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The mechanical theory of glaucoma in terms of prelaminar, laminar, and postlaminar factors

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Abstract:

The mechanical theory is one of the oldest concepts regarding the development of glaucomatous neural degeneration. However, after a prolonged period of relative monopoly among the various theories explaining the pathogenesis of glaucoma, this concept gradually faded away from discourse. Several developments in the recent past have rekindled interest in the mechanical theory of glaucoma. Now we know a lot more about the biomechanics of the eye, prelaminar changes, mechanisms of retinal ganglion cell death, biomechanical features of the optic nerve head and sclera, extracellular matrix composition and its role, astrocytic changes, axoplasmic flow, and postlaminar factors such as translaminar pressure difference. These factors and others can be categorized into prelaminar, laminar, and postlaminar elements. The objective of this review was to present a concise analysis of these recent developments. The literature search for this narrative review was performed through databases, such as PubMed, Google Scholar, and Clinical Key.

Keywords:

Glaucoma, intraocular pressure, optic nerve head

Introduction

Glaucoma is characterized by degeneration of retinal ganglion cells (RGCs) in the retina and their axons in the optic nerve head (ONH). It is often not clear the factors that trigger this process and lead to a progressive decline in the structural-functional abilities of the eye over time.

Several theories have been propounded to explain the pathogenesis of glaucomatous optic atrophy (GOA). The earliest mention of increased intraocular pressure (IOP) causing this condition is attributed to the medieval Arab thinker Abu Al-Hassan Ali Al-Tabari. A 10th century physician, he wrote in his book Firdaus Al-Hikma about certain blind patients having relatively hard eyes, pointing to the possible role of IOP.[1] In 1858, Heinrich Muller proposed a scientific explanation for high IOP compressing and causing the death of retinal neurons.[2] This led to the foundation of the mechanical theory of GOA, which for many years was the most acceptable concept for the development and progression of glaucoma.

The initial mechanical theory was a simple concept, explaining the development of GOA, in terms of high IOP compressing the axons at the lamina and damaging them in the ONH. However, there are several other factors which became conspicuous over time and the mechanical theory was unable to explain them. These include normal tension glaucoma (NTG), ocular hypertension (OHT), progression of glaucomatous changes despite apparently adequate control of IOP, acute elevation of IOP causing ONH damage in the absence of cupping, detection of biochemical factors that could be responsible for glaucomatous damage, and the exploration of non-IOP treatment options over the recent past.

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Consequently, several other theories came up to explain these perplexing elements and the mechanical theory lost its monopoly.

Recently, interest in the mechanical theory has re-emerged with a better understanding of the disease process, newer diagnostic methods, and largely with the introduction of biomechanics. This evolving field involves the application of mechanical principles and technology to biological systems.[3,4] Recent research focuses on finite element models and three-dimensional (3-D) reconstruction of ocular tissues to better understand the biomechanical changes occurring in glaucomatous eyes.

To integrate the numerous concepts of the biomechanical model of glaucoma the various factors involved in the process of glaucomatous degeneration can be divided into the following elements:

1. Prelaminar factors
2. Laminar factors
3. Postlaminar factors

This article reviews the mechanical theory of glaucoma based on the above-mentioned classification of factors.

Prelaminar Factors

The retina is the light-sensitive layer situated inside the eye. The photoreceptors (rods and cones) form the primary neurosensory cells, responsible for the conversion of light into an electrochemical impulse. This impulse is transmitted to interneurons, which process this visual information and then relay it to the RGCs. The axons of the RGCs then travel from all parts of the retina toward the ONH. The axons exit through the lamina cribrosa (LC), forming the optic nerve and carrying the sensations to the higher centers in the brain. Recent research has pointed to the possibility of 30 different types of RGCs, each being sensitive to a distinct visual feature.[5] Therefore, a set of parallel, highly processed images are sent to the brain from the retina.

The ONH forms a dynamic confluence of 1.2–2.0 million RGC axons. The axons converge, turn, and then leave through the inner (Bruch's membrane opening) and the outer, scleral portions of the neural canal.[6] The nerve fibers form approximately 1000 fascicles or bundles, supported by astrocytic processes. The nerve fibers from the arcuate areas of the retina pass through the characteristic hourglass superior and inferior poles of the ONH. The forces of IOP are supposed to act uniformly on the ONH. However, regional differences in the disc, due to larger pore size in the poles, make these regions more sensitive to the changes.[7-9] The fibers from the papillomacular bundle intermingle with extramacular fibers and are most resistant to glaucomatous damage. Thus, central vision is usually retained even in advanced glaucoma.[7,10,11]

The prelaminar tissue is the region present within the Bruch's membrane opening of the ONH. It occupies the area between the internal limiting membrane (ILM) and the anterior surface of the LC. It is formed by RGC axons, astrocytes, capillaries, and extracellular material.[12,13] Cupping or excavation of the ONH seen in glaucoma ostensibly consists of two pathophysiologic components: Prelaminar thinning and laminar deformation. The former is defined as the enlargement of the cup due to the thinning of prelaminar tissues as a consequence of physical compression and/or loss of RGCs.[14,15] Prelaminar cupping occurs on the ONH surface, characterized by progressive loss of prelaminar neural tissues. This leads to an increase in the depth and width of the cup, clinically presenting as an increased cup:disc ratio.[16]

A large number of studies have shown that prelaminar tissues respond actively in glaucoma patients. Swept-source optical coherence tomography (OCT) analysis of both eyes of glaucoma patients who showed visual field (VF) defects in one eye only revealed peculiar prelaminar tissue characteristics even in the unaffected eyes. The authors reported the anterior prelaminar depth to be significantly greater and prelaminar tissue significantly thinner in the fellow eyes of perimetrically confirmed glaucoma patients, as compared to normal controls. The authors concluded that subclinical or preperimetric changes in the prelaminar region of apparently healthy eyes in unilateral glaucoma patients appear before other signs of glaucoma, such as retinal nerve fiber layer (RNFL) defects. It is assumed that IOP-related stress, even when the IOP is within the normal range can affect the prelaminar tissue.[17] Agoumi *et al*. have studied the response of the prelaminar tissues to acute IOP elevations. They reported the mean ± standard deviation (SD) prelaminar tissue displacement (PTD) as 6.8 ± 13.7 μm in glaucoma patients versus 20.8 ± 17.5 μm in age-matched controls ($P = 0.045$) and PTD had a positive association with the degree of IOP elevation ($P = 0.013$). Thus, PTD was significantly higher in nonglaucomatous individuals. The authors suggested that the disc changes in acute IOP elevation models can be due to prelaminar changes since the LC is relatively rigid in acute cases.[18]

Jung *et al*. have compared the prelaminar thickness among primary open-angle glaucoma (POAG) and NTG patients. The mean prelaminar thickness was significantly thinner in patients with POAG, compared to NTG patients. The difference was greater in patients who had early VF defects. On multivariate analysis, the mean PLT was positively correlated to IOP, mean deviation,

cup:disc ratio, and cup volume.[13] Conversely, Arish *et al*. compared NTG and POAG patients and found that the mean Lamina Cribrosa Thickness (LCT) was significantly greater in NTG patients, while the Prelamina Cribrosa Depth (PLCD) and Optic Nerve Head Depth (ONHD) means were thinner in this group of patients, compared to POAG patients.[19] Park *et al*. evaluated the association between prelaminar tissue thickness (PLT) and peripapillary choroidal thickness. They found a positive correlation of PLT with peripapillary choroidal thickness, VF Index, and anterior lamina cribrosa depth.[15]

Chiou *et al*. have studied prelaminar wedge defects (PLWDs) in POAG patients. They found PLWDs in 27.5% of POAG patients (compared to 4.3% in controls; $P = 0.04$). According to them, PLWDs can form an important imaging biomarker in assessing glaucoma damage.[12] However, Yang has concluded that prelaminar thinning results in clinically shallow cupping and is seen in all forms of RGC axon degeneration, irrespective of the cause. Therefore, it is regarded as a non-specific feature and the role of IOP is not clear. In their study, prelaminar thickening was found in most ONHs, especially inferonasally.[14] Reis has also reported thickening of prelaminar tissue after reduction of IOP surgically.[20]

Several prelaminar factors directly or indirectly influence the development of mechanical and/or vascular glaucomatous changes.

Intra-ocular pressure

Intra-ocular pressure is the most consistent factor associated with the prevalence, incidence, and progression of glaucoma in numerous population-based studies and landmark trials. The direct mechanical effect of IOP on the laminar and parapapillary structures is undeniable. This has been the foundation of the development of the mechanical theory.[21-24] The stresses and strains experienced by the tissues at a given level of IOP can be physiologic or pathophysiologic, depending on the response of the tissues that experience them. The physiologic stress/strain induces changes that are normal for aging and for the given IOP response. Conversely, pathophysiologic stress/strain causes pathologic changes in cell synthesis and tissue architecture, ending up with detrimental mechanical failure of the tissues.[25]

The Ocular Hypertension Treatment Study, showed that reduction of IOP was able to lower the risk of OHT patients converting to POAG over a period of time. Patients with a 20% lowering of IOP had their 5-year risk of developing glaucoma significantly reduced to 4.4%.[26] The Collaborative Normal-Tension Glaucoma Study showed that lowering IOP by 30% resulted in slower rates of glaucoma progression in NTG patients.[27] In the Early Manifest Glaucoma Trial elevated IOP was a strong factor in the progression of glaucoma. It was also found that the risk of progression decreased by about 10% with each millimeter of mercury IOP reduction from the baseline.[28] Cartwright and Anderson have shown that in NTG patients with asymmetric IOP (a difference of 1–6 mmHg between the two eyes), the degree of cupping and VF loss is greater in the eye with higher pressure. The authors concluded that "the close correspondence of the direction of asymmetry of VF loss with the direction of asymmetry of pressure constitutes evidence that the IOP participates in the production of damage."[29] Therefore, IOP is the foremost prelaminar factor responsible for the mechanical changes occurring in a glaucomatous eye.

In the Advanced Glaucoma Intervention Study, patients who had initial average IOPs higher than 17.5 mmHg showed greater worsening of VF defect scores, compared to eyes in which the average IOP was <14 mmHg ($P = 0.002$). A 6-year follow-up of patients showed that eyes with IOP <18 mmHg had mean changes in their VF defect scores close to zero, compared to their baseline scores.[30] Palmberg has reported that in patients undergoing glaucoma filtering surgeries when IOP was reduced from a mean preoperative value of 26 mmHg to a mean of 11 mmHg, there was no net change in either mean deviation or pattern SD, over 5 years of follow-up.[31] These studies show that reducing IOP is an important therapeutic option since high IOP remains one of the major mechanical risk factors for glaucomatous damage.

Retinal ganglion cell demise

Some studies have demonstrated that RGCs are the first to be damaged in glaucoma.[32,33] Glaucomatous degeneration is characterized by selective damage to the RGCs without the involvement of other non-RGC neurons in the outer or inner nuclear retinal layers. This loss of RGCs occurs in a characteristic geographical pattern of pie-shaped sectors.[34] Both acute and chronic IOP elevations have been implicated in causing inner retinal injury.[35] Acute IOP elevation can induce morphological changes in the microglia, which are support cells for RGCs, within an hour after the event. The activated microglia begin to release pro-inflammatory mediators such as complement proteins, nitric oxide (NO), Tumor necrosis factor α (TNFα), and interleukin-6, which lead to RGC damage and ultimately cause apoptotic cell death.[35]

Many studies have demonstrated the effect of chronic IOP elevation on RGC populations. Ji *et al*. used a rat model of argon laser-induced elevated IOP. The authors reported a twofold IOP increase over baseline, which led to a 27%–30% loss of RGCs at 2 months.[36] Using a rat model of bead-injected IOP elevation, Tao *et al*., produced a 41.7% IOP differential between injected and un-injected eyes

over a 3-month period. The authors reported a gradual and mild reduction in RGC somas over time, to the extent of a 7.4% reduction at 6 weeks and an 11.2% reduction at 12 weeks.[37] A study by Guo *et al*. reported that RGC apoptosis in glaucoma is strongly related to exposure to elevated IOP. High IOP induces a significant increase in matrix metalloproteinases (MMP)-9 activity, thus causing changes in specific extracellular matrix (ECM) components of the RGC layer. This abnormal ECM remodeling in the retina of glaucomatous eyes causes RGC death, emphasizing the retina being the primary site of glaucomatous injury.[33] These studies show that prelaminar factors, such as raised IOP can directly or acting through certain mediators, induce RGC death and contribute to glaucomatous damage.

Prelaminar optical coherence tomography changes

Several prelaminar changes have been observed in OCT scans of glaucoma patients, providing direct evidence of the mechanical factors at play in the development of glaucomatous damage. A common pathophysiologic mechanism attributed to them is biomechanical changes, especially differential shear forces, in and around the ONH occurring in acute or chronic glaucoma.[38,39] According to Fortune, these conditions share a strong common tendency to develop in association with severe and/or rapidly progressing disease.[40]

The most common condition, reportedly 10 times more often seen in glaucoma patients compared to healthy controls, is peripapillary retinoschisis.[41-45] This condition is defined as the visible splitting of the inner or outer retinal layers accompanied by floating retinal vessels that are cleaved from the underlying prelaminar structures. In a study by Lowry, the frequency and severity of prelaminar schisis were found to be greater in glaucoma and glaucoma suspect eyes, compared to healthy eyes (P = 0.009). Almost half of glaucoma/suspect eyes had some degree of schisis, while only 33% of healthy eyes showed some features of schisis. Among the healthy controls, no eye had Grade 3 (severe) schisis, while more than 5% of glaucoma/suspect eyes had Grade 3 schisis.[43] In a study of 116 patients with advanced glaucoma, Sung *et al*. found ONH prelaminar schisis in 41.38% of individuals.[41] According to Lowry, peripapillary retinoschisis is due to mechanical stresses causing deformation and remodeling of the load-bearing tissues in the ONH, and also impacting distant tissues through retinal vessels, ILM, and macroglia (Muller cells). This condition is regarded as a possible risk factor for further damage.[46]

Hypodense holes of the RNFL were first reported by Xin. On OCT scans, these areas appeared as small round or oval regions with very low or absent ("hypodense") reflectance. In Xin's study, 16% of glaucomatous eyes showed these holes but none were present in healthy controls.[47] Muraoka has described paravascular inner retinal defects (PIRDs) which appear on fundus photography as spindle or caterpillar-shaped dark regions along the major retinal blood vessels. On OCT scans, PIRDs appear as cystoid or fissure-like wide defects in the inner retina or underneath the major retinal vessels. In Muraoka's study, out of 41 eyes having PIRDs, 35 demonstrated VF defects corresponding to the locations of the PIRDs.[48] Hood has also validated the appearance of paravascular defects being consistent with PIRD in his study.[49] Microcystic macular edema (or microcystic macular degeneration) are pseudo-cysts (lacunae or vacuolar inclusions) seen in the inner nuclear layer in the form of a perifoveal ring on OCT scans in patients with glaucoma. These cysts are associated with the thinning of the ganglion cell layer and the thickening of the inner nuclear layer of the macula. The cysts have been reported in eight eyes of 218 glaucoma patients by Brazerol and in 13 eyes of 217 patients by Hasegawa. Among Hasegawa's patients, a larger proportion of advanced glaucoma was seen associated with microcystic edema (P = 0.013). There was significant worsening in the VF mean deviation slope in eyes with microcysts (P = 0.027).[50,51]

While the etiopathogenesis of the abnormalities seen on OCT scans is still conjectural, yet, the mechanical forces acting on prelaminar structures appear to be the most likely cause.

Laminar Factors

The ONH is the distal portion of the optic nerve extending from the retinal surface to the beginning of the myelinated portion of the optic nerve posterior to the LC.[52] The LC inserts and anchors itself into the parapapillary scleral connective tissue which provides substantial support to counteract IOP.[11] The LC forms a biomechanically sensitive region imparting structural and functional support to the RGC axons during their journey from the relatively high-pressure intra-ocular environment to the low-pressure post-laminar area.[53,54]

The LC comprises multiple "plates" of connective tissue including interstitial collagen, proteoglycans, and elastin.[52] The posterior or scleral portion of the LC contains significantly higher amounts of collagen compared to the anterior or choroidal part of the LC. However, the anterior portion of the LC contains large numbers of astrocyte processes rich in glial fibrillary acidic protein (GFAP). These processes surround the bundles of axons passing through the LC.[55]

The retinal nerve fibers pass through the LC, become aggregated to form the optic nerve behind the eyeball, and travel toward the brain.[56] The central retinal

artery and vein also pass through the ONH. Due to the proximity of the vascular channels to the neural elements, it can be surmised that biomechanical changes in the ONH can lead to vascular changes as well. This indicates that several different mechanisms might be active in the same patient.[7,10,11]

The cribriform plates of the LC have abundant collagen Type IV, irregularly distributed between elastin fibers, fibronectin, and laminin, some amounts of collagen Type III, and negligible collagen Type I. Conversely, the sclera is devoid of Type IV collagen and has only a few elastin fibers. Compared to the postlaminar region, the LC contains a higher concentration of macromolecular elements, the ECM appears lamellar and is perpendicularly oriented to nerve bundles. The unique mechanical properties of the ECM in the cribriform plates play an important role in the maintenance of the compliance and resiliency of the laminar tissues in response to IOP-induced compression. Age-related changes in the ECM may have individual differences concerning the type, amount, or architectural distribution of the macromolecular components of this matrix. This could contribute to the development of the glaucomatous degenerative process in the ONH.[57,58] Huang has proposed that genetic mutations leading to a primary collagen disturbance could be the initial factor in the development of glaucoma. The variations in the properties of collagen could cause inter-individual differences in the behavior of the LC and sclera.[54] These macro/micro-mechanical differences could determine the individual's susceptibility to IOP.

Biomechanics

Biomechanics involves the study of physical forces affecting the movement or structure of living organisms. The principles of biomechanics are emerging as a useful application in the study of glaucoma, giving rise to the biomechanical paradigm of glaucoma.[3,4] Multiple mechanosensory mechanisms and signaling pathways have been recognized in the ocular tissues, improving our understanding of the pathophysiology of glaucoma.[59] Biomechanical models have shown that the thickness of the posterior sclera, especially the peripapillary sclera has a strong influence on the ONH biomechanics, which modulates glaucomatous degeneration.[60] The sclera has nonlinear, anisotropic, and viscoelastic mechanical properties which contribute to the susceptibility of the eyes to IOP.[39]

It has been known for many years that the ONH is the vulnerable part of the eye which gets progressively damaged as a consequence of various factors which promote glaucomatous optic nerve degeneration.[61] Although the ONH has a major role to play in glaucomatous damage, the sclera cannot be regarded as a "passive bystander" in this disease process. Biomechanics has shown how elevated IOP induces remodeling in the sclera, which sets up a complex biomechanical interaction between the sclera and ONH.[59,60]

A computational tool, called finite element modeling, is being used to analyze the biomechanical characteristics of the human sclera when exposed to varying degrees of mechanical load, mainly IOP-related stress and strain.[3,60] Regional analyses have shown that for the same amount of stress, the anterior sclera is most resistant, and the posterior sclera least resistant to deformational forces. The peripapillary region shows a smaller strain ratio, compared to normal controls and the meridional strain is even lower. The level of stress borne by the ocular tissues is dependent on the 3D geometrical shape of the affected tissues.[3,59]

The ONH is a complex 3-D load-bearing structure, where IOP can produce conformational changes. However, the sclera, LC, cells in the surrounding areas (RGCs, astrocytes, glial cells, endothelial cells, and vascular pericytes), and the RGC axons are also subjected to constant stress (measured as the internal force per unit area) by IOP. The mechano-biologic response of these tissues to stress is by the production of reactionary strain (a measure of tissue deformation).[4,39] In the ONH, multiple biomechanical factors modulate the individual's response to IOP. Some of the variables acting on the ONH include (i) the level and fluctuation of IOP (ii) the orientation of collagen fibers in the peripapillary sclera (iii) the stiffness of the ONH and scleral tissues, and (iv) the geometry of the LC and sclera. In this regard, a highly aligned and oriented collagen fiber ring in the parapapillary sclera is protective for the ONH against IOP-induced stress. Similarly, a thick lamina may seemingly prevent extensive mechanical damage.[59]

It is reported that different individuals exhibit significant variations in the material properties, thickness, and geometry of the sclera, the main load-bearing layer of the eye, which probably determines their susceptibility to IOP-induced changes.[60] The anatomy of the sclera shows a unique "basket-weave" formation of collagen fibers around the scleral canal. This is assumed to protect the fragile structures in the ONH by efficiently dispersing the mechanical loads to the equatorial sclera. Apart from collagen, certain ECM components, such as sulfated glycosaminoglycans also take part in scleral remodeling.[59]

The mechanical strain imposed on the ONH leads to a cascade of cellular events which ultimately lead to RGC dysfunction and apoptosis.[39,60] On application of mechanical strain, scleral fibroblasts activate the release

of MMPs and tissue inhibitors of metalloproteinase. These phenomena aid in scleral remodeling. As IOP is increased, different creep mechanisms are also activated. In the initial stages of raised IOP, the ONH shows a posterior displacement, regulated by the uncrimping of collagen fibers. However, with progressive elevation of IOP, the collagen fibrils become stretched and take part in the posterior displacement of the ONH.[3] Sigal points out that, not only the magnitude of stretch but also the rate of application of stretch are paramount.[39]

In the eye, IOP constantly produces a pressure load normal to the sclera from the inside to the outside. This produces a circumferential stress on the ocular structures, known as "hoop stress." A significant amount of this IOP-induced stress is borne by the sclera. The retina and the nerve fiber layer being unable to withstand this stress, get damaged with progressive elevation or prolongation of IOP.[62] Studies have shown that strains in the range of 5%–8% induce significant and varied biological effects in neural cells.[3]

Ocular rigidity, which can be regarded as a crude measure of scleral stiffness, shows an initial period of scleral hypercompliance as IOP increases. However, later in the course of the disease, the parapapillary sclera tends to develop a stiffer meridional strain response. This could be a protective mechanism, wherein scleral fibroblasts through the process of mechano-transduction, and ECM modeling, lead to a stiffer parapapillary sclera that is resistant to IOP-induced changes. An argument put against this mechanism is that in old age there is stiffening of the sclera yet the patients in this age group are more prone to develop glaucoma. This, however, can be explained by the fact that the collagen fibers in old age are more brittle and this is a suboptimal protective mechanism, unable to prevent the formation of a biomechanically unstable ONH and the development/progression of glaucoma.[4]

Abnormalities in the optic nerve head

A number of innate abnormalities of the ONH could make this structure susceptible to GOA.[55] Once glaucomatous degeneration starts, the subsequent process tends to occur at a faster rate, apparently due to some unique characteristics in the glaucomatous eye, which make the remaining optic nerve fibers much more susceptible to IOP.[52] The forces of IOP acting on the LC consist of two vector components. The first is a posterior force compressing the laminar plates outwards. The second acts mainly through stress in the walls of the globe and has a radial direction of action on the scleral insertion of the LC. These forces produce physical changes in the LC leading to compression of nerve fibers as well as nutrient capillaries in the LC. This affects normal neural function and ultimately causes mechanical structural component loss and even death of the optic nerve.[7,63]

Changes in the ONH can be based on the microarchitecture of this structure. Thus, changes can be nonaxonal, such as in the LC, ECM, or astrocytes, and can be axonal, characterized by disturbances in axoplasmic flow.

Changes in the lamina cribrosa

Cupping or excavation of the ONH is caused by several factors working together, such as the loss of RGC axons and the collapse and posterior bowing of the connective tissue sheets in the LC.[52] A crucial pathophysiologic component in the development of cupping is laminar deformation. Increased IOP causes pathological configurational changes in the LC and parapapillary scleral connective tissue.[9] The laminar deformations caused by IOP lead to acute yield/and or failure in the anterior laminar beams. This load is transferred to adjacent laminar beams, leading to a surge of further damage and ultimately causing GOA.[17] Elevating IOP for several minutes leads to posterior movement of the LC, which returns to the baseline, once the IOP comes back to normal. This phenomenon is called compliance.[52] Findings in experimental glaucoma show that in early stages the anterior scleral canal wall and LC demonstrate hypercompliance, that is, greater than usual posterior movement of the LC. Hypercompliance can be regarded as a biomechanical marker for connective tissue damage.[25]

Computer modeling has demonstrated that the increase in IOP always significantly elevates the laminar stress and strain, even in the absence of frank posterior displacement of the LC. This occurs due to the tensile stretch occurring in the LC as a result of the acutely expanding scleral canal.[16] Burgoyne *et al*. have also shown through finite element modeling that IOP can create stress of the order of 10–17 times the normal IOP within scleral tissues at points away from the ONH, 30 times higher in the connective tissues of the parapapillary sclera, 30–100 times of IOP in the scleral canal wall, and in the range of 50–180 times of IOP within the laminar beams. Therefore, the ONH and surrounding tissues are the prime targets for IOP-induced mechanical stress.[25,64]

A study has shown that in early glaucoma, the total connective tissue volume (CTV) of the LC is considerably increased compared to normal eyes. However, the relative proportion of connective to neural tissue (average CTV fraction), changes minimally.[65] Thicker laminar beams which appear to distribute the elevated stress are also noted *in vivo*.[66] This shows that significant alterations in connective and non-connective tissue components of the LC happen early in the course of the disease. With consistently elevated IOP, permanent posterior deformation of the LC takes place and ONH excavation becomes clinically apparent.[25]

Extracellular matrix changes

The development of glaucomatous changes in the LC could also occur through abnormalities in ECM composition, which influences optic nerve function and biomechanical properties of the ONH. The LC cells show altered expression levels of several genes responsible for ECM formation, cellular proliferation, growth factor secretion, and activity of cell surface receptors when exposed to certain deleterious factors.[67] These triggers include mechanical strain, hypoxia, and oxidative stress. The LC cells respond by upregulating profibrotic genes and consequently, increased production of collagen, α-smooth muscle actin, and elevated expression of ECM-associated factors such as macrophage migration inhibitory factor and discoidin domain receptor.[11] Therefore, activation of pro-fibrotic pathways leads to ECM remodeling and transformation in the LC, making this structure highly susceptible to damage from raised IOP.[68] The IOP-induced mechanical strain in connective tissues in the ONH and parapapillary sclera activates molecular signaling pathways which increase the ECM turnover in the scleral tissues.[69]

Astrocytic changes

The astrocytes have been implicated as the cells modulating the evolution of ECM changes in GOA. When exposed to external stimuli such as raised IOP, astrocytes undergo hypertrophy, round up and migrate, produce increased amounts of GFAP, and reduce connections with each other and connective tissues.[70] Johnson *et al*. reported a loss of labeling for connexin-43, a component of gap junctions between astrocytes in the ONH early after the elevation of IOP.[71] As a result of these structural and functional changes in the astrocytes, the physiological properties of these cells are affected. Over the long term, the astrocytes may stop performing their usual axonal support functions, probably through reduced production of neurotrophins.[52]

Reactive astrocytes in glaucoma migrate into the nerve bundles from the cribriform plates by activation of the PI-3K signaling pathway and the pressure-induced erbB2, EGFR1, and PDGFR kinases. These astrocytes release neurotoxic mediators such as NO and TNF-α, which have a role in the neural damage characteristic of glaucoma. The reactive astrocytes express significant amounts of elastin, which leads to elastotic ECM degeneration in the ONH. As a result, there occurs a loss of resiliency and deformability of the ONH in glaucomatous eyes. Pathologically, astrocytes have a significant role in the formation of glial scar, influencing the survival and growth of axons.[70] According to one hypothesis, astrocytic dysfunctions could be the initiating factors in the development of GOA, as they are vital for the health of RGCs. These changes could cause abnormalities in the axonal environment and lead to the collapse of cribrosal beams, ending up with mechanical changes seen in the ONH.[72] Astrocytes also promote cupping through increased expression of MMP9, ECM remodeling, and activation of neurotoxic type A1 astrocytes.[73]

Axoplasmic flow

Axoplasmic flow or axonal transport is also affected by mechanical changes occurring in glaucoma. It is defined as a complex movement of material (axoplasm) bi-directionally, along the axon of the nerve and follows a predictable, energy-dependent process. These flows are critical for the structural integrity and function of axons.[10,74,75] The axons have a primary function of conducting action potential along them, but they also allow the soma to communicate metabolically with the terminal neuronal targets in the cortical structures such as the lateral geniculate nucleus and the superior colliculus.[76] The axoplasmic flow occurring from the soma towards the brain is called orthograde (anterograde) transport and that from the brain to the cell body is known as retrograde transport.[76] Axoplasmic flow is required for the transport of organelles, metabolic substances, and neurotrophic factors from and to the RGCs.[77] Abnormalities in the axoplasmic flow can be regarded as both a retrolaminar as well as a laminar factor.

Both acute and chronic IOP elevations disrupt the axonal flow.[78-81] These flow abnormalities, as a consequence of axonal compression validates the mechanical principle of GOA. Gaasterland has demonstrated a sharp localization of the initial axoplasmic abnormalities immediately adjacent to the LC, suggesting that mechanical compression was responsible for these changes. The axons appeared swollen with plasma membrane fragmentation and accumulation of axoplasm and organelles such as dense bodies and swollen mitochondria within them.[74] Anderson and Hendrickson have also shown the effect of rapid elevation of IOP in monkey eyes using an intravitreal tritiated leucine tracer. The authors concluded that axoplasmic transport is influenced by IOP, with partial effects seen even with moderate elevation in pressures.[77]

Quigley has reported that increasing the arterial oxygen levels does not protect the optic nerve axons from damage when IOP is abnormally raised. When axonal transport is blocked by elevated IOP and even if hyperbaric oxygen is provided, the axons continue to show damage even in the presence of adequate vascular supply.[82] Minkler, in his experiment, injected nucleated avian erythrocytes into monkey eyes with moderate elevation of IOP. He demonstrated that these cells were able to enter scleral capillaries, indicating intact ONH capillary circulation, despite IOP levels ranging from 25 to 50 mmHg and elevated arterial PO2 levels achieved

by inhalation of 100% oxygen.[80] This shows that poor vascular or oxygen supply to the ONH is not the cause of axonal damage, pointing to mechanical compression of the axons.

Like acute, chronic IOP elevation was found to block axonal transport in the LC. When IOP was kept high for less than a week, some axons showed a return to normal axonal transport, while others led to RGC death. When IOP was kept elevated for more than 1 week, there was loss of the anterior disc fibers and the LC showed lateral and posterior movement, leading to optic disc cupping. There were minimal changes noted in the capillaries and astrocytes, again pointing to mechanical compression being responsible for the glaucomatous changes.[79]

However, it is yet to be confirmed whether alterations in axonal transport or cytoskeleton occur as a primary initiator of glaucomatous degeneration or if these changes are a consequence of the disease process. Perhaps both scenarios can occur depending on the pathological context.[75]

Postlaminar Factors

The retrolaminar or retrobulbar factors that play a part in the mechanical influence on GOA include the unique structural characteristics and specific abnormalities in the optic nerve and its sheaths. The CSF bathing the optic nerve sheaths and IOP produce a pressure differential across the LC. These retrolaminar mechanical factors are being increasingly identified in the development of glaucomatous ONH changes.

Translaminar pressure difference

While IOP is identified as an important, and currently the only modifiable factor in the development and progression of glaucoma, another important parameter being recognized is the pressure difference between the IOP and intra-cerebral pressure (ICP) at the level of the ONH. This pressure difference (IOP-ICP) across the LC is called translamina cribrosa pressure difference (TLCPD). According to Jonas, the physiology and pathophysiology of the ONH are dependent mainly on the TLCPD. This is so, because IOP denotes the trans-corneal pressure difference, present in the anterior part of the eye, and it is the TLCPD that forms a more important parameter, directly influencing the ONH.[53,83,84] Thus, an increase in IOP or a decrease in ICP will lead to optic disc cupping, depending on the thickness of the LC, the rigidity of ECM, and the tension of the peripapillary scleral flange.[85] The difference between IOP and retrolaminar tissue pressure, divided by the thickness of the LC forms the translamina cribrosa pressure gradient.[86] Recently, many researchers have emphasized the importance of ICP in determining the translamina cribrosa pressure gradient.[39,83,87,88]

The ONH in general and the LC in particular is the principal site of axonal insults.[39] When the LC is unable to resist the TLCPD, a circumscribed herniation of the LC occurs in the retrobulbar cerebrospinal fluid (CSF) space. This happens due to the CSF being unable to prevent a focally accentuated posterior bowing of the LC. It can occur in predisposed eyes with larger LC pores and significant interpore connective tissue in the border of the optic disc.[53]

The LC forms the barrier between the high-pressure intraocular region and the low-pressure extraocular space.[53,54] The optic nerve is bathed by the CSF in the retrolaminar region. Some studies show that the dynamics and composition of the CSF within the optic nerve sheath are different from those present in the brain.[89,90] The optic nerve sheath is traversed by trabeculae which reduce the effect of fluctuations in CSF flow.[55,91] These factors maintain homeostasis in the retrobulbar compartment and could be protective against the effect of fluctuating CSF pressure in the optic nerve sheath.

The eyeball is a spherical structure forming the corneoscleral shell, and the LC is the region most vulnerable to changes occurring in a glaucomatous eye. Therefore, respecting the formulae regarding stress and Laplace's law, the LC responds to the pressures affecting it on either side, that is, IOP and ICP.[87,90] A large number of studies have shown that the LC is thinner in glaucomatous eyes compared to normal controls.[84,92] Also, the ICP is lower in individuals with NTG, compared to that in POAG and OHT.[84,93,94] These two factors are inter-related in the development of glaucomatous changes, by their influence on TLCPD and translaminar pressure gradient.

The optic nerve sheath subarachnoid pressure is probably the same as ICP.[83] It is lower than IOP and gets further reduced in the standing position, coming down from 12.9 ± 1.9 mmHg from supine upto -10 to 0 mmHg in standing position.[86] If the translaminar pressure gradient is high, it produces a mechanical shearing force on the ONH, contributing to glaucoma progression.[82] According to Wostyn, fluctuations in ICP cause significant changes in the TLCPD which lead to repetitive shear stress on the LC and axons, ultimately contributing to glaucomatous damage.[94] If the TLCPD is high, it causes altered axonal transport, structural changes in the LC, ischemia, or a combination of these factors, which leads to abnormal functioning and damage to the optic nerve.[88] Again, we see here the interaction of mechanical and vascular factors in the development of glaucomatous changes in the ONH. According to Baneke, if IOP plays a significant role in glaucomatous degeneration through a direct mechanical effect, then the role of ICP in glaucoma also cannot be ruled out.[90]

Therefore, the mechanical factors that influence the dynamics across the LC have a crucial role in certain forms and vulnerable populations to develop glaucoma.

Conclusions

Several risk factors that can lead to the development of glaucoma have been identified in various studies. These factors can be classified according to their location in relation to the ONH. Therefore, they can be prelaminar, laminar, or postlaminar. The mechanical theory was one of the first concepts to explain glaucomatous neural degeneration. However, now we know that glaucomatous damage extends beyond the neural elements. The role of sclera, astrocytes, axoplasmic flow, ECM remodeling, and translaminar pressure difference indicate that multiple sites and factors affecting them can be significant in the development of glaucoma-related visual loss. This can be crucial in our quest for neuroprotective and neuro-regenerative agents in glaucoma patients.

An understanding of astrocyte-axon interactions in the pathogenesis of GOA is opening up the possibility of new therapeutic interventions in glaucoma beyond IOP control.[87] Studies have been performed to increase the stiffness of the sclera to protect against IOP-related LC deformations.[95] Unfortunately, the results of this intervention have been discouraging so far. In conclusion, it is now evident that multiple factors apart from IOP and involving structures beyond the retina and ONH play a decisive role in the development of glaucoma. Therefore, the target of future glaucoma therapies should extend to the entire visual system.[96]

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

The authors declare that there are no conflicts of interest in this paper.

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