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EDITED BY

Sobha Sivaprasad,
Moorfields Eye Hospital NHS Foundation Trust,
United Kingdom

REVIEWED BY

Kishu Ranjan,
Yale University, United States

*CORRESPONDENCE

Ningli Wang
✉ wningli@vip.163.com

[†]These authors have contributed equally to this work

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Biomechanical homeostasis in ocular diseases: A mini-review

Ying Cheng^{1†}, Tianmin Ren^{1†} and Ningli Wang^{1,2,3*}

¹Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing Tongren Eye Center, Beijing Institute of Ophthalmology, Beijing Tongren Hospital, Capital Medical University, Beijing, China, ²Collaborative Innovation Center for Brain Disorders, Beijing Institute of Brain Disorders, Capital Medical University, Beijing, China, ³Beijing Key Laboratory of Fundamental Research on Biomechanics in Clinical Application, Capital Medical University, Beijing, China

Diabetes mellitus-induced hyperglycemia is responsible for multiple pathological ocular alternations from vasculopathy to biomechanical dyshomeostasis. Biomechanical homeostasis is crucial to maintain the normal physiological condition of the eyes. Biomechanical features vary in eye tissues regarding different anatomical positions, tissue components, and cellular functions. The disturbance in biomechanical homeostasis may result in different ocular diseases. In this review, we provide a preliminary sketch of the latest evidence on the mechano-environment of the eyeball and its possible influencing factors, thereby underscoring the relationship between the dyshomeostasis of ocular biomechanics and common eye diseases (e.g., diabetic retinopathy, keratoconus, glaucoma, spaceflight-associated neuro-ocular syndrome, retinal vein occlusion and myopia, etc.). Together with the reported evidence, we further discuss and postulate the potential role of biomechanical homeostasis in ophthalmic pathology. Some latest strategies to investigate the biomechanical properties in ocular diseases help unveil the pathological changes at multiple scales, offering references for making new diagnostic and treatment strategies targeting mechanobiology.

KEYWORDS

biomechanical homeostasis, keratoconus, glaucoma, diabetic retinopathy, myopia

Introduction

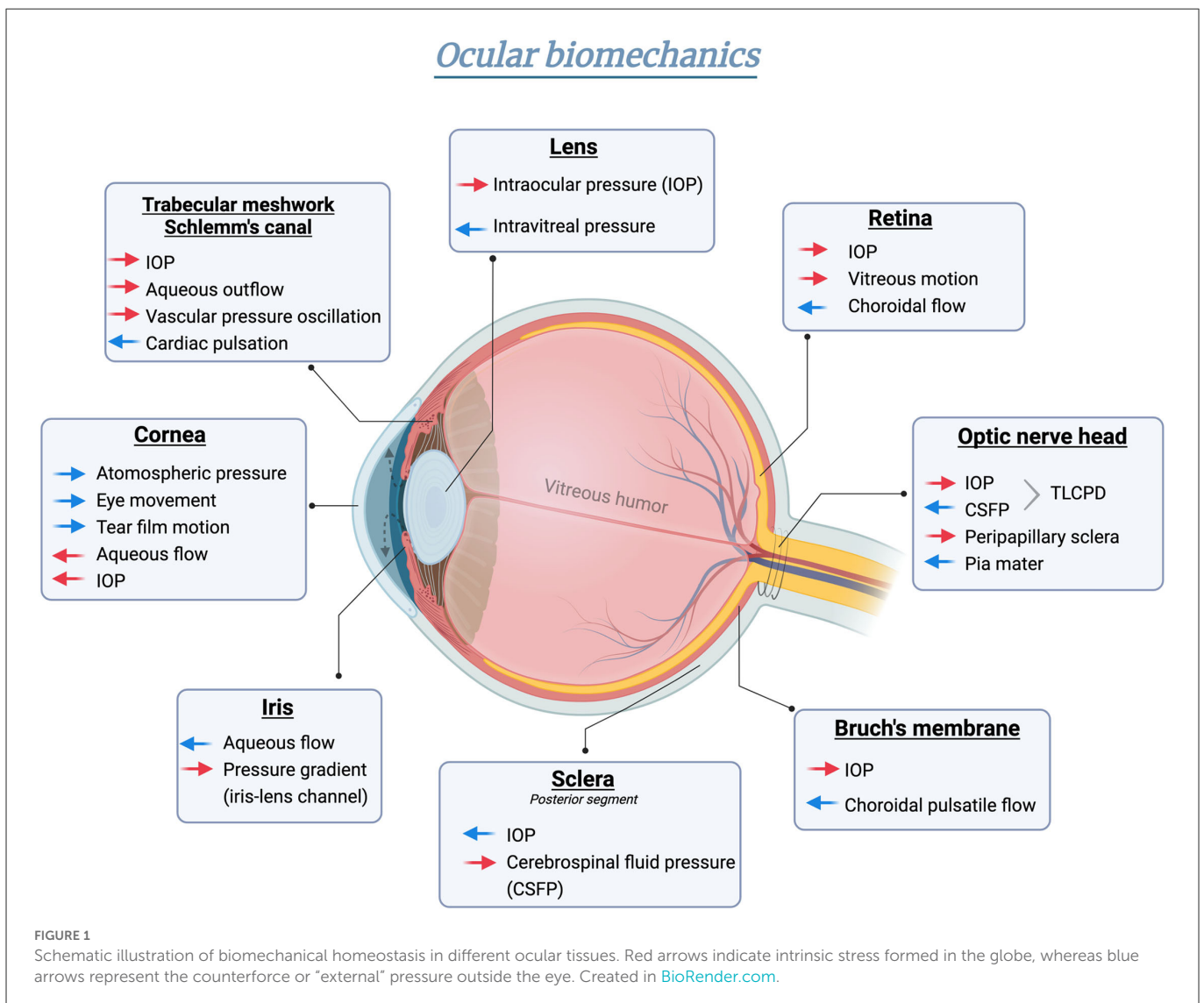
Diabetes mellitus (DM) imposes a heavy economic burden worldwide with a detrimental impact on ocular health. Chronic exposure to hyperglycemia exerts toxicity to cells and aggravates the metabolic dysfunction in ocular tissues at both physiological and pathophysiological scales. Glucose-rich ambiance is the major culprit of DM-related eye diseases, which could stimulate the polyol pathway, boost the production of advanced glycation end-products (AGEs), activate protein kinase C, increase oxidative stress, and upsurge inflammatory pathways (1). For instance, hyperglycemic conditions promote the activity of aldose reductase in the polyol pathway and induce chronic accumulation of sorbitol in the lens, which further raises the osmotic pressure along with the excessive oxidative stress, and eventually contributes to the onset of cataracts (2). Meanwhile, DM-induced hyperglycemia could trigger subsequent ocular changes that range from the impairment of vascular supply to the elevation of intraocular pressure (IOP). As reported, for every 10 mg/dL increase in fasting serum glucose, IOP increases by 0.09 mmHg in men and 0.11 mmHg in women (3). The IOP level was found to be lower in DM patients with adequate control of the blood sugar than in those without (4). Moreover, owing to the end-organ effect of uncontrolled glucose levels, DM has also been considered as a potential risk factor for other deleterious abnormalities such as glaucoma (5). Therefore, maintaining biomechanical homeostasis is vital for eye health in the context of ophthalmology management including DM and glaucoma.

As the only visual sensation organ, the eye is physiologically subjected to multiple sources of pressure, which is referred to as ocular biomechanics (Figure 1). The term “biomechanics” defines the physical responses of biological tissues under different pressure influences (6).

Starting with the anterior compartment, the cornea is the outermost component of the eye globe. Exposed to the open air, the cornea directly bears the exterior stimuli generated by atmospheric pressure (7), eye movement (8), and tear film motion (9), etc. To counterbalance, the internal stresses were fostered by aqueous humor (10) and IOP (7). As the continuous tissue of the cornea, the anterior sclera also perceives comparable stresses and strains (11). However, the posterior sclera [peripapillary sclera and scleral canal connected to lamina cribrosa (LC)] is mainly affected by “external” stresses imparted by cerebrospinal fluid pressure (CSFP) from the back of the eye globe (12). Regarding the anterior chamber angle, the aqueous outflow is driven by the mechanical strain on the trabecular meshwork (TM) and the shear stress arising from the circumferential flow through the Schlemm’s canal (SC), thereby modulating the IOP homeostasis (13). Additionally, SC and TM are also subjected to the ocular pulse generated from either cardiac pulsation in the retina and choroid or the pressure oscillations in the episcleral vessels (14). The lens capsule completely encloses the crystalline lens, with its thicker and more durable anterior capsule (toward aqueous humor) accommodating to the IOP (15), and the posterior capsule (toward vitreous cavity) facing the intravitreal pressure (16). The viscosity and

elasticity properties of the capsule membrane exhibit high resistance to extrinsic mechanical strength and intrinsic deformative stress occurring in the lens shape alterations (16). Under physiological status, the anterior and posterior chamber is interconnected by the iris-lens channel allowing the aqueous flow. The pressure difference between these two chambers is relatively equilibrated, with only <1 mmHg difference in human eyes estimated by a mathematical model (17).

The posterior chamber of the eye is a spherical cavity filled with gel-like vitreous humor buffering the mechanical stimuli exerted on the lens or retina under both static and dynamic nature (18, 19). Specifically, the vitreous chamber serves as a torsionally oscillating sphere in the eye rotation process. The subsequent vitreous motion would result in a small shear stress on the retina in a radius manner (20). Bruch’s membrane (BM) is a thin acellular lamina at the inner layer of the choroid, subjected to constant pressure-induced mechanical stress resulting from the choroidal flow changes resonating cardiac pulsation (21). As the physical and biochemical barrier between the retinal pigment epithelium and the choroid, BM facilitates metabolic transportation across tissues *via* the stress-strain (22). The biomechanics at the optic



nerve head (ONH) of the posterior orbit are regulated in a more complex way. Anatomically, the eye and the brain are connected by the optic nerve passing through the translaminar region and the subarachnoid space. Biochemically, the translaminar cribriform pressure difference (TLCPD), formed by IOP and intracranial pressure (ICP) across the ONH, establishes significant levels of pressure gradient along the nerve tract (23). Meanwhile, other properties, including orbital tissues and pia mater, are also involved in the mechanical features imposed on the optic nerve (12). Taken together, these features delicately manifest the regional specialization of ocular biomechanical dynamics.

Under normal physiological conditions, the ocular biomechanics is generally kept in a dynamic-balanced fashion, with temporary fluctuations in stresses and strains. As the predominant and solely modifiable risk factor in glaucoma, IOP has a clear circadian oscillation pattern. Thus, the 24-h IOP recording is better at reflecting the biological features of IOP (24). The normal IOP, lying between a range of 10–21 mmHg, can be termed as “normal resting IOP.” The normal resting IOP is influenced by multiple extrinsic factors. Specifically, the IOP level alters with eye movement, generally increasing in the eye upgaze phase, and decreasing in the inferonasal gaze phase (25). Weekly and seasonal variations of IOP are also observed (26). Notably, eyelid-related maneuvers such as eyelid squeezing or rubbing can trigger a transient IOP spike exceeding normal range on a time scale of less than a second (27). Here, we defined this specific type of IOP elevation as “transient IOP fluctuation.” Under normal conditions, these transient “attacks” would not lead to any observable functional or structural damage. One possible speculation is that these short-term IOP spikes are managed by some mechanical response units which can help neutralize and prevent the potential damage caused by pressure insults.

At the cell level, the mechanical response unit mainly refers to the mechanosensitive channels, categorized into Na⁺-permeable, K⁺-permeable, and non-selective cation (TRP, Piezo) channel families. These channels serve as bandpass filters allowing transmission of certain types of mechanical loading pressure such as tension, stretch, shear flow, and compression at specific amplitude. Previous studies identified the expression of Piezo and TRP family channels in the cornea (28), TM (29), and retina (30), which exerts a vital impact on the regulation of inflammation, oxidative stress, cell apoptosis, and neurotransmission, etc. (31). Widely distributed mechanosensitive channels serve as the multi-functional mechanical transducer and play parts in maintaining ocular biomechanics. The disruption of mechanical homeostasis initiated by the dysfunction of mechanosensitive channels or other pathological stimuli may exacerbate the damage to the stressed tissues, thus leading to the occurrence and progression of ocular diseases.

Disorder of biomechanical homeostasis in ocular diseases

Diabetic retinopathy

Diabetic retinopathy (DR) is one of the most prevalent complications of DM. The progression of DR is associated with chronic DM status, hyperglycemia, hypertension, dyslipidemia, higher body mass index, and smoking (32). Recent studies

demonstrated the potential association between glaucoma and DR, as they share several common risk factors (e.g., blood pressure, obesity, serum total cholesterol, etc.) and pathophysiological features (e.g., impairment of vascular supply, and neuroretina degeneration, etc.) (33, 34). We previously confirmed that the body mass index (BMI) is positively correlated with CSFP (35), and the latest meta-analysis demonstrated that obesity (BMI > 30 kg/m²) was a risk factor for non-proliferative DR. Collectively, we speculated that the high BMI induces the elevation of CSFP, which may lead to the dysfunction of capillary reflux and the upregulation of retinal venous pressure. Retinal venous pressure is reported to be increased in both DR and glaucoma (36). The elevated retinal venous pressure causes hypoxia and tissue edema, resulting in potential pathologic changes including microaneurysm and cotton wool spots at the early stage of DR. Moreover, the increased retinal venous pressure may trigger mechanosensitive channels such as TRPV4 in endothelial cells. TRPV4 activation is linked to higher BRB permeability, and the genetic ablation of TRPV4 could efficiently alleviate retinal edema and BRB compromise in diabetic mice (37, 38). Thus, targeting mechanosensitive channels like TRPV4 could be a promising therapeutic strategy for the treatment of DR.

Intriguingly, the possible association between DM and keratoconus (KC) was also reported. McKay et al. (39) proposed a similar collagen crosslinking mechanism in the development of both diseases, they hypothesized that DM is associated with increased ACEs that led to inter- and intramolecular crosslinking, thus increasing the corneal rigidity. On the contrary, KC is characterized by decreased mechanical stiffness and secondary corneal ectasia. Hence, excessive crosslinking in DM may protect against KC development, but further studies are required to verify this hypothesis.

Keratoconus

The cornea is the outermost transparent tissue of the eye, its biomechanical properties, such as strength and stiffness, are determined by its five composing layers, namely epithelium, bowman's layer, stroma, Descemet's membrane, and the endothelium. The imbalance of biomechanical homeostasis across cornea contributes to the occurrence of corneal diseases such as KC. KC is a progressive corneal ectasia condition featured as a cone-shaped cornea with local thinning corneal stroma. Top risk factors of KC include family history, eye rubbing, eczema, asthma and allergy (40). Associated with disorganization and undulation of tissue structure, the alteration in ocular biomechanics plays an essential role in the pathogenesis of KC. Bettahar et al. (41) reported that eye rubbing is a considerable contributing factor in corneal degeneration of KC patients. Rubbing action triggers several mechanical insults, including IOP spikes, altered shear stress, and high hydrostatic tissue pressure. For instance, vigorous rubbing can skyrocket the IOP to more than 10 times of a normal resting IOP, generating more dramatic pressure strain on the cornea (7). Mechano-transducers like YAP in stromal cells and β -catenin in epithelial cells are associated with the regulation of substrate stiffness and protease production in KC (42, 43). A comprehensive understanding of the mechanobiology of corneal diseases may pave the way for new avenues for therapeutic approaches.

Glaucoma

Glaucoma is an irreversible visual impairment disease with substantial changes in ocular biomechanical properties. The main risk factors for glaucoma include aging, elevated IOP, family history of glaucoma, and high myopia (44). The biomechanical disturbance is indispensable in the pathogenesis of glaucoma. Moreover, the glaucomatous biomechanical stress is generated by several ocular tissues (e.g., TM, iris, peripapillary sclera, and ONH), which exert direct or indirect biomechanical roles in various subtypes of glaucoma. Here, we mainly discuss the biomechanical features of glaucoma in predominant clinical subtypes including primary congenital glaucoma (PCG), primary angle-closure glaucoma (PACG), malignant glaucoma and primary open-angle glaucoma (POAG).

PCG is characterized by the abnormal anatomical structure of the TM and anterior chamber angle, thus resulting in aqueous outflow resistance and IOP elevation in infancy (45). With the progression of the disease, the affected eye may display a larger cornea or eyeball size than normal individuals, which is named “hydrophthalmos” or “buphthalmos.” Of note, these two terms involve different etiologies and clinical features. Hydrophthalmos mainly refers to the enlargement of the cornea, with or without the whole eyeball expansion. Here, we speculate that the vitreous biomechanics might be involved in the formation of hydrophthalmos. The vitreous cavity is full of intact, dense and regularly structured vitreous gel without vitreous liquefaction in infancy (46), which acts as a favorable mechanical buffer to counteract the anterior pressure derived from the elevated IOP. The posterior segment of the eye tissues is less susceptible to mechanical stimuli than the cornea, thus the primary ocular deformation occurs in the cornea. However, with the constant IOP elevation and chronic damage to the eye tissues, the biomechanical buffering role of the vitreous cannot fully offset the excessive pressure impacted on the still-elastic young eye, eventually forming “buphthalmos” featured by sclera distension and eyeball enlargement (47).

The relative pupillary block between the iris and lens is the common mechanism of PACG. The pathogenic structural changes include lens antedisplacement, plateau iris configuration and iris bombe, sequentially inducing the pupillary block accompanied by the obstruction of aqueous humor. These changes raise the pressure difference between the posterior chamber and anterior chamber, contributing to the angle closure and IOP elevation (48). Severe acute angle-closure glaucoma can lead to morphological changes of lens, known as the glaucomatous fleck, which is an irregular grayish-white spot in the anterior lens capsule at the pupillary area. It might relate to nutritional disorders, or direct contact between the iris and the anterior lens capsule under a high IOP attack (49).

Malignant glaucoma is featured with the progressive elevation of IOP and resistance to therapeutics. It is also termed as ciliary block glaucoma, vitreous displacement glaucoma, aqueous humor misdirection syndrome, or vitreociliary block glaucoma. Although the underlying etiology of malignant glaucoma is not well-elucidated, some widely-accepted theories indicate that it may result from the anterior displacement of irido-crystalline diaphragm elicited by the swelling, hypertrophy, or anterior displacement of the ciliary body, or by the laxity of zonular (50). The increasing pressure difference in these compartments blocks the normal forward passage of aqueous humor and traps the refluxed aqueous flow in the

vitreous cavity. The excessive pressure difference between vitreous cavity and anterior chamber escalates the anterior displacement of irido-crystalline diaphragm, accompanied by a flattened anterior chamber (51). Recent research proposed potential risk factors such as choroidal expansion and anterior vitreous abnormalities in malignant glaucoma, subsequent confirmation still needs to be performed (52).

The prominent role of TLCPD, established by IOP and CSFP across the ONH, is well-acknowledged in the POAG etiology. Our previous studies identified that patients with normal-tension glaucoma had significantly lower CSFP and a higher TLCPD when compared with the normal subjects (53). The increased TLCPD may contribute to the LC deformation involving astrocyte migration, axonal bundle disorganization and extracellular matrix alternation (54, 55). Specifically, the individual role of these two forming ingredients is not equivalent, IOP-driven biomechanical effects display a more dominant role than CSFP (56). Multiple mechanosensitive channels such as Piezo, TRPV4, and TREK-1 are proven to have biomechanical effects in glaucoma on an experimental basis. The chemical inhibition or genetic ablation of these channels significantly ameliorates pathological phenotypes of optic nerve degeneration caused by IOP elevation, indicating the potential therapeutic roles of targeting mechanosensitive channels in glaucoma (57).

Spaceflight-associated neuro-ocular syndrome

After a long-term spaceflight, some astronauts were bothered by visual changes associated with ocular conditions, which were termed spaceflight-associated neuro-ocular syndrome (SANS) (58). The occurrence of SANS is primarily attributed to the chronic exposure of the astronauts to the unique microgravity environment during long-term spaceflight. Other associated risk factors include radiation exposure, inflated ambient CO₂ concentrations, high salt diets, intense resistance exercise, nutritional disturbance, and genetic variations in the one-carbon metabolism pathway (59, 60). Due to the prolonged microgravity exposure, SANS is generally characterized as fluid redistribution in the optic nerve sheath (ONS) and cerebrospinal fluid cavity (61). The cephalad fluid shifts occurring with weightlessness elevate the biomechanical strain transmitted to the ONH, as evidenced by progressive papilloedema and globe-flattening (62). To better distinguish the pathologies, a terrestrial analog called 6-degree head-down tilt bed rest (HDTBR) was established. After 30 days of examination, similar ocular changes of SANS were also identified in the HDTBR model with elevated ICP (63). Moreover, the alterations of TLCPD are also suspicious in the development of optic disc edema with increased ONS pressure protruding the LC anteriorly (64). Several countermeasures have been proposed to rebalance the biomechanical homeostasis at the site of ONH in SANS cases. A lower body negative pressure apparatus has been used to combat the cephalad fluid shift and showed a significant reduction of ICP in HDTBR testing (65). To rebuild the positive and posteriorly-directed pressure gradient, a swim goggles compression experiment was adopted to increase IOP and restore the normal TLCPD (64). These discoveries highlight the malignant impacts of imbalanced TLCPD induced by idiopathic intracranial hypertension, underscoring the fundamental role of biomechanical homeostasis in ocular health.

Retinal vein occlusion

Retinal vein occlusion (RVO) is a constellation of hypertensive retinopathies associated with multiple risk factors like aging, systemic hypertension, cardiovascular disorders, hyperlipidemia, diabetes, glaucoma, and thrombophilic mutations (e.g., antithrombin, protein C or protein S) (66, 67). The physical obstruction of the retinal venous system is generally induced by thrombosis, deformation of the vein wall, and external biomechanical compression secondary to glaucoma (68). Mechanically, it is postulated that the elevated IOP compresses the LC and optic disc, thereby leading to the stretching and weakening of the vessel wall, which further predisposes the retinal vein to occlusion (69). An excessive dropout of parapapillary choroidal microvasculature is also observed in RVO patients (70). Meanwhile, the direct biomechanical insult of IOP obstructs the retinal vein drainage and induces venous stasis, consequently exacerbating the intimal proliferation in the vein (71). Substantial evidence is required to further elucidate the underlying biomechanical changes in RVO etiology.

Myopia

As the most common refractive condition, myopia often starts in childhood and is manifested as short- or near-sightedness. Emerging evidence has supported the role of nature (genetics and inheritance) and nurture (environment and lifestyle) in the onset of myopia (72). Specifically, the major risk factors include higher education levels, prolonged near-work time, reduced outdoor activities, and inherited genetic predispositions (e.g., MYP1 family, ZNF644, SCO2, BSG, APLP2, etc.) (72–74). The biological deformation of myopia is typically characterized by an elongated posterior scleral shell. Severe scleral thinning in high myopia can lead to the biomechanical deformation of the posterior scleral wall, manifested as posterior staphyloma. It has been validated in several animal studies that the sclera thins during experimental myopia, suggesting the distinct role of scleral remodeling in the pathological axial elongation (75, 76). Scleral remodeling is a process of micro-deformation in a volume-conserving pattern, which results in the rearrangement of existing tissue materials. In highly myopic eyes, this mechanical adaptation to the scleral tension is even greater than an equivalent IOP attack in the aspect of globe enlargement and posterior thinning of the eye wall (77). Besides, David et al. (78) have studied the impact of vitreous torsional oscillation stress on the retina secondary to regular ocular motion. They found that the high myopia eye is hypersensitive to this chronic mechanical torsional stress, speculating it as the underlying cause of rupture-induced retinal detachment occurred in pathological myopia.

Discussion

Emerging evidence has associated biomechanical homeostasis with ocular health. The biomechanical features of the anterior segment (cornea, sclera, drainage route, and lens capsule) and the posterior segment (vitreous, Bruch's membrane, choroid, retina, and optic nerve) of the eye have been documented with substantial evidence, whereas the understanding of inner homeostasis between different tissues remained unclear. Knowledge of these physical

interactions is pivotal not only to clarify the underlying pathogenesis of a vast range of retinal and vitreoretinal diseases, such as DR, KC and glaucoma, but also to optimize the surgical handling of ocular tissues and the design of novel therapies.

Till now, the present studies of biomechanical analysis mainly focus on glaucoma (79), DR (80) and high myopia (81). The mainstream analytical methods of ocular biomechanics can be summarized into three subcategories, including (1) computational modeling (e.g., finite element modeling): a simplified model under ideal conditions with substantial variations from real-life situations (79); (2) microfluidic eye chips: a newly emerging 3D cell culture system providing novel insights for biomechanical studies *in vitro* (82); (3) the commercially available medical equipment (e.g., Corvis ST and wearable IOP biosensor) for clinical assessment (83, 84).

Novel treatment approaches and concepts have been proposed for the restoration of biomechanical homeostasis in ocular disorders. For the anterior segment, corneal cross-linking is widely utilized to increase corneal biomechanical resistance in treating ectasia and KC (85). Similarly, as collagen fiber crimping and re-alignment are observed in the development of myopia, collagen crosslinking has also been recommended as a potential therapeutic strategy for progressive myopia (86). For the posterior segment, LC stiffening is a common pathology in multiple ocular diseases like glaucoma and DR, which can be triggered by elevated IOP and increased AGEs, respectively. To alleviate the stresses and strains, collagenase treatment has been investigated in human cadaver eyes for the reduction of the biomechanical stiffness of LC (87). Besides, the posterior segment ring implantation (e.g., intrascleral or subarachnoid space ring) has been proposed as a potential countermeasure to delay the LC deformation in glaucoma at the conceptual level (12).

Altogether, biomechanical homeostasis is crucial to maintain the physiological function of the eye. In-depth acknowledgment of ocular biomechanics could help us better understand the underlying mechanical properties and molecular mechanisms in different ophthalmic conditions, further providing novel diagnostic methods and countermeasures from the perspective of mechanobiology.

Author contributions

The topic was devised and conceptualized by NW. YC and TR conducted the literature review and wrote the manuscript. All authors have read and agreed to the published final version.

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Conflict of interest

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