allows one to find similarities in terms of glymphatic fluid flow. It is believed that the vitreous body has a mesenchymal and ectodermal genesis.

Diverse investigators have assumed that the composition of the intra-ocular fluid (IOF) filtering through outflow routes [18] and containing products of inflammatory-destructive immune processes [19] may cause pathological changes to ocular tissues. The composition of the aqueous humor in primary glaucoma is altered. Total amount of proteins in the aqueous humor of glaucoma patients is approximately two times higher than in controls [20], and a decrease in osmolarity is also observed [21]. In glaucoma the oxidative processes predominate over anti-oxidative [22]. The oxidation of glycoseaminoglycans results in degradation of its structural bonds with collagen fibrils and in the synaeresis of the vitreous [23].

A high intra-ocular pressure (IOP) increases the accumulation of tau-protein, amyloid Aß in the retina, nucleus of outer geniculate body and occipital cortex in experimental glaucoma in primates [24]. Also the high IOP is a risk factor of the migration of silicone oil drops into the brain cavity and/or chiasmus [25, 26]. On the other hand, cerebro-spinal fluid (CSF) not only flows along the human visual pathways via glymphatic routes but enters into the vitreous body [4], and in glaucoma animal models there is a decrease of CSF inflow to the optic nerve [17]. Decreased thickness of the peripapillary nerve fibers in patients with Alzheimer disease [27] suggests a common pathogenic pathway of the brain neurodegenerative diseases and glaucoma. There is a bidirectional fluid flow along the optic nerve and its sheaths and interdependence of the glymphatic fluid circulation of the brain and the eye. This is also confirmed by the fact of strong correlation observed between the CSF pressure and the type of glaucoma [28]. IOF secretion, circulation and outflow within the eye, as well as CSF in the brain, is dependent on circadian rhythm [29].

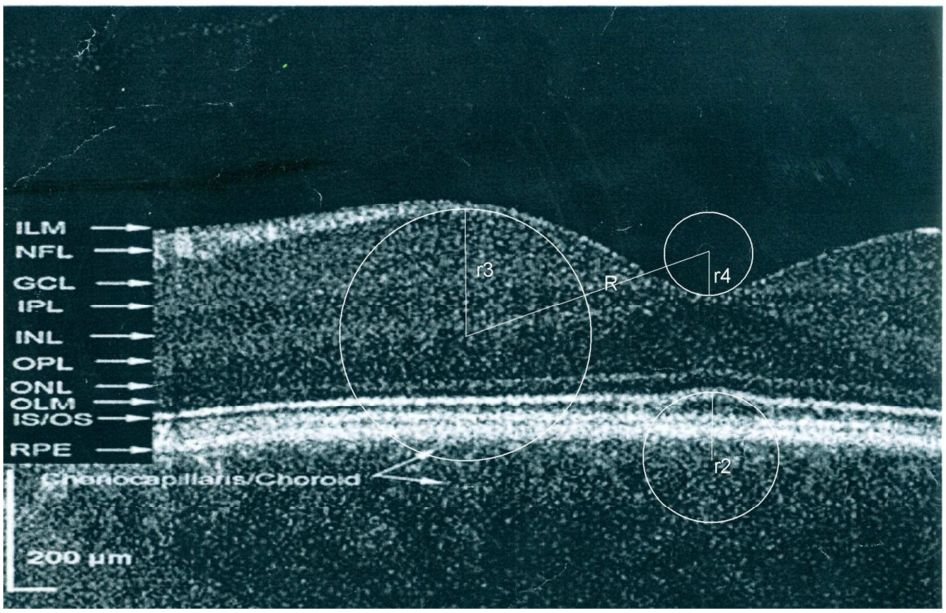

Figure 1. *Scaled OCT image with inscribed circles (2D) that were used for calculation of pressure gradients.*

2.1. Pressure Gradients in the Posterior Segment of the Eye and Its Analysis

To determine the direction of fluid flow in the posterior segment of the eye we should perform mathematical calculations of the pressure gradients. According to Laplace's law a gradient pressure of a substance in a sphere is inversely proportional to the radius of the sphere. We calculated linear sum of pressure gradients in the macular region. It consists of positive gradients between the premacular bursa (P5), the bottom of the foveal pit (P4), and the sclera (P1), and negative gradient of foveal roof vertices (P3). P (pressure

gradient) in Laplace's law for a sphere: P= 2γ/r, where γ is the coefficient of surface tension of intra-ocular fluid (aqueous humor) equal to 0,065 N/m [30], r is the radius in meters of the curvature of the sphere. P is the pressure in Pascals (N/m^2). The radius of curvature of the sclera in the macular region and the optic disc was calculated from the axial length of emmetropic eyes (r1 = 23.5/2 = 11.7 * 10^{-3} m) was taken from the literature [31]. Temporal and nasal parafoveal elevations of the retina surface (vertices) were conditionally equated to each other and were obtained using circinus from a scaled OCT image (Figure 1). The radius of an imaginary sphere inscribed into a foveal pit bottom (r4=0.03 * 10^{-3} m which correlates with foveal pit distance found in literature 0,15 mm), and two circles, inscribed into curvature along the ILM border around the fovea (r3 = 0.021 * 10^{-3} m), which are part of the torus figure, in which foveal pit sphere is inscribed (Figure 1). If assuming that force acting in various points of the eye is equal, then from torus' and circle area formulas we get the formula of pressure gradient in the macula: P_3 = 4γr4/(r3R), where R_{macula} is radius of the torus which was gained from the scaled OCT image and equaled 0.96 * 10^{-3} m. The radius of the sieve-like convex curvature of the bursa premacularis (r5 = 1.35 * 10^{-3} m) was obtained from its sizes described in the literature [32], using the formula with chord's length and sector's height.

The radius of a circle inscribed into physiological cupping of the optic disc (r8 = 0.18*10^{-3} m) was gained from a scaled OCT image (Figure 2) which correlates with statistical data of normal optic disc cup area 2.09±0.32 mm^2 and cup/disc ratio 0.21±0.032 [33, 34]. Data on curvature of temporal and nasal peripapillary nerve fibers of optic disc (r9 = 0.46*10^{-3} m) also were conditionally equaled and obtained from the scaled OCT image. There is a torus figure formed between a sphere inscribed into disc cup and peripapillary nerve fibers' vertices, with radius R_{disc} = 1,1 * 10^{-3} m (See Figure 2). The pressure gradient for vertices and inscribed optic disc cup was calculated as mentioned above with r8 and r9 (P = 4γr9/(r8R_{disc}),. The radius of the pre-optic bursa was obtained from the OCT image in Figure 2 using the formula with chord's length and sector's height (r 7=1.15 * 10^{-3} m).

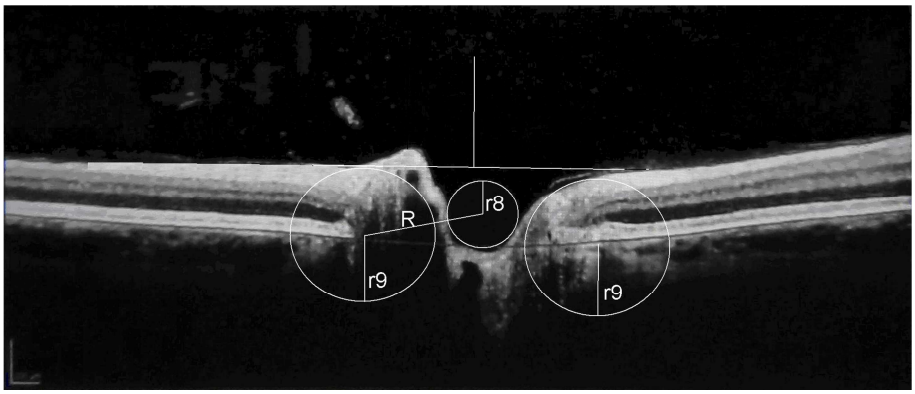

Figure 2. *Scaled OCT image (2D) of normal eye with inscribed circles into the optic disc cup and vertexes of optic nerve's peripapillary fibers; preoptic bursa chord and sector's length also are outlined.*

Summarized pressure gradient above the foveal pit turned out to be +1950 Pa which is about 14.6 mm Hg. Considering the presence of an umbo in the projection of the foveal pit with radius 0,1 mm (r2), which was obtained from the formula with a segment height and chord's length of 200 mkm, the pressure gradient of r2 under the foveola (P2) turned out to be negative: -1.29 kPa (9.6 mm Hg) on the assumption that the coefficients of surface tension of subretinal fluid and aqueous humor are equal. So, ΔP in the fovea turned out to be 5 mm Hg.

Summurized pressure gradient above the optic disc consisted from positive gradients - above the optic disc cup and the sclera, and negative - above the pre-optic bursa and torus formed by optic disc cup and nerve fiber vertices, and turned out to be 0.56 kPa or 4.14 mm Hg. So, the pressure above the macula (14.6 mm Hg) is about 3 times higher than above the optic disc cup in normal conditions. In case of flattening of peripapillar fibers, and especially in optic disc head and cupping enlargement, the pressure gradient becomes even negative. This may explain the fact that the highly myopic eyes are more susceptible to glaucoma.

Positive pressure gradient from posterior curvature of the lens (fossa patellaris) doesn't significantly change pressure gradients index above fovea and optic disc, yet slightly increases both of them. The radius of curvature of lens' posterior curvature (r6 = 2.77*10^{-3} m) was obtained from the area of cross section of the lens 24.1±1.1 mm^2 [35], and pressure gradient behind the lens turned out to be 0.047 kPa which is 4.8 H_2O and less than 1 mm Hg.

Lower hydrostatic pressure gradient above the optic disc cup may suggest a protective function of the preoptic bursa in normal condition. Also it may suggest that growth factors such as brain derived neurotrophic factor (BDNF) or other unknown neurotrophic substances from the brain penetrate CSF through the pia mater and glia into the eye, mainly at nights in horizontal body position when pressure of CSF rises by 7-8 mm Hg [36, 37]. Assuming that hydrostatic pressure in the retro-laminar region measured in humans is 8,5 mm Hg [38], there should be physiological interstitial fluid outflow force from the macula to the optic disc due to higher incoming pressure gradient in macular retina, confirmed in animal models [16]. This physiologic outflow occurs within

the whole retina through glymphatic pathways but obviously it is more efficient in the papillomacular region. The fovea is located below the optic disc level and one third of the optic nerve fibers come from the central part of the retina. Interstitial fluid gravitates mainly to the inferior-temporal quadrant because of our predominately upright posture. This is where damage is most severe in advanced primary glaucoma.

According to the findings of Morgan and colleagues the trans-laminar pressure gradient is effective only if the CSF pressure is about -0.5 mm Hg [39], i.e. in vertical body posture, when the pressure gradient of the CSF is about zero [37]. In recumbent body position there is a rise of CSF pressure below the lamina cribrosa and a height of water column also increases the pressure on both the optic disc and macula for 187,1 Pa or 1.4 mm Hg for emmetropic eye. Nevertheless, the pressure gradient above the foveola is higher than the CSF pressure even at nights, thus, the glymphatic outflow through and along the retina occurs. This may explain the formation of peripapillary atrophy first and mainly at the lateral edge of the optic disc.

The inter-bursal canaliculus is detected by OCT [40, 41]. It acts in one way in normal condition and has a valve or mechanism that makes difficult the retrograde filling of the canalis optico-ciliaris from the bursa premacularis, as shown by Makhacheva [42].

It is believed that IOF formed by the ciliary body passes posterior and flowing along the paravascular spaces of the retina, exiting through the optic nerve [43]. Due to the presence of the pressure gradient, fluid from the vitreous flows and seeps into the retina's thickness in the foveal pit probably with the participation of putative astrocytes located in this region [44], fibrillin-1 [45] and Muller cells. Fluid from bursa premacularis and from the RPE-choriocapillaries complex, considering Z-like arrangement of Muller cells, flows both into the internal and outer retina layers. Convex or concave form of the sieve-like wall of bursa premacularis has little effect on the value of pressure gradient above foveola and doesn't change its sign. Major influence to this parameter has the flattening of the retina and foveal pit bottom enlargement and in certain conditions the pressure gradient could turn out to be negative. Especially in high myopic patients flattening of the foveal contour leads to an increase of radius inscribed into foveal pit circle and therefore to a decrease of pressure gradient through it. This may explain the myopic foveoschisis and posterior subcapsular cataract development in high myopic patients due to failed flow route directions and consequent disturbance of metabolic processes of the lens.

2.2. Interstitial/Glymphatic and IOF Flow

Potassium channels and aquaporin-4 are expressed on the membranes of Muller cells [46, 47]. Aquaporin-1 is expressed on the membranes of mature RPE cells derived from human embryological stem cells [48], as well as in the epithelium of the choroid plexus and in the iris [21]. A significant fraction of aqueous flows posteriorly through the vitreous and retina, exiting via the RPE [49, 50]. The RPE is a unique layer of cells with an epithelial, phagocytic and glial functions [50, 51]. It performs the water-metabolic transport through interaction with receptors to dopamine, serotonin, adenosine, and epinephrine, etc. due to interactive transport systems and ion-channels depended on pH [51-54].

Despite the high transepithelial resistance of the RPE, we suggest that it may contribute to IOF formation and its further outflow into the vitreous body by Muller cells especially in case of fluid retention in the interphotoreceptor matrix. Possible mechanisms of fluid secretion include pyruvate – lactate reactions with H_2O formation. Other active processes of fluid outflow from or toward the choroids via RPE, require the presence of ATP and O_2 and therefore require the proper functioning of mitochondria. Between outer limiting membrane of the retina and RPE, i.e. in subretinal space, there is a fluid/ion/protein exchanging depot. It assumes the presence of sodium, potassium and chlorine ions and relatively large amounts of water as well as products of cellular metabolism. Optic disc axons are protected from these substances by intermediate Kunt's tissue. Muller cells' endplates in outer and inner limiting membrane provide in normal conditions, exchange between vitreous cavity and subretinal space through active and passive transport mechanisms according to the osmotic and oncotic gradients. Muller cells remove some water and products of metabolism from the subretinal space into the vitreous cavity. This is confirmed by the presence of such photoreceptor proteins as arrestin and inter-photoreceptor retinoid binding protein [55, 56] and glutamate, the main neurotransmitter of the photoreceptor [57], in the vitreous body.

Early retinal detachment usually leads to slight hypotony of several mm Hg compared to the unaffected eye, except in cases of Schwartz-Matsuo syndrome. From the glymphatic point of view this hypotony could be explained by termination of fluid filtration to the vitreous body from choriocapillaries because it requires adjacent retina, whose Muller cells provide intra- and extra-cellular water transport. IOP in case of retinal detachment usually decreases by 3-5 mm Hg that correlates with a level of IOP elevation in normal-tension glaucoma (NTG) which fits to so-called "high normal parameters" but not to an individual tolerance IOP value. On the other hand, in monkeys with retinal detachment a greater outflow of IOF is detected by photofluorometry [58] suggesting that the retina acts as a pad-sieve-like mechanism and prevents direct fluid outflow to the choroid. In non-infectious anterior uveitis lowering of IOP is usually observed, and this is believed to be secondary to decreased ciliary body secretion, so, probably a detachment of non-pigmented epithelium from pigmented or dysfunction of both of them leads to transient decrease in secretion of aqueous.

Chemical reactions that take place in the vitreous body also contributes to IOF formation, for example, ascorbic acid and hydrogen peroxide transformation reactions with oxidase, peroxidase and superoxide dismutase enzymes occur with formation of H_2O molecules.

We assume that in normal conditions there is interstitial fluid flow in the retinal layers along channels formed by

Muller cell processes, i.e. between ILM, superficial capillary plexus and axons of ganglion cells with astrocytes; in the inner plexiform layer between horizontal processes of Muller cells and paravascular spaces of intermediate capillary plexuses with pericytes; in the outer plexiform layer in cavities formed by Muller cell processes and deep capillary plexus above them. The latter is the most potentially pathological, and all of them discharge mainly into the paravascular spaces, where it is possible.

We suppose that the driving forces of the interstitial/glymphatic fluid flow in the plane of retina's layers and in the vitreous body are: head and body postural positions, pulse wave, breath depth and rate, movements of external and accommodation muscles, contractions of circular and longitudinal elastic fibers of the optic nerve sheath, eye saccades and blinking. On the cellular level mechanisms of this flow include contractions of Muller cell processes, aquaporins functioning depended on pericytes, trans-epithelial potential difference of the RPE and circadian rhythm signals. The retinal interstitial fluid probably converts posteriorly into intra- and interfascicular fluid flow in the optic nerve thickness provided by endo- and perineurium. In health, the amount of interstitial glymphatic flow in intra- and interfascicular pathways probably toward the suprachiasmatic cisterna is relatively low. Due to myelination of the optic nerve axons in its retrolaminal part, there is resistance to outflow of interstitial fluid. Absorbed by aquaporins of the astrocytes enveloping optic nerve axons, glymphatic fluid in normal and pathologic conditions flows into the optic nerve's subarachnoid space.

The inner nuclear and two plexiform layers with bodies of Muller cells, horizontal, interneurons, bipolar and amacrine cells, probably, play a buffer role separating the ECM of ganglion cells from the photoreceptor's intercellular matrix. The outer plexiform layer's thickness, measured by OCT in vivo and in histology specimens that have been prepared with vascular perfusion is always bigger than the thickness that is observed after the usual ways of tissue fixation with dehydration, both in the macular region and in the 3 mm around the optic disc. That is consistent with the presence of channels or cavities in the plane of the outer plexiform layer formed between Muller cell processes and deep capillary network with loop ends [59, 60].

We suppose that woven fibers of the anterior vitreous base in the pars plana acts as «pre-lymphatic anchoring filaments» [61], probably providing outflow of the excess IOF from the vitreous body into uveal lymphatic spaces, and later through paravascular spaces of anterior ciliary vessels to the suprachoroidal space. IOF flows from there partly diffusing through sclera to lymphatic collectors of the conjunctiva [62], and into the subarachnoid space of the optic nerve via paravascular spaces of the posterior ciliary vessels [63]. Probably there is over-flooding of these pathways in case of excess fluid in the vitreous body besides an enhancing flow through the conventional route. Figure 3 represents schematic image of the eye with possible direction of fluid flow in posterior segment under normal conditions. The avascular zone of the far periphery of the retina is likely to get its oxygen supply from capillaries of the pars plana of the ciliary body through retinal bays and dentate processes.

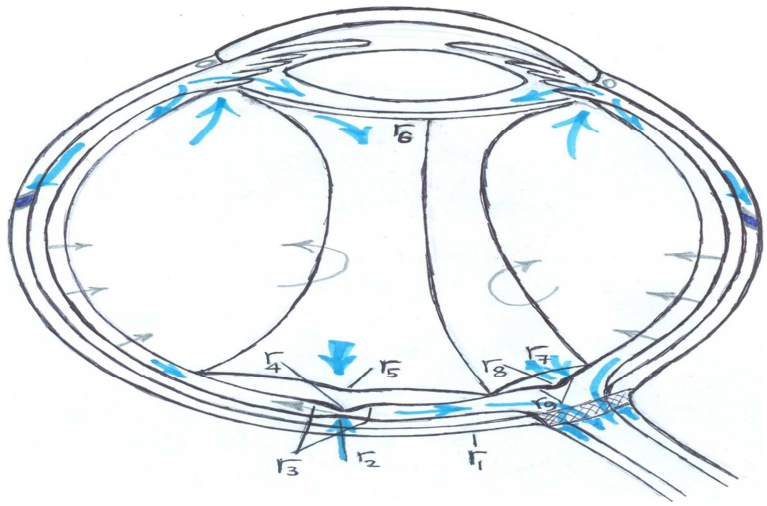

Figure 3. *Calculation elements of pressure gradients and probable flow directions in the eye structures in the posterior segment in normal conditions (r1 – radius of the eye-ball, r2 - radius of umbo's curvature, r3 – radii of the curvature of elevated nerve fibers around the foveola, r4- radius of the sphere inscribed into the foveal pit, r5 – radius of the bowl-like wall of the premacular bursa, r6 – radius of the fossa patellaris, r7 – radius of the preoptic bursa's wall, r8 – radius of the sphere inscribed into the optic disc cup, r9- radii of the curvature of elevated nerve fibers. Blue arrows – outflow pathways within the retina toward the optic nerve and its sheaths, toward the vorticoid veins, and bidirectional above the optic disc. Grey arrows – possible fluid secretion from choroids into the vitreous and IOF circulation inside the vitreous body).*

The direction of fluid flow through "anchoring filaments" around optic disc, i.e. in preoptic bursa walls, is questionable. Baiborodov showed that in optic disc pit there is a valve mechanism of fluid flow, which is into the vitreous cavity: in systole and IOP lowering - and out of it in diastole and when the IOP is increased. In addition, high CSF pressure leads to relapse of macular schisis; and if the location of an optic disc pit is closer to the disc margin it is associated with serous

retinal detachment, whereas if it is located closer to optic disc center it is not [64].

There is a group of congenital and acquired conditions that show no dye leakage from the retinal or choroidal capillaries in fluorescent angiography (FA) but on OCT, there is fluid accumulation in the outer or inner retinal layers [65]. This may occur on the first day after uncomplicated cataract surgery, probably due to cefuroxime toxicity [66] and as a side effect of nicotinic acid and drugs from taxans group. The fact that these resolve without treatment during a week after surgery or after drug withdrawal is evidence for the presence of interstitial outflow routes in the retina. Microcystic maculopathy with intra-retinal cysts in the internal nuclear layer is observed in systemic multiple sclerosis [46]. Transient microcystic changes and enlargement of inner nuclear layer thickness in the macular region were detected, not only in optic neuritis, but in primary glaucoma as well [67]. In hypotonic macular edema after penentrative anti-glaucoma surgery [68] there is also no capillary leakage on FA, but only slightly from optic disc capillaries. This is similar to that, observed in other transient macular edemas caused by dysfunction of the proton pump of the RPE [69].

It is interesting to note that normally the pressure in the anterior chamber is higher by 1.5 mm Hg than in the Schlemm's canal [70], and the pressure in the choroid and suprachoroidal space is lower by 2 mm Hg than in the vitreous [36]. This fact corresponds with summarized pressure gradients of Berger's space and fluid column in the posterior segment in the recumbent position of about 2 mm Hg, which we have calculated above.

In primary glaucoma there is fluid retention mainly in the posterior segment of the eye not anterior, as would be expected [71]. In terminal uncompensated glaucoma vitreous syneresis and posterior detachment of vitreous body (PVD) is usually observed. In angle closure glaucoma the presence of PVD is associated with higher IOP than if it is absent [72]. At terminal stages of glaucoma there is dilation of optic nerve para-sheath spaces (personal observation).

2.3. Membrane-glymphatic Theory of Glaucoma Etiopathogenesis

Impairment of the barrier function of basal membranes of pigmented and non-pigmented ciliary epithelium leads to excess secretion of aqueous or/and change of its composition. One may see structural changes of the iris, with pigment being dispersed into the anterior chamber. In posterior segment the RPE may also be affected, but structural changes are not usually visible excluding peripapillary atrophy of the RPE, and «whitened» ends of ciliary processes, which may be apparent during an endoscopic cyclophotocoagulation. The hydro-permeability of the RPE-Bruch's membrane complex towards the choriocapillaries decreases with age [73], and the ion-dependent transport system in the RPE may reduce. The brain and the eye constitute together an united system regulated by dopamine-mediated circadian and light-adaptive modulation [74, 75] and other neuroendocrine systems. Theoretical and practical researches on CSF pressure confirm that in brain cavity in vertical position the pressure gradient could be even negative [76]. Zero CSF pressure in occipital region in vertical position probably promotes interstitial fluid flow along the optic tract. There is disturbed passive and active fluid absorption towards the choroid in glaucoma which is normally provided by tissue convexity, ion gradients, G-proteins, aquaporins, ion channels and other factors. In certain conditions the inflow of fluid toward the vitreous may occur [54].

Disturbance of the outer blood-ocular (BOB) and blood-aqueous (BAB) barriers leads to abundant interstitial fluid flow in the posterior segment of the eye and excess glymphatic flow through the optic nerve. Initially fluid accumulates in the outer retinal layers and passes through inner plexiform layer to the paravascular spaces of the inner retina. It is known that dendrites of ganglion cells connected to Off-bipolar cells initially die in early stages of glaucoma [77], and On- and Off center pathways are initiated at the photoreceptor to bipolar and horizontal cell contacts in the outer plexiform layer [78]. Nork in the beginning of this century proposed and confirmed the anterograde death of ganglion cells from the photoreceptors in glaucoma [79]. All these suggest that fluid accumulation initially occurs mainly in the outer retinal layers.

Redundant glymphatic IOF flow initiates a pathogenic circle that leads to structural changes of avascular eye elements along with a major, metabolic failure in the retina due to vascular supply impairment and glial cell damage. In glaucoma, due to excess water amount there is disturbance in fluid flow routes resulting in IOF redistribution in the outflow pathways in both anterior and posterior segments. High pressure gradient in the lateral part of the central channel eventually causes a typical disc cupping along with an increase in the medial one, which directly affects the pre-laminar part of the optic disc. In paravenous space of the pre-laminar part of optic disc at night, at least during 7 hours of sleep, glymphatic fluid accumulates and may initiate optic disc cupping. Later on cup enlargement may continue due to para-axonal interstitial fluid flow from outer retina contributing to disease initiation or/and progression in case of normal-tension (NTG) or/and drug normalized, initially high IOP glaucoma patients. This is possible because the intermediate glial cell layers in pre-laminar part of the optic nerve fails as "dams" at certain pressure gradients, as may be observed in the reverse direction in Terson's syndrome [80].

Besides excess flow of interstitial fluid with altered composition through the thickness of the retina towards the optic disc, metabolic changes involving failure of neurotrophic functions of the RPE, and secondary dysfunction of Muller cells, worsen the process.

Failure of the outer blood-ocular-barrier (BOB) is not detectable by fluorescein angiography because there is impairment of intracellular transport. Besides direct flow into the vitreous cavity, excess fluid is discharged through paravascular vitreo-retinal contacts. We speculate that this also results in accumulation within retinal ganglion and glial cells of substances from the outer retina, which are harmful for

them. NTG along with low CSF pressure is characterized by absence of IOF outflow resistance in the trabecular meshwork which probably has a genetic background through matrix metalloproteinase's (MMP) polymorphisms. However, RPE function is compromised, so in conditions of sympathetic predominance of the choroid, leads to redundant interstitial fluid flow in retina's thickness, discharged toward optic disc. Anterior segment's pigment epithelium dysfunction is less involved in these patients than in the high IOP ones.

Excess amount of fluid from outer retina and/or anterior segment is absorbed into para-vascular spaces of the inner retina, probably affecting not only venules, but also peri- and para-arterial spaces. Thus, angio-OCT shows a decrease in the density of deep capillary layer, obviously mainly due to the effect of pigment epithelium derived factor on vessels' endothelium through laminin receptors. This interstitial fluid has altered molecular composition due to the presence of interphotoreceptors' matrix proteins and/or inflammatory factors. This leads to the activation of glial cells in a manner that indicates apoptosis of ganglion cells. Some of the intra- and interfascicular flow within the optic nerve goes into brain ventricles and cortex, but mainly it discharges into the optic nerve sheath in its retro-laminar part.

We suggest, accumulation of IOF in the premacular bursa and later in the preoptic bursa largely contributes to disc cupping: because of flow both within the inter-bursal canaliculi and within the retina. Disturbance in flow routes in the vitreous body cisterns and retina results in accumulation of fluid in front of the lamina cribrosa and alteration of the hydrodynamic pressure. Discharge of the excess fluid into the subarachnoid space leads to a reflective decreasing of the CSF inflow rate with metabolic consequences.

Not only the connective tissue disorder, due to autoimmune or congenital mechanisms, leading to a decrease in permeability of basal membranes and sclera, contributes to retention of IOF. But various functional and/or structural failures at the level of choriocapillaries-basal membranes-pigment epithelium complex due to mechanisms provided by reticular-endothelial system functioning, may lead to disturbance of water-metabolic function of the pigment epithelium of retina and/or ciliary body. This starts a pathological cascade involving glymphatic routes being over-loaded and resulting in glaucomatous optic retinopathy.

3. Discussion

In our model the eye-ball is considered as a sphere, which is only an approximation. Normally the diameter of the eye is 1 mm less in the frontal plane than in the sagittal. Our simplification has negligible influence on the final results. Use of Laplace's law for the modeling of biophysical processes within the eye was pioneered by the study of Johnson and Johnson, where the pressure required for a gas bubble to penetrate under the retina was calculated [81]. Cell membranes with ionic channels and G-protein receptors define their own patterns of fluid transport between cell layers, but directions of flow of intra-ocular fluid should still be in accordance with Laplace's law.

We have presented the linear comprehension of possible hydrodynamic processes in the central retina through approximate calculations of hydrostatic gradients that do not take into account biochemical changes of aqueous humor tension coefficient. However a change in the value of this parameter cannot be so high as to change the sign of calculated pressure gradients. All calculations were made for normal IOP condition. Assuming that IOP is equal in different points inside the eye, as Pascal's law says, an increase in IOP will lead to increase in fluid flow through the central channel into the fovea. We see this in clinical practice when IOP elevation leads to resorption of cystoid macular oedema in cases of hypotony, and more rarely in drug-induced macular edema. Nesterov [71] once said that IOP is a driving force of fluid circulation in the eye. According to the presence of various membranes of vitreous body's cisterns, it is possible that the preoptic bursa contributes to the so called "hydrostatic buffer effect" due to which in normal conditions the pre-laminar part of the optic disc doesn't experience the whole pressure measured at sclera or cornea. The pressure gradient above the optic disc remains slightly positive (about 0,56 kPa or 4,1 mm Hg) in different axial length values and with huge flattening of peripapillary nerve fibers, but it becomes negative with cup/disc ratio enlargement, i.e. in discs with big area. This observation may explain the clinical findings of macular schisis formation in patients with glaucoma and enlarged optic discs [82] when the pressure gradient from macular side could not pump toward the optic nerve and its sheath. The probability of reflux of CSF into the subretinal space in such cases is low, but it might occur due to hydrostatic pressure gradients.

If the lamina cribrosa exposes with its small diameter foramens or defects, the pressure gradient locally becomes highly positive about 30 mm Hg. The latter occurs for example, in optic disc pit, also resulting in interstitial fluid accumulation in outer retinal layers. After a decade of follow-up an optic disc pit may resemble the "mini-glaucoma" cupping with grey color, local "excavation" and change in the pigmentation of the disc's temporal margin [83]: despite their different etiologies these diseases may share aspects of pathogenesis with mis-circulation of intra-ocular fluid.

In primary glaucoma avascular structures which pass fluid through themselves, such as ciliary body, cornea, lens, outer retina and the fluid outflow routes including paravascular spaces and glial lining, as well as the sclera become "edematous" and then undergo degenerative changes. Secondary vascular changes due to paravascular flooding cause ischemic consequences in both anterior and posterior eye segment tissues.

This membrane-glymphatic theory of glaucoma accounts for a similar appearance of glaucoma that is secondary to uveitis, in which disturbance of BAB or BOB occurs. High levels of MMPs were observed in uveitis-related secondary glaucoma as in primary glaucoma [84], explaining connective tissue remodeling due to biochemical and biomechanical factors and similar cupping of the optic disc in these diseases.

There is retinopathy in glaucoma that affects all layers of the retina, which is confirmed by histology specimens [79, 85], OCT [85, 86] and electroretinography [85, 87]. In the initial stages outer retinal layers thicken in the macular region [86, 88-90], but they become thinner later on together with the inner ones. In primary glaucoma dysfunction of photoreceptors, bipolar cells and horizontal cells are observed, as are changes in color and contrast sensitivity [85, 87, 91]. Peripapillary retinoschisis is observed in 1-6% of patients with all types of glaucoma [92-96] and associated with vitreous traction and dysfunction of Muller cells, and it correlates with disease progression. We suggest that discharge of the interstitial fluid into the vitreous is more likely as an explanation of peripapillary retinoschisis rather than vitreous traction because the PVD correlates with thickening of peripapillary fiber layer [97]. It is noted that peripapillary retinoschisis usually occurs in high IOP condition and disappears with IOP normalization or spontaneously [96], or due to drugs or surgery [98], and sometimes results in peripapillary hemorrhages [99].

The RPE expresses genes confirming its participation in processes of oxidative phosphorylation, local glycosaminoglican turnover, synthesis of ATP and ribosomes, membrane transport, metabolism of aminosugars and in phosphatidylinositol signaling [100]. Also it expresses genes of the complement system, interleukin 6 and 8, MMPs, and genes of the Major histo-compatibility complex with high inter-individual variability [51, 100]. The basal lamina of the RPE and some structural elements of ECM of Bruch's membrane are secreted by RPE cells; but the choroid contributes significantly to the synthesis of components of the Bruch's membrane [73].

This membrane-glymphatic theory of glaucoma is a missing element of the well-known aspects of glaucoma pathogenesis, and allows one to unite all existing theories of pathogenesis of glaucoma (biomechanical, vascular, metabolic, infectious) into one. It needs to be proved in future investigations.

4. Conclusion

There are many unresolved questions concerning the IOF pressure inside vitreous body cisterns and tracts. Inside eye flow routes and pressure gradients should be further investigated. Glymphatic outflow pathways of the eye includes vitreous body's cisterns and fibers connected to Muller cells and pars plana uveolymphatic spaces. Our results highlighted, for the first time to our knowledge, new possible glymphatic flow routes in the posterior segment of the human eye, and offer new insight into the etiology and pathogenesis of glaucoma. The vitreous body, retina, optic nerve and uveal tract constitute a unified structural and functional complex, providing constant physiological glympho-lymphatic fluid circulation in the eye and glympho-glymphatic circulation between eye and brain provided by the two-directional fluid flow along the optic nerve and its sheaths. The inter-regulation between eye and brain is complex, probably with corticoliberins or other brain derived factors of hypothalamic region affecting permeability of the blood-aqueous and outer blood-ocular barriers in conditions of stress, providing the development of acute angle-closure glaucoma. It is also possible that other aldosteron-like system exists that allow the regulation of fluid secretion/outflow rate in the eye.

5. Recommendations

Future work on this topic may help to answer many questions which ophthalmologists have. For example, why the retina sometimes swells in a diffuse manner and sometimes in cystoid in the macula? Or why subretinal fluid in proliferative diabetic retinopathy does not undergo resorption despite traction resolution due to surgery? And of course, future investigations in the field of glymphatic fluid circulation may predict glaucoma development by finding the main regulatory genes that control fluid exchange between the eye and the brain. Also, a key metabolic substances such as oxides, probably influence these genes expression.

Author Contributions

J. B. and J. K. designed the study and drafted the manuscript. S. Beisekeev made mathematic calculations. All authors contributed to the literature review, manuscript writing and editing. S. K made scientific editing of the manuscript. All authors approved the submitted version.

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Conflict of Interests

The authors declare that they have no competing interests.

References

[1] Quigeley H, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol, 2006; 90 (3): 262-267.

[2] Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid ß. Sci Transl Med, 2012; 4 (147): 147-151. doi: 10/1126/scitranslmed.3003748.

[3] Ringstad G, Valnes LM, Dale AM, Pripp AH, et al. Brain-wide glymphatic enhancement an d clearance in humans assessed with MRI. JCI Insight. 2018; 3 (13): e121537. doi: 10.1172/jci.insight.121537.

[4] Jacobsen HH, Ringstad G, Jorstad OK, et al. The human visual pathway communicates directly with the subarachnoid space. Invest Ophthalmol Vis Sci. 2019; 60: 2773-2780. doi: 10.1167/iovs.19-26997.

[5] Mestre H, Mori Y, Nedergaard M. The brain glymphatic system: current controversies. Trends in Neurosciences, 2020; 43 (7): 458-466. doi: 10.1016/j.tins.2020.04.003.

[6] Bakker E, Bascani BJ, Arbel-Ornath M, et al. Lymphatic clearance of the brain: perivascular, paravascular and significance for neurodegenerative diseases. Cell Mol Neurobiol, 2016; 36: 181-194. doi: 10.1007/s10571-015-0273-8.

[7] Wostyn P. The glymphatic system: a new player in ocular diseases? Invest Ophthalmol Vis Sci. 2016; 57: 5426-5427. doi: 10.1167/iovs.16-20262.

[8] Wostyn P, De Groot V, Van Dam D, et al. The glymphatic hypothesis of glaucoma: a unifying concept incorporating vascular, biomechanical, and biochemical aspects of the disease. BioMed Res Int. 2017, article ID 5123148. doi: 10/1155/2017/5123148.

[9] Wostyn P, Van Dam D, Audenaert K, et al. A new glaucoma hypothesis: a role of glymphatic system dysfunction. Fluids Barriers CNS, 2015; 12: 16. doi: 10.1186/s12987-015-0012-z.

[10] Petzold A. Retinal glymphatic system: an explanation for transient retinal layer volume changes? Brain, 2016; 139 (11); 2816-2819. doi: 10.1093/brain/aww239.

[11] Ferris CF. Rethinking the conditions and mechanism for glymphatic clearance. Front /neurosci. 2021, 15: 624690. doi: 10.3389/fnins.2021.624690.

[12] [Petrov S. Yu. Lymphatic system of the eye. Russian journal of glaucoma. 2011; 3: 58-62 (In Russ)].

[13] Subileau M, Vittet D. Lymphatics in eye fluid homeostasis: minor contributors or significant actors? Biology 2021, 10, 582. doi: 10.3390/biology10070582.

[14] Yücel YH, Johnston MG, Patel M, et al. Identification of lymphatics in the ciliary body of the human eye: a novel "uveolymphatic" outflow pathway. Exp Eye Res. 2009; 89 (5): 810-819. doi: 10.1016/j.exer.2009.08.010.

[15] Mathieu E, Gupta N, Ahari A, et al. Evidence for cerebrospinal fluid entry into optic nerve via glymphatic pathway. Invest Ophthalmol Vis Sci. 2017; 58: 4784-4791. doi: 10.1167/iovs.17-22290.

[16] Wang X, Lou N, Eberhardt A, Yang Y, et al. An ocular glymphatic clearance system removes ß-amyloid from the rodent eye. Sci. Transl. Med. 2020; 12, eaaw3210. doi: 10.1126/scitranslmed.aaw3210.

[17] Mathieu E, Gupta N, Paczka-Giorgi LA, et al. Reduced cerebrospinal fluid inflow to the optic nerve in glaucoma. Invest Ophthalmol Vis Sci. 2018; 59: 5876-5884.

[18] Marshall GE, Konstas AG, Reid GG, et al. Collagens in the aged human macula. Graefes Arch Clin Exp Ophthalmol 1994; 232:: 133-140.

[19] Chernykh VV, Bgatova NP, Orlov NB, et al. Local inflammatory process as a possible manifestation of intraocular fluid uveolymphatic outflow defects in glaucoma. Part 2. National journal of glaucoma. 2018; 17 (1): 3-11 (in Russ)] doi: 10.25700/NGJ.2018.02.01.

[20] Dos Santos Prata T, Navajas EV, Soares Melo Jr LA et al. Aqueous humor protein concentration in patients with primary open-angle glaucoma under clinical treatment. Arq Bras Oftalmol. 2007; 70 (2) doi: 10.1590/s0004-27492007000200006.

[21] Huang OS, Seet L-F, Ho HW, et al. Altered iris aquaporin expression and aqueous humor osmolality in glaucoma. Invest Ophthalmol Vis Sci. 2021; 62 (2): 34. doi: 10/1167/iovs.62.2.34.

[22] Benoist d'Azy C, Pereira B, Chambaretta F, Dutheil F. Oxidative and anti-oxidative stress markers in chronic glaucoma: a systematic review and meta-analysis. PLoS ONE 11 (12): e0166915. doi: 10.1371/journal.pone.0166915.

[23] [Egorov EA. Azhigalieva MN. Possible mechanisms of vitreous body participans in primary glaucoma pathogenesis. Vestnik Ophthalmologii. 1993; 109 (2): 6-9. (in Russ.)].

[24] Yan Z, Liao H, Chen H, et al. Elevated intraocular pressure induces amyloid-ß deposition and taupathy in the lateral geniculate nucleus in a monkey model of glaucoma. Inv Ophthalmol Vis Sci. 2017 (58): 5434-5443. doi: 10.1167/iovs.17-2312.

[25] Cao J, Bian L, Zhou P, Tu J. Watch out for the special location of intraventricular silicone oil following an intraocular tamponade – a 10-year follow-up case report based on CT/MRI. BMC Ophthalmology. 2019; 19: 269.

[26] Boren RA, Carson DC, Gupta AS, Dewan VN, Hogan RN. Retrolaminar migration of intraocular silicone oil. Journal of neuro-ophthalmology 2016; 36: 439-447. doi: 10.1097/WNO.0000000000000440.

[27] Paquet C., Boissonnot M, Roger F et al. Abnormal retinal thickness in patients with mild cognitive impairment and Alzheimer's disease. Neurosci. Lett. 2007; 420: 97-99. DOI: 10.1016/j.neulet.2007.02.090.

[28] Berdahl JP, Fautsch MP, Stinnett SS, Allingham RR. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: a case-control study. Invest Ophthalmol Vis Sci. 2008; 49: 5412-5418.

[29] Goldberg I, Clement CI. The water drinking test. Am J Ophthalmol, 2010; 150 (4): 447-449. doi: 10.1016/j.ajo.2010.06.035.

[30] Carbrerizo J, Urcola JH, Vecino E. Changes in surface tension of aqueous humor in anterior segment ocular pathologies. Vision (Basel) 2016; 1 (1): 6. doi: 10.3390/vision1010006.

[31] [Egorov EA, Eskina EN, Gvetadze AA et al. Myopic eyes: morphometric features and their influence on visual function. RMJ. Clinical Ophthalmology. 2015; 4: 186-190 (in Russ)].

[32] [Faizrahmanov RR, Zainetdinov AF, Salavatova VF. Vitreomacular interface structure in pathology of the retina. Point of view. Vostok-Zapad, 2017; 2: 82-84. (in Russ)].

[33] [Strakhov VV, Alekseev VV, Ermakova AV. Assymetry of the tonometric, gemodynamic and bioretinometric parameters of the twin eyes in normal state and in primary glaucoma. Russian Journal of Glaucoma, 2018; 4: 11-16 (in Russ)].

[34] Savini G, Zaini M, Careli V. Correlation between retinal nerve fibre layer thickness and optic nerve size: an optical coherence tomography study. Brit J Ophthalmol. 2005; 89 (4): 489-495.

[35] [Sorokin EL, Marchenko AN, Danilov OV. Morphometrical datas of intraocular structures in hyperopic patients at different age groups and finding of risk factors of phakomorphik glaucoma. Fareast medical journal, 2009; 3: 22 (in Russ)].

[36] [Nesterov A. P. Glaucoma 2nd edition, 2008 Medical informational agency Moscow, p. 41 (in Russ)].

[37] Klarica M, Rados M, Erceg G, Petosic A, Jurjevic I, Oreskovic D. The influence of body position on cerebrospinal fluid pressure gradient and movement in cats with normal and impaired craniospinal communication. PLoS One. 2014; 9 (4): e95229. doi: 10.1371/journal.pone.0095229.

[38] Liu D, Michon J. Measurement of the subarachnoid pressure of the optic nerve in human subjects. Am J Ophthalmol, 1995; 119: 81-5.

[39] Morgan WH, Yu DY, Alder VA et al. The correlation between cerebrospinal fluid pressure and retrolaminal tissue pressure. Invest Ophthalmol Vis Sci 1998; 39 (8): 1419-28. PMID: 9660490.

[40] Engelbert M. A new understanding of vitreous structure. Review, 2016 http://www.reviewofophthalmology.com/article/a-new-understanding-of-vitreous-structure

[41] Leong BCS, Fragiotta S, Kaden TR, et al. OCT en face analysis of the posterior vitreous reveals topographic relationships among premacular bursa, prevascular fissures, and cisterns. J. Ophthalmol. 2020, 4 (1): 84-89. doi: 10.1016/j.oret.2019.09.002.

[42] [Makhacheva Z. A. New in anatomy of the vitreous body. Moscow, 2006, p. 10-13 (in Russ)] http://eyepress.ru/referateng.aspx?45227doi:org/10.25276/978-5-903624-24-9.

[43] [Selected lectures in Ophthalmology. Lection # 12, p. 3. Glaucoma Part 2 http://eyepress.ru/article.aspx?19446 (in Russ)].

[44] Delaunay K, Khamsy L, Kowalczuk L et al. Glial cells of the human fovea. Mol Vis 2020; 26: 235-245.

[45] Morishita S, Sato T, Oosuka S, et al. Expression of lymphatic markers in the Berger's space and bursa premacularis. Int J Mol Sci 2021; 22 (4), 2086. doi: 10.3390/ijms22042086.

[46] Balk LJ, Killestein J, Polman CH, et al. Microcystic macular oedema confirmed, but not specific for multiple sclerosis. Brain, 2012: 135: 1-2. doi: 10.1093/brain/aws216.

[47] Nagelhus EA, Veruki ML, Torp R, et al. Aquaporin-4 water channel protein in the rat retina and optic nerve: Polaryzed expression in Muller cells and fibrous astrocytes. J. Neurosci. 1998, 18: 2506-2519.

[48] Juuti-Uusitalo K, Delporte C, Gregoire F, et al. Aquaporin expression and function in human pluripotent stem cell-derived retinal pigmented epithelial cells. Invest Ophthalmol Vis Sci. 2013; 54 (5): 3510-3519. doi: 10.1167/iovs.13-11800.

[49] Smith D, Lee C-J, Gardiner BS. No flow through the vitreous humor: how strong is the evidence? Prog Ret Eye Res 2020; 78: 100845. doi: 10.1016/j.preteyeres.2020.1000845.

[50] Steinberg RH. Interactions between the retinal pigment epithelium and the neural retina. Doc Ophthalmol. 1985; 60: 327-346.

[51] Strauss O. The Retinal Pigment epithelium in visual function. Physiological reviews, 2005; 85 (3): 845-881. doi: 10.1152/physrev.00021.2004.

[52] Peterson WM, Meggyesy C, Yu K, Sheldon SS. Extracellular ATP activates calcium signaling, ion, and fluid transport in retinal pigment epithelium. J Neurosci. 1997; 17 (7): 2324-2337. doi: 10.1523/JNEUROSCI.17-07-02324.1997.

[53] Reigada D, Mitchell CH. Release of ATP from retinal pigment epithelial cells involves both CFTR and vesicular transport. Am J Physiol Cell Physiol 2005 (288): 132-140. doi: 10.1152/ajpcell.00201.2004.

[54] Dvoryashyna M, Foss AJE, Gaffney EA, Repetto R. Fluid and solute transport across the retinal pigment epithelium: a theoretical model. Journal of the Royal society interface, 2020, 17; 163. Doi: 10.1098/rsif.2019.0735.

[55] Yamane K, Minamoto A, Yamashita H, et al. Proteome analysis of human vitreous proteins. Mol Cell Proteom. 2003, 2, 1177.

[56] Murthy KR, Goel R, Subbannayya Y, Jacob HKC et al. Proteomic analysis of human vitreous humor. Clin Proteom. 2014, 11, 29.

[57] Dreyer EB, Zurakowski D, Schumer RA, et al. Elevated glutamate levels in the vitreous body of humans and monkeys with glaucoma. Arch Ophthalmol. 1996; 114: 299-305.

[58] Tsuboi S. Fluid movement across the blood-retinal barrier: a review of studies by vitreous fluorophotometry. Jpn J Ophthalmol 1990; 34 (2): 133-41. PMID: 2214357.

[59] Tan PE, Balaratnasingam C, Xu J, et al. Quantative comparison of retinal capillary images derived by speckle variance optical coherence tomography with histology. Invest Ophthalmol Vis Sci, 2015 (56): 3989-3996. doi: 10.1167/iovs.14-15879.

[60] Chandrasekera E, An D, McAllister IL, et al. Three-dimensional microscopy demonstrates series and parallel organization of human peripapillary capillary plexuses. Inv Ophthalmol Vis Sci. 2018; 59: 4327-4344. doi: 10.1167/iovs.18-24105.

[61] Gerli R, Solito R, Weber E, et al. Specific adhesion molecules bind anchoring filaments and endothelial cells in human skin initial lymphatics. Lymphology 2000; 33: 148-157.

[62] Camelo S, Lajavardi L, Bochot A, et al. Drainage of fluorescent liposomes from the vitreous to cervical lymph nodes via conjunctival lymphatics. Ophthalmic Res. 2008; 40: 145. doi: 10.1167/iovs.06-1305.

[63] [Zolotarev AV, Pavlov DV, Nikolaeva GA. Morphology of aquous fluid flows in posterior segment of t he eye. New technologies of eye microsurgery. Vestnik OGU, 2018; (12): 37-39 (in Russ)].

[64] [Baiborodov Y. V. Izmailov A. S. Detachment of the retina caused by the pit of the optic nerve disk and its surgical treatment. Fyodorov Journal of Ophthalmic Surgery. 2017 (4): 20-25. (in Russ)]. doi: 10.25276/0235-4160-2017-4-20-25.

[65] Ouyang Y, Keane PA, Sadda SR et al. Detection of cystoid macular edema with three-dimansional optical coherence tomography versus fluorescein angiography. Invest Ophthalmol Vis Sci. 2010; 51 (10): 5213-18.

[66] [Beisekeeva J, Bezrukov AV, Kochergin SA, et al. Acute transient macular edema after uneventful cataract surgery. Ophthalmology in Russia. 2021; 18 (3): 442-450 doi: 10.18008/1816-5095-2021-3-442-450 (in Russ)].

[67] Hasegawa T, Akagi T, Yoshikawa M et al. Microcystic inner nuclear layer changes and retinal nerve fiber layer defects in eyes with glaucoma. pLoS One. 2015; 10 (6): e0130175. doi: 10.1371/journal.pone.0130175.

[68] [Erichev VP, Petrov S. Yu, Orekhova A, et al. Hypotony maculopathy after glaucoma surgery: pathogenic mechanisms, diagnostic tools, and treatment modalites. Russ Journal of Clin Ophthalmol. 2020; 20 (1): 26-31 (in Russ)] doi: 10.32364/2311-7729-2020-20-1-26-31].

[69] Massa H, Pipis S. Panos GD. Macular edema associated with non-infectious uveitis: pathophysiology, etiology, prevalence, impact and management challenges. Clin Ophthalmol. 2019; 13: 1761-1777.

[70] [Nesterov A. P. The Intraocular pressure. Moscow: Science, 1974, p. 112 (in Russ)] http://www.ngpedia.ru/pg3427798YUxgCA30022128901

[71] [Nesterov AP Glaucoma 2nd ed, 2008 Medical informational agency Moscow, p. 133 (in Russ)].

[72] [Erichev VP, Poleva RP, Hadiri Kh. New capabilities of optical coherence tomography in the diagnostics of primary angle-closure glaucoma. The national Journal glaucoma 2021; 20 (2): 14-22. (in Russ) doi: 10.25700/2078-4104-2021-20-2-14-22].

[73] Booij JC, Baas DC, Beisekeeva J, Gorgels TGMF, Bergen AAB. The dynamic nature of Bruch's membrane. Prog Eye Ret Res. 2010; 29 (1): 1-18.

[74] Goel M, Mangel SC. Dopamine-mediated circadian and light/dark-adaptive modulation of chemical and electrical synapses in the outer retina. Front. Cell. Neurosci. 15: 647541. doi: 10.3389/fncel.2021.647541.

[75] [Pavlenko TA, Chesnokova NB, Nodel MP, Kim AR, Ugryumov MV. Molecular mechanisms and clinical features of catecholamine regulation disturbance in Parkinson's disease as basement for early diagnostic methods creation. Acta Naturae, 2020; 12; 2 (45): 52-62 (in Russ.)]. doi: 10.32607/actanaturae.10906.

[76] Klarica M, Rados M, Erceg G, et al. The influence of body position on cerebrospinal fluid pressure gradient and movement in cats with normal and impaired craniospinal communication. PLoS One. 2014; 9 (4): e95229. doi: 10.1371/journal.pone.0095229.

[77] El-Danaf RN, Huberman AD. Characteristic patterns of dendric remodeling in early-stage glaucoma: evidence from genetically identified retinal ganglion cell types. J Neyrosci. 2015; 35 (6): 2329-2343. doi: 10.1523/JNEUROSCI.1419-14.2015.

[78] The organization of the Retina and Visual system. Webvision Book. Outer plexiform layer by Helga Kolb. www.webvision.med.utah.edu.

[79] Nork TM. Aquired color vision loss and possible mechanisms of ganglion cell death in glaucoma. Tr Am Ophth Soc 2000; 98: 331-363.

[80] Luliano L, Fogliato G, Codenotti M. Intrasurgical imaging of subinternal limiting membrane blood diffusion in Terson Syndrome. Case Rep Ophthalmol Med. 2014; 2014: 689793.

[81] Johnson TM, Johnson MW. Pathogenic implications of subretinal gas migration through pits and atypical colobomas of the optic nerve. Arch Ophthalmol. 2004; 122 (12): 1793-1800. doi: 10.1001/archophth.122.12.1793.

[82] Zumbro D, Jampol LM, Folk JC, et al. Macular schisis and detachment associated with presumed acquired enlarged optic nerve head cups. Am J Ophthalmol. 2007; 144 (1): 70-74. doi: 10.1016/j.ajo.2007.03.027.

[83] Theodossiadis GP, Panopoulus M, Kolia KG, et al. Long-term study of patients with congenital pit of the optic nerve and persistent macular detachment. Acta Ophthalmol. 1992; 70 (4): 495-505. doi: 10.1111/j.1755-3768.1992.tb02120.x.

[84] Maatta M, Tervahartiala T, Vesti E, et al. Levels and activation of matrix metalloproteinases in aqueous humor are elevated in uveitis-related secondary glaucoma. Glaucoma. 2006; 15 (3): 229-237.

[85] [Strakhov VV, Alexeev VV, Yartsev AV. Towards the question of pathogenesis of POAG: glaucomatous neuropathy. Russian Journal of Clinical Ophthalmology. 2010; 4: 110 (in Russ)].

[86] Garcia-Medina JJ, del-Rio-Vellosillo M, Palazon-Cabanes A et al. Glaucomatous maculopathy: thickness differences on inner and outer macular layers between ocular hypertension and early primary open-angle glaucoma using 8*8 posterior pole algorithm of SD-OCT. J. Clin. Med. 2020, 9, 1503; doi: 10.3390/jcm9051503.

[87] Egorova I. V., Shamshinova A. M., Erichev V. P. Functional methods in glaucoma diagnosis. Vestnik oftalmologii Russian annals of Ophthalmology, 2001, 117 (6): 38-40 (in Russ).

[88] Nork TM. Swelling and loss of photoreceptors in chronic human and experimental glaucomas. Arch Ophthalmol. 2000; 118: 235-245.

[89] Fan N, Huang N, Lam DSC, Leung C K. Measurement of photoreceptor layer in glaucoma: a spectral-domain optical coherence tomography study. Journal of ophthalmology. 2011; 264803. doi: 10.1155/2011/264803.

[90] Fujihara FMF, de Arruda Mello PA, Lindenmeyer RL et al. Individual macular layer evaluation in normal and glaucomatous eyes. Opht. 2020; 14: 1591-1599. doi: 10.2147/OPTH.S256755.

[91] Janssen P, Naskar R, Moore S, et al. Evidence for glaucoma-induced horizontal cell alterations in the human retina. Ger J Ophthalmol 1997; 5: 378-385.

[92] Grewal DS, Merlau DJ, Giri P, et al. Peripapillary retinal splitting visualized on OCT in glaucoma suspect patients. PloS ONE 12 (8): e018216. doi: 10.1371/journal.pone.0182816.

[93] Fortune B, Ma KN, Gardiner SK, et al. Peripapillary retinoschisis in glaucoma: association with progression and OCT signs of Muller Cell involvement. Invest Ophthalmol Vis Sci. 2018; 59: 2818-2827. doi: 10.1167/iovs.18-24160.

[94] Lee EJ, Kee HJ, Han JC, Kee C. The progression of peripapillary retinoschisis may indicate the progression of glaucoma. Invest Ophthalmol Vis Sci. 2021; 62 (2): 16. doi: 10.1167/iovs.62.2.16.

[95] Nishijima R, Ogawa S, Nishijima E, et al. Factors determing the morphology of peripapillary retinoschisis. Clinical Ophthalmology. 2021; 15: 1293-1300.

[96] Farjard H, Besada E, Frauens BJ. Peripapillary schisis with serous detachment in advanced glaucoma. Optom Vis Sci. 2010; 87 (3): E205-17. doi: 10.1097/OPX.0b013e3181d1dad5.

[97] Liu Y, Baniasadi N, Ratanawongphaibul, Chen TC. Effect of partial posterior vitreous detachment on spectral-domain optical coherence tomography retinal nerve fibre layer thickness measurements. Br J Ophthalmol. 2020; 104 (11): 1524-1527. doi: 10.1136/bjopthalmol-2019-314570.

[98] [Andreev AN, Shvaikin AV, Svetozarskii SN. Papillomacular retinoschizis associated with glaucoma Vestnik ophthalmologii Russian annals of Ophthalmology. 2019; 135 (6): 100-107 (in Russ)] doi: 10.17116/oftalma2019135061100.

[99] Lee WJ, Seong M. Disc hemorrhage following peripapillary retinoschisis in glaucoma: a case report. BMC Ophthalmol, 2021 (21): 253. doi: 10.1186/s12886-021-02010-5.

[100] Booji JC, van Soest S, Swagemakers SMA, Essing AHW, Verkerk AJMH, van der Spek P, Gorgels TGMF, Bergen AAB. Functional annotation of the human retinal pigment epithelium transcriptome. BMC Genomics 2009, 10: 164-182.