Glaucoma and biomechanics

Babak N. Safa, Cydney A. Wong, Jungmin Ha, and C. Ross Ethier

Purpose of review
Biomechanics is an important aspect of the complex family of diseases known as the glaucomas. Here, we review recent studies of biomechanics in glaucoma.

Recent findings
Several tissues have direct and/or indirect biomechanical roles in various forms of glaucoma, including the trabecular meshwork, cornea, peripapillary sclera, optic nerve head/sheath, and iris. Multiple mechanosensory mechanisms and signaling pathways continue to be identified in both the trabecular meshwork and optic nerve head. Further, the recent literature describes a variety of approaches for investigating the role of tissue biomechanics as a risk factor for glaucoma, including pathological stiffening of the trabecular meshwork, peripapillary scleral structural changes, and remodeling of the optic nerve head. Finally, there have been advances in incorporating biomechanical information in glaucoma prognoses, including corneal biomechanical parameters and iridial mechanical properties in angle-closure glaucoma.

Summary
Biomechanics remains an active aspect of glaucoma research, with activity in both basic science and clinical translation. However, the role of biomechanics in glaucoma remains incompletely understood. Therefore, further studies are indicated to identify novel therapeutic approaches that leverage biomechanics. Importantly, clinical translation of appropriate assays of tissue biomechanical properties in glaucoma is also needed.

Keywords
angle-closure glaucoma, intraocular pressure, normal-tension glaucoma, optic nerve head, trabecular meshwork

INTRODUCTION AND BACKGROUND

Although glaucomatous optic neuropathy can occur at any level of intraocular pressure (IOP), significant, sustained IOP reduction benefits patients [1–4]. This fact, as well as evidence from multiple studies [5–8], indicate that biomechanical effects are important in glaucoma; indeed, all current therapeutic approaches seek to reduce IOP. However, despite the existence of many IOP control strategies (drugs, devices, and surgical procedures), 25–45% of patients unfortunately continue to progress even with treatment [1,3,9], indicating that factors other than IOP are important in the disease process. Nonbiomechanical factors that play a role in the glaucomatous pathology include genetics [10,11] vascular abnormalities [12–14], metabolism [15–17], and immune function [18–20]; regrettably, we do not have space to review these factors here, and instead focus specifically on reviewing the recent literature on biomechanics in glaucoma, including but not limited to IOP, as shown schematically in Fig. 1.

There are several general concepts (and associated terminology) to be aware of when considering the role of biomechanics in glaucoma. All cells and tissues experience, and respond to, forces (also called 'loads') [21–24], and the eye is no exception. In glaucoma, we have historically focused on the loading on the trabecular meshwork (TM) and optic nerve head (ONH) due to IOP, yet there are suggestions that other loads, including optic nerve sheath (ONS) traction and intracranial pressure (ICP) transmitted by the cerebrospinal fluid (CSF), may contribute to the disease process (see below). Of course, it is not just the magnitude of the load that determines a tissue's mechanobiologic response: the properties of a tissue (stiffness, compressibility, viscoelasticity [25–27]) determine the magnitude and type of deformation that a given load induces. Ultimately it is these deformations, experienced at the cellular level, which affect cell phenotype. Thus, inter-individual

Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta, Georgia, USA

Correspondence to C. Ross Ethier, Petit Biotechnology Building (IBB), 315 Ferst Drive, Room 2306, Atlanta, GA 30332-0363, USA.
E-mail: ross.ethier@bme.gatech.edu

Curr Opin Ophthalmol 2022, 33:80–90
DOI:10.1097/ICU.0000000000000829

KEY POINTS

- Tissue biomechanics and mechanobiology are significant aspects of glaucoma pathophysiology.
- Stiffening of the trabecular meshwork and remodeling of the optic nerve head are two prominent biomechanics-related events in glaucoma.
- The biomechanical properties of the optic nerve sheath may play a role in normal-tension glaucoma.
- The mechanical properties of the cornea and of the iris have been suggested to be important in assessing the risk of primary open-angle and of primary angle-closure glaucoma, respectively.
- Transpupillary stiffening of the sclera has been proposed as a potential future therapeutic approach to manage glaucomatous optic neuropathy, yet preclinical data are not supportive.

differences in tissue properties can be a critical factor in determining whether a given load induces a pathological response in a patient, and measurement of such tissue properties is important.

TRABECULAR MESHWORK STIFFNESS IN GLAUCOMA AND OCULAR HYPERTENSION

We first consider biomechanical factors associated with IOP elevation. Ocular hypertension can arise due to several causes, but Grant [28] first showed that in human eyes with primary open-angle glaucoma (POAG), IOP elevation was due in large part to reduced outflow facility. We now know that much of the outflow resistance in the conventional pathway is localized to the outer TM and inner wall of Schlemm's canal [29,30], and thus TM pathobiology has been a major focus of studies in ocular hypertension in POAG. Relevant to this review, we now understand that ocular hypertension is associated with several biomechanically-associated changes to the TM: increased TM stiffness [31], increased actin cross-linking [32], and, in the case of steroid glaucoma, increased extracellular matrix (ECM) accumulation [33▪▪,34]. Consider first TM stiffness, where much of our current knowledge comes from *ex vivo* atomic force microscopy (AFM) measurements on both normal and diseased TM cells and tissues [35]. Due to limitations of AFM technology, it is not possible to assess TM biomechanical properties *in vivo*. However, advances in optical coherence tomography (OCT) and computational engineering modeling have provided methods to noninvasively measure the biomechanical properties of the TM *in vivo*, providing novel insights into the effects of potential treatments [33▪▪,36] (Fig. 2). Importantly, phase-sensitive OCT has identified differences in pulsatile TM motion between POAG and healthy patients, providing an intriguing potential method to clinically assess changes in TM biomechanics [37▪].

We now understand that the TM responds to mechanical stimuli, such as IOP-induced stretch and shear stress due to aqueous humor flow [38,39,40▪], and that many proteins and cell signaling pathways contribute to this mechanosensitivity. For instance, Piezo1 is a stretch-sensitive ion channel that is important in certain types of mechanotransduction. It is expressed in human and mouse TM cells [41], as well as in retinal ganglion cells (RGCs). Piezo1 activation results in decreased contractility in human TM cells [40▪] and facilitates changes in AH outflow in response to mechanical stimuli [41,42], whereas pharmacological activation of Piezo1 lowers IOP in mice [43]. TRPV4, another mechanosensitive ion channel modulating Rho signaling, has a role in TM remodeling [42,44]. Primary cilia, long, slender cell surface organelles, are present in TM cells, serving as mechanosensors [45] and play a key role in stretch-induced autophagy signaling in human TM cells [38]. Nitric oxide seems to be another important IOP-related signal: its shear stress-induced production by Schlemm's canal endothelial cells both decreases TM hydraulic resistance and facilitates flow through the distal aspects of the aqueous drainage pathway [46–50]. Cytokine levels also play a role in TM mechanics by impacting actin stress fibers, cell contractility, and deposition of fibrotic ECM proteins [32,51]. Further, the Wnt signaling pathway has been associated with changes in TM cell stiffness and glaucoma, and activation of this pathway after inhibition may provide protection from glucocorticoid-induced ocular hypertension [35,52]. Since dysfunction in any of these signaling pathways can result in ocular hypertension, they represent excellent research targets for development of novel strategies to treat ocular hypertension.

The cellular microenvironment, including ECM stiffness, greatly influences TM cell behavior. For example, changes in substrate stiffness alter transcriptomic profiles of human TM cells [53], and mechanical stretch itself, lead to differential expression of RNAs related to ECM–receptor interaction [39]. Recent work has revealed information about cell-matrix adhesion complexes in TM cells [54], and hydrogels have been engineered to include relevant ECM components as laboratory models of TM cell–ECM interactions [55▪]. Further, the use of cell-derived matrices from healthy and glaucomatous tissues has shown the importance of the cell's own matrix in creating a homeostatic cellular

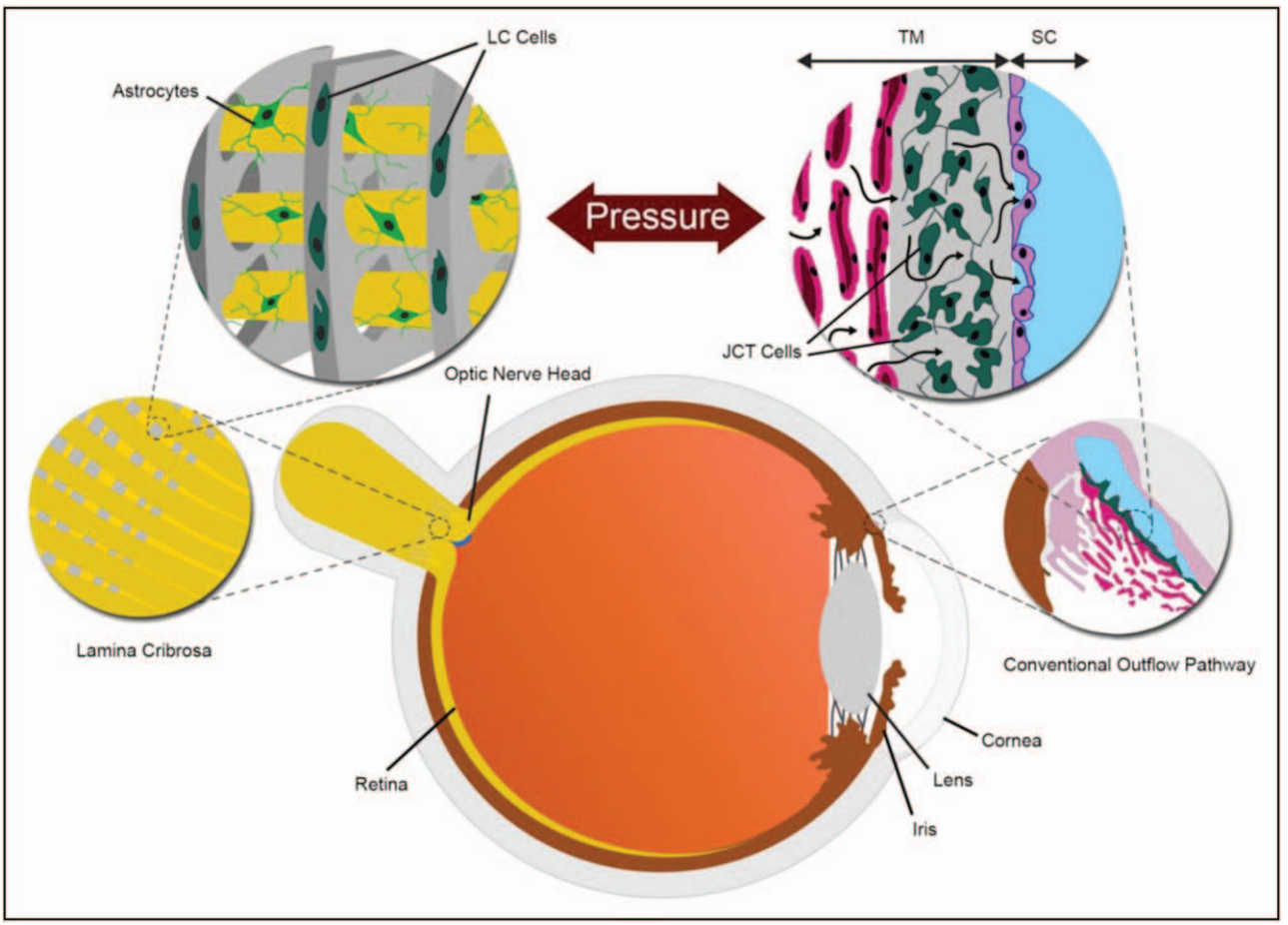

FIGURE 1. Schematic of the human eye. The biomechanics of the eye is closely related to pathophysiology of glaucoma. In the anterior section of the globe, the outflow of aqueous humor through the trabecular meshwork (TM) and Schlemm's canal (SC) is affected by the mechanical properties of the TM; for example, in primary open-angle glaucoma (POAG) the stiffness of TM is increased, likely due to biological remodeling of the TM extracellular matrix (ECM) under elevated IOP. Additionally, new devices that measure the biomechanics of the cornea may aid in monitoring the risk of glaucoma. Further, the biomechanics of the iris is a new topic of interest in primary angle-closure glaucoma (PACG), where the role of tissue mechanical properties and muscular contractions of the iris are important. In the posterior globe, the sclera's biomechanics, especially the peripapillary sclera, is known to strongly influence the mechanical loads on the optic nerve head (ONH). Lastly, the mechanical properties of the ONH and lamina cribrosa (LC) and their pathological remodeling in POAG (i.e., cupping) are important aspects of RGC loss in glaucoma, and are associated with mechanobiological remodeling of the ONH by resident cells, especially astrocytes and LC cells. (Figure reproduced from Paula *et al.* 2016 [134] with permission from the publisher.). IOP, intraocular pressure; POAG, primary open-angle glaucoma.

environment [56]. A better understanding of cell–ECM interactions in the TM may hold great potential for novel IOP-lowering strategies in certain types of glaucoma, such as steroid glaucoma [33▪▪].

CORNEAL BIOMECHANICS IN GLAUCOMA

Corneal biomechanics influence the interpretation of clinical IOP measurements. Further, recent technical developments have allowed the clinical measurement of a variety of corneal biomechanical properties. Specifically, the Ocular Response Analyzer (ORA) is a noncontact device that determines several corneal biomechanical properties, including corneal hysteresis, corneal resistance factor, and corneal-compensated IOP *in vivo* [57] (Fig. 3). Similarly, the Corvis ST noncontact tonometer estimates corneal mechanical properties through dynamic Scheimpflug imaging of the deforming cornea [58]. Both technologies yield corrected IOP measurements which attempt to standardize for the effect of corneal biomechanics.

With new technologies measuring many more corneal biomechanical properties, recent clinical research focuses on elucidating the relationship between those measurements and conventionally

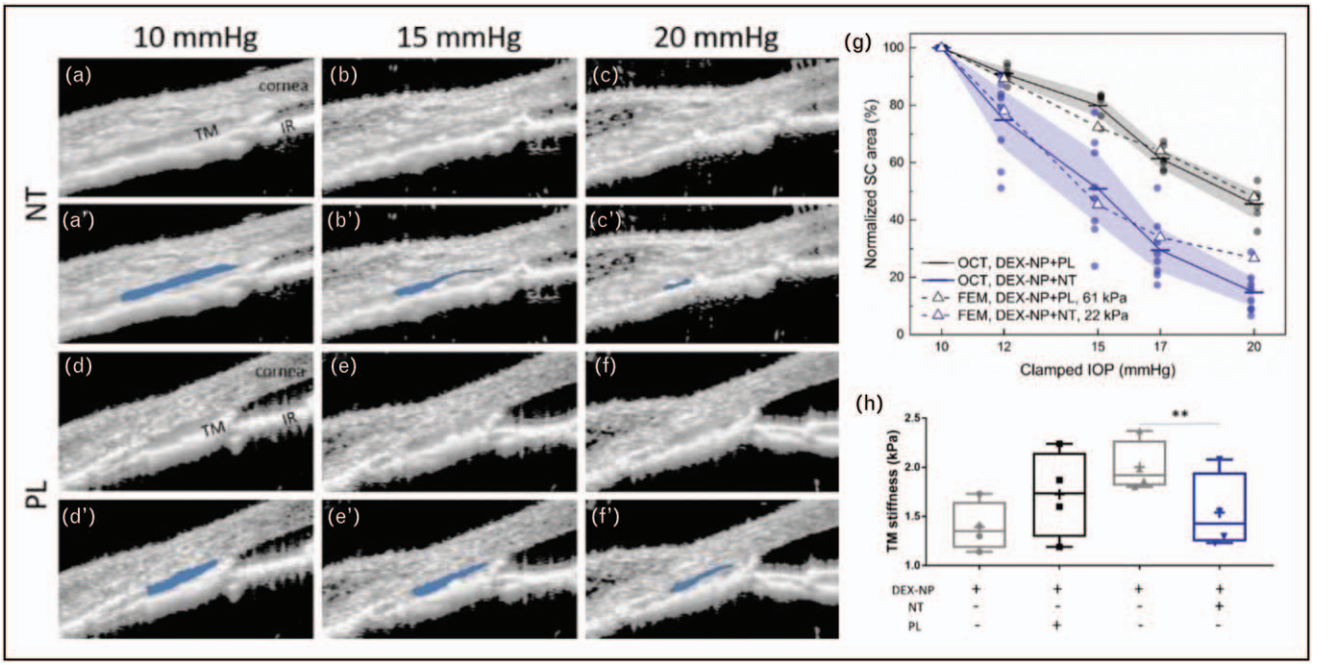

FIGURE 2. Estimation of TM stiffness in mice with induced steroid glaucoma. (a–f) Spectral domain-optical coherence tomography (SD-OCT) images of the limbal region in living C57BL/6 mouse eyes at different imposed IOP levels. Eyes were treated with netarsudil, an FDA-approved rho-kinase inhibitor, or placebo. The blue shading shows the automatically identified SC lumen. (g) Estimation of TM stiffness based on OCT images by inverse finite element modeling (iFEM), showing a stiff TM in a steroid glaucoma model, with restoration of normal TM stiffness by netarsudil. (h) TM stiffness directly measured by atomic force microscopy (AFM) in mice receiving steroid and netarsudil or placebo. DEX, dexamethasone; NT, netarsudil; PL, placebo; TM, trabecular meshwork. (Figure reproduced from Li *et al.* 2021 [33▪▪].).

measured properties [59]. These devices allow determination of corneal biomechanical parameters that may be associated with progression of glaucoma [60], although mechanistically associating parameter values with tissue structural features is challenging. These devices have also been used to elucidate relationships between corneal biomechanics and clinically relevant features such as retinal ganglion cell layer thickness [61▪▪], rates of visual field change [62], and incidence of optic disc hemorrhage (DH) [63].

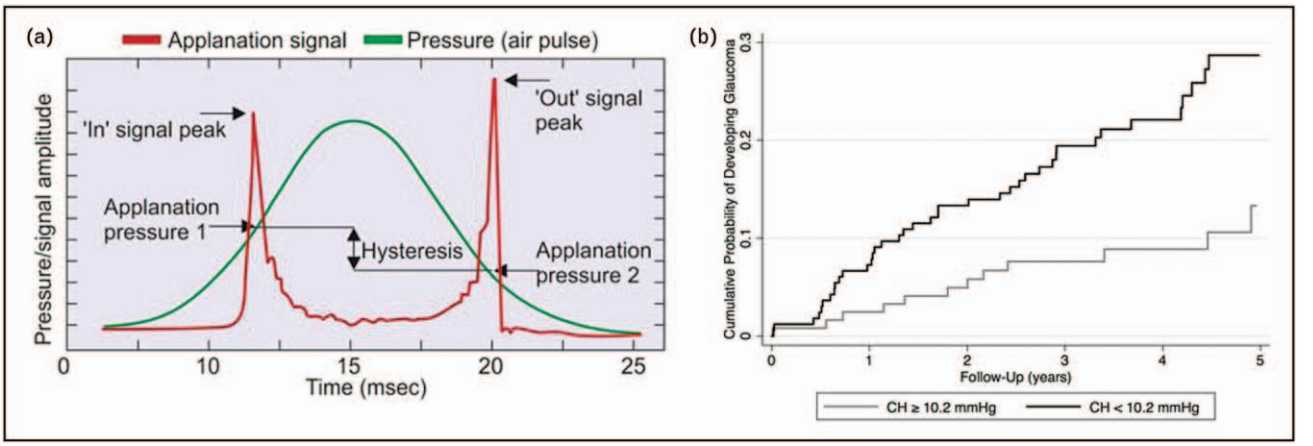

FIGURE 3. The use of the Ocular Response Analyzer (ORA) in glaucoma. (a) Schematic of typical data from the ORA, in which an air pulse is delivered to the cornea (green) and corneal deformation is measured by a photodetector (red). Corneal hysteresis (mmHg) is defined as the difference between the applanation pressure 1, as the cornea moves inwards, and applanation pressure 2, as it returns to its normal shape. (b) Cumulative probability of glaucoma development in two groups of OH subjects classified by corneal hysteresis (CH) values measured with an ORA. (a) is reproduced from Kaushik *et al.* [157], and (b) is reproduced from Susanna *et al.* [158] with permission from the publishers. OH, ocular hypertension.

Table 1. Corneal hysteresis values measured in patients with different forms of glaucoma and ocular structure parameters

Clinical condition	Reference	Corneal hysteresis (mmHg; mean ± std. deviation)
POAG & NTG	Uchida *et al.* [159▪]	• Female: 10.05 ± 1.41 • Male: 9.86 ± 1.26 • No significant trend with age
POAG after TRAB	Fujino *et al.* [60]	• 9.4 ± 1.2
Before and 6 months after TRAB + MMC and AGV	Kaderli *et al.* [160]	• Preop (TRAB + MMC): 7.38 ± 1.75 • Postop (TRAB + MMC): 8.51 ± 1.55 (significantly different postop vs. preop) • Preop (AGV): 6.67 ± 1.05 • Postop (AGV): 9.45 ± 1.05 (significantly different postop vs. preop)
POAG	Yang *et al.* [161]	• NTG: 10.17 ± 1.02 • HTG: 10.11 ± 1.23 • Not different between groups
POAG, OH, normal	Potop *et al.* [162▪▪]	• Normal: 11.71 ± 1.32 • POAG: 8.52 ± 1.39 • OH: 9.61 ± 0.91
Unilateral DH vs. contralateral non-DH eye	Radcliffe *et al.* [63]	• DH: 8.7 ± 1.9 • non-DH: 9.2 ± 1.7 • Statistically significant difference DH vs. non DH

AGV, Ahmed glaucoma valve implantation; DH, optic disc hemorrhage; MMC, mitomycin C; NTG, normal tension glaucoma; OH, ocular hypertension; POAG, primary open angle glaucoma; TRAB, trabeculectomy.

These devices have also been used to identify differences in corneal biomechanics between healthy individuals and patients with several types of glaucoma, as well as the effects of filtering surgery (Table 1). However, the prognostic value of these corneal measurements remains an open question. Therefore, recent studies also focus on associating measurable corneal properties to supplement more conventional outcome measures and hence better quantify glaucoma risk [64], and the impact of these parameters for clinical use is a work in progress.

THE ROLE OF SCLERAL BIOMECHANICS IN GLAUCOMATOUS OPTIC NEUROPATHY

In glaucoma, much evidence suggests that biomechanical factors acting on the cells and matrix of the ONH contribute to RGC loss [65,66]: RGC damage occurs within the lamina cribrosa (LC) [67] where significant physical tissue deformation occurs [68], patterns of vision loss in glaucoma are consistent with the heterogeneous physical structure of the LC [69], and ONH astrocytes are mechanosensitive [70–73]. Importantly, the biomechanical properties of the sclera strongly influence the deformation of ONH tissues by IOP [74–77], which has led to significant interest in the role of the sclera, particularly the peripapillary sclera, in glaucoma. We now understand that the sclera is not a 'passive bystander' in the glaucomatous eye: it remodels in response to elevated IOP [78–80], setting up a complex biomechanical interaction between the sclera and ONH when IOP is elevated [81–84]. This has caused somewhat of a renaissance in studies on scleral structure and physiology [85–87], building on the very earliest work of Kokott [88,89]; see for example, the detailed summaries in the context of myopia and glaucoma in [90] (Fig. 4). Importantly, there is significant variation in scleral properties from one human to the next, which perhaps may explain some differential susceptibility to ocular hypertension [91–93].

An important aspect of assessing the role of the sclera in glaucoma is better understanding scleral micro- and ultra-structure, and how they influence scleral biomechanical properties. For example, it has been long noted that the scleral canal is surrounded by a reinforcing 'ring' of collagen fibers [94–96], but recent imaging studies suggest that the situation is more complex [90], with collagen fibers forming a 'basket-weave' architecture around the scleral canal to protect the fragile cells of the ONH while efficiently transferring loads towards the equatorial sclera [97▪,98]. In addition to the role of collagen, we are coming to appreciate the role that other ECM components play in modulating scleral mechanics. Recently, specific attention has been focused on sulfated glycosaminoglycans (sGAGs) [99–102]. Generally, sGAGs appear to thicken the sclera, as expected, and also to make it less stiff. The role of such effects in glaucoma remains to be determined. Ultimately, scleral adaptation to ocular hypertension and intrinsic differences in scleral properties must be mediated by scleral fibroblasts. There is a pressing need to better understand the basic biology of these cells; for example, recent important work shows surprising variation spatial in scleral fibroblast morphology [103▪▪].

Because scleral stiffness influences the transmission of mechanical load to the ONH, there has been

interest in stiffening the sclera as a possible therapy in glaucoma [104–107,108▪]. Computational and laboratory studies suggest that stiffening the peripapillary sclera would have therapeutic benefit [66,92,109] by reinforcing the region around the soft, delicate ONH, therefore reducing the IOP-linked biomechanical insult delivered to this tissue. This 'biomechanical shielding' paradigm is consistent with data from mouse studies [110–112], with some clinical evidence [113] and with the observation that patients with early diabetes, where collagen crosslinking occurs naturally via glycation, are less likely to get open-angle glaucoma [114]. Despite this promising outlook, animal studies seem not to support this approach; indeed, it has been reported that there is increased axonal loss in mice with induced OHT after scleral stiffening with glyceraldehyde [115]. Another paradox arises from the observation that the sclera stiffens with age [116]; why then does the incidence of glaucoma increase with age rather than decrease? A possible answer to this important question hinges on the location/extent of scleral stiffening. We know that stiffening the entire sclera increases ocular rigidity and thus increases the magnitude of IOP fluctuations (ocular pulse amplitude) [117]. Perhaps greater IOP fluctuations may overwhelm the protective effects of 'biomechanical shielding', so that stiffening the entire sclera is detrimental. To overcome this issue, there has been progress in spatially localized (targeted) scleral stiffening [108▪], yet emerging data suggests that even this approach may not have benefit in an animal model of glaucoma [118].

THE ROLE OF THE OPTIC NERVE HEAD AND OPTIC NERVE SHEATH BIOMECHANICS IN GLAUCOMATOUS OPTIC NEUROPATHY

As noted above, the ONH is a primary site of RGC damage in glaucoma, yet the root cause of this vulnerability remains unknown. However, it is widely accepted that the gross morphology and biomechanics of the ONH are important in the pathological remodeling of the ONH in glaucoma (Fig. 5).

Interestingly, advances in imaging have made it possible to investigate ONH biomechanics in greater detail than ever before. For instance, by employing elastography, a noninvasive imaging-based technique

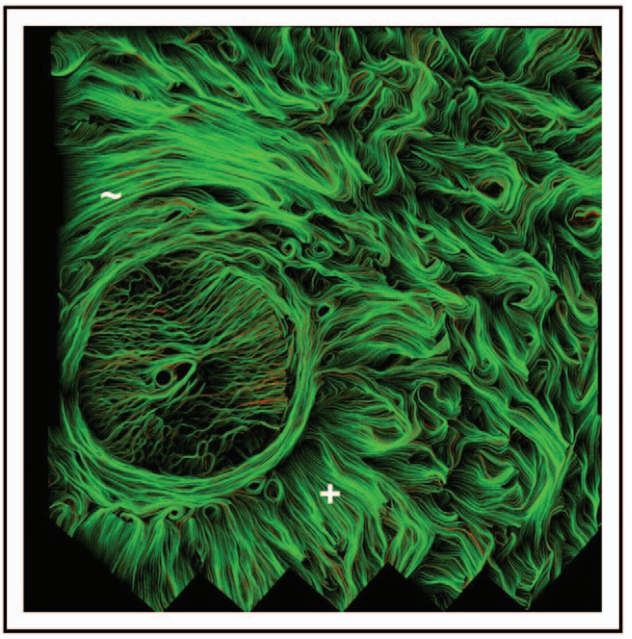

FIGURE 4. Optical imaging was used to identify the trajectories of collagen fibers in the ONH and peripapillary sclera of a post mortem human eye. One can observe both (+) radial and (~) circumferential fiber orientations, as well as the less aligned interweaving regions of the sclera (right side of image). The fibrous lamina cribrosa, within the scleral canal, can also be seen on the left side of the image. (Reproduced from Gogola *et al.* [163].).

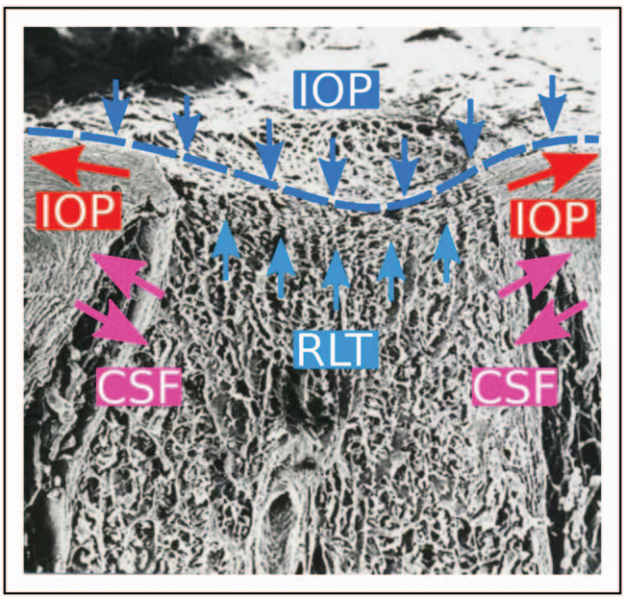

FIGURE 5. Schematic showing the major loads acting on the tissues of the optic nerve head. The IOP acts directly at the vitreoretinal interface to posteriorly displace ONH tissues (dark blue arrows), as well as enlarging the eye globe and thus causing tension in the scleral wall which is transmitted to the ONH (red arrows). The cerebrospinal fluid (CSF) is also pressurized (purple) which in turn causes a retrolaminar tissue (RLT) pressure that anteriorly displaces the lamina cribrosa (light blue arrows). Not shown is tension in the optic nerve sheath. Modified from Albon *et al.* [164], from a scanning electron micrograph of the connective tissue of a human ONH. ONH, optic nerve head.

that uses mechanical waves, one can directly probe the biomechanical properties of tissues *in vivo*. Xiao *et al.* [119] used ultrasonic shear wave elastography to show that patients with increased intracranial pressure (ICP) have a stiffer ONH, and this technique can potentially be used to measure changes to the mechanical properties of the ONH in glaucoma patients. In addition, using *ex vivo* ultrasonic elastography of porcine eyes it was shown that elevation of IOP increases ONH stiffness [120], and causes a nonhomogenous strain field on the ONH [121], important in understanding the relation between ONH mechanics and the patterns of vision loss in glaucoma. The ability to measure the biomechanical properties of the ONH *in vivo* is an exciting opportunity that is currently at the basic science stage, with translation to clinical practice remaining a significant challenge [122]. Further, despite ultrasonic elastography's great potential, it is limited by low spatial resolution. On the contrary, OCT, and its derivative elastography technique (optical coherence elastography [OCE]) [123,124], has superior spatial resolution, and in combination with biomechanical modeling, is a potent alternative for investigating ONH biomechanical properties *in vivo* [61▪▪,125▪,126]. Interestingly, OCT-driven morphologic reconstructions of the ONH can be used to generate patient-specific computer models to study ONH biomechanics [127] and hemodynamics [128], which may eventually be used as new tools for assessing progression of ONH pathological remodeling in glaucoma.

A critical aspect of ONH pathological remodeling in glaucoma is change in the architecture of the ONH's complex ECM and thus in the interaction between the ECM and resident neurons and glial cells. It has long been observed that the heterogeneous fibrous structure of the human LC is consistent with a heterogeneous distribution of mechanical deformation in the ONH, which in turn is associated with clinical patterns of preferential axonal damage [129]. *Ex vivo* imaging in the mouse ONH has also demonstrated a highly heterogeneous distribution of strains, even though the mouse has a noncollagenous lamina [130]. More recent work has shown that radial collagen fibers within the LC reduce posterior displacement of the LC, while circumferential fibers, in concert with radial fibers, reduce strain within the peripapillary sclera and prelaminar neural tissue [97▪], as further evidence for the role of LC microstructure in the mechanical stresses in the ONH. Interestingly, local defects in the LC's fibrous structure can cause significant local stress concentrations on RGC axons, which may elevate the risk of axonal damage and loss of vision [131]. However, the detailed mechanobiology of axonal damage and of pathological remodeling of the ONH by astrocytes and LC cells are still unknown. It is likely that the dynamics of IOP in concert with the dynamic mechanical behavior of the ONH [132,133] play a key role in this process [134]. Further studies are needed to investigate the mechanics and biology of the ONH's pathological remodeling, including using physiologically suitable *ex vivo* culture systems based on 3D hydrogels and decellularized animal tissue explants [135▪].

In addition to IOP, other loads acting on the ONH may also be important in glaucoma. Recently, it has been suggested that tension in the ONS may mechanically load the ONH and optic nerve during adduction in some patients and is potentially related to normal-tension glaucoma (NTG) [136,137]. Relevant to this observation, it was shown that the ONS has a higher stiffness compared to optic nerve [138], with complex, anisotropic (direction-dependent) mechanical properties, with the inner layer of the ONS having a significantly larger mechanical stiffness compared to its outer layer [139]. This layering can induce significant bending and shear loads on the ONH during globe movements. On a related note, the mechanical properties of the ONS have recently been assessed *in vivo* in human subjects [140], which can inform future studies of the role of the ONS in glaucoma. In addition, cerebrospinal fluid (CSF) pressure is another load on the ONH, where there are strong indications of CSF pressure being lower in certain forms of glaucoma, implying a role in glaucoma pathophysiology [141,142]. However, further studies, including clinical assessment of ONS biomechanics and CSF pressure, are needed to better understand the role of non-IOP loads in glaucoma.

BIOMECHANICAL FACTORS IN ANGLE-CLOSURE GLAUCOMA

Iris biomechanics is important in primary angle-closure glaucoma (PACG), where the size and deformations of the iris are among the main risk factors for PACG [143,144]. The other risk factors for developing PACG include having an anatomical deficit, such as a narrow-angle, or having Asian descent; however, these factors have poor predictive power and often PACG presents unexpectedly as a clinical emergency [145]. Therefore, there is a need to better understand PACG pathophysiology. Intriguingly, the mechanical properties of the iris are directly connected to its deformations in response to internal and external mechanical loading, and it is possible to evaluate the mechanical properties of the iris using engineering methods, such as OCE [146,147], and a combination of *in vivo* imaging (e.g., OCT and ultrasound) with inverse FEM [148,149] (Fig. 6).

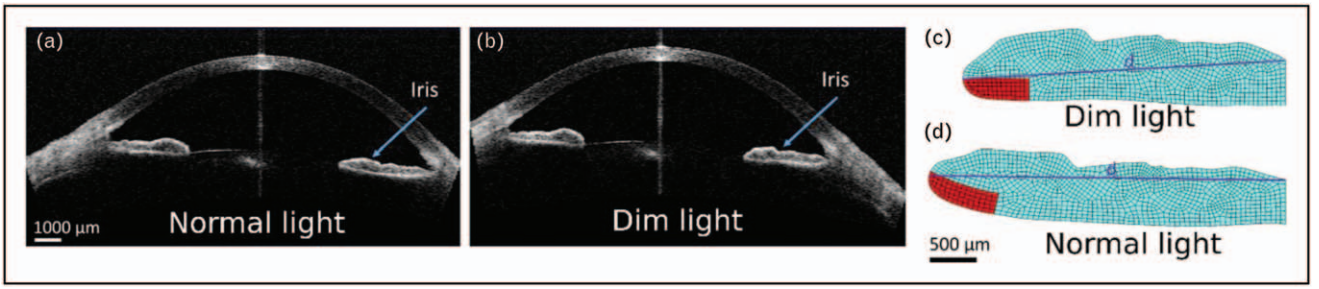

FIGURE 6. Iris deformation is shown under (a) normal and (b) dim light conditions using anterior segment OCT. Using inverse finite element modeling (c and d), where the stroma [blue region] is deformed by the sphincter smooth muscle [red region] Pant *et al.* calculated the mechanical properties of the iris, and showed that subjects with a history of PACG (post-LPI) tend to have a ca. 3 times greater stromal stiffness compared to healthy subjects. OCT, optical coherence tomography; LPI, laser peripheral iridotomy; PACG, primary angle-closure glaucoma. (Figure adapted from Pant *et al.* [150] with permission from the publisher.).

Interestingly, Pant *et al.* [150] and Panda *et al.* [151] showed that patients with a history of PACG tend to have a higher-than-normal iridial mechanical stiffness, suggesting that high iris stiffness is a risk factor for PACG and raising the possibility that measurement of iridial mechanical properties could be used to better assess the risk of developing PACG. Although it is likely that genetics influence iris stiffness, it is also likely that biological remodeling driven by mechanical loading can stiffen the iris, as is the case for most other connective tissues [152,153]. For instance, the iris stromal cell's nuclei elongate in response to iridial muscle contractions [154▪▪], and mechanostimulation of nuclei can trigger the secretion of ECM proteins to change (remodel) the surrounding tissue, including stiffness [155]. Interestingly, iris biomechanics can also play a secondary role in complications associated with PACG. For example, the postoperational decrease in corneal cell density in laser peripheral iridotomy (LPI) as a standard treatment for PACG appears to be correlated with cornea-scleral mechanical contact [156]. Despite the importance of the iris in certain forms of glaucoma, the literature on iris biomechanics is scarce, and there is a great need for more research on this important and emerging topic.

CONCLUSION

Biomechanics has long been recognized as an important aspect of glaucoma, yet we are far from fully understanding all the roles of biomechanical factors in this disease. Ongoing basic science research will hopefully help us understand mechanisms of ocular hypertension and RGC loss, leading eventually to novel therapeutic interventions. Closer to the clinic, technical advances seek to aid diagnosis and monitoring, for example, association between glaucoma risk factors and corneal properties, and *in vivo* assessment of tissue mechanical properties based on OCT elastography. Clearly, more basic research on tissue biomechanics in normal and diseased states is needed; such work must use physiologically appropriate model systems such as tissue-engineered 3D culture systems. Equally pressing is the need to devise novel strategies to translate the basic science and engineering knowledge about biomechanics to clinical practice.

Acknowledgements

None.

Financial support and sponsorship

We acknowledge our funding sources NIH (R01 EY031710 [CRE, CAW], R01 EY030071 [CRE], R21 EY033142 [CRE]), the Georgia Research Alliance (CRE), the BrightFocus Foundation (G2021005F [BNS], Special Opportunities Award [CRE]), and a Science ATL Communication Fellowship (CAW).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Heijl A, Leske MC, Bengtsson B, *et al.* Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002; 120:1268–1279.
2. Leske MC, Heijl A, Hussein M, *et al.* Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol 2003; 121:48–56.
3. Anderson DR, Drance SM, Schulzer M. Natural history of normal-tension glaucoma. Ophthalmology 2001; 108:247–253.
4. Gaasterland DE, Ederer F, Beck A, *et al.* The Advanced Glaucoma Intervention Study (AGIS). 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130:429–440.
5. Stowell C, Burgoyne CF, Tamm ER, *et al.* Biomechanical aspects of axonal damage in glaucoma: a brief review. Exp Eye Res 2017; 157:13–19.
6. Liu B, McNally S, Kilpatrick JI, *et al.* Aging and ocular tissue stiffness in glaucoma. Surv Ophthalmol 2018; 63:56–74.
7. Campbell IC, Coudrillier B, Ross Ethier C. Biomechanics of the posterior eye: a critical role in health and disease. J Biomech Eng 2014; 136:021005. doi: 10.1115/1.4026286.

8. Girard MJA, Dupps WJ, Baskaran M, *et al.* Translating ocular biomechanics into clinical practice: current state and future prospects. Curr Eye Res 2015; 40:1–18.
9. Noecker RJ. The management of glaucoma and intraocular hypertension: current approaches and recent advances. Ther Clin Risk Manag 2006; 2:193–206.
10. Youngblood H, Hauser MA, Liu Y. Update on the genetics of primary open-angle glaucoma. Exp Eye Res 2019; 188:107795. doi: 10.1016/j.exer.2019.107795.
11. Wiggs JL, Pasquale LR. Genetics of glaucoma. Hum Mol Genet 2017; 26(R1):R21–R27.
12. Wareham LK, Calkins DJ. The neurovascular unit in glaucomatous neurodegeneration. Front Cell Dev Biol 2020; 8:452. doi: 10.3389/fcell.2020.00452.
13. Grzybowski A, Och M, Kanclerz P, *et al.* Primary open angle glaucoma and vascular risk factors: a review of population based studies from 1990 to 2019. J Clin Med 2020; 9:E761. doi: 10.3390/jcm9030761.
14. Wan KH, Leung CKS. Optical coherence tomography angiography in glaucoma: a mini-review. F1000Research 2017; 6:1686. doi: 10.12688/f1000research.11691.1.
15. Liebmann JM, Cioffi GA. Nicking glaucoma with nicotinamide? N Engl J Med 2017; 376:2079–2081.
16. Kong GYX, Van Bergen NJ, Trounce IA, *et al.* Mitochondrial dysfunction and glaucoma. J Glaucoma 2009; 18:93–100.
17. Williams PA, Harder JM, John SWM. Glaucoma as a metabolic optic neuropathy: making the case for nicotinamide treatment in glaucoma. J Glaucoma 2017; 26:1161–1168.
18. Bell K, Funke S, Grus FH. Autoimmunity and glaucoma. Ophthalmol Z Dtsch Ophthalmol Ges 2019; 116:18–27.
19. Tezel G. Immune regulation toward immunomodulation for neuroprotection in glaucoma. Curr Opin Pharmacol 2013; 13:23–31.
20. Tezel G, Wax MB. The immune system and glaucoma. Curr Opin Ophthalmol 2004; 15:80–84.
21. Klein-Nulend J, Bacabac RG, Mullender MG. Mechanobiology of bone tissue. Pathol Biol 2005; 53:576–580.
22. Humphrey JD. Vascular mechanics, mechanobiology, and remodelling. J Mech Med Biol 2009; 09:243–257.
23. Zhou Y, Horowitz JC, Naba A, *et al.* Extracellular matrix in lung development, homeostasis and disease. Matrix Biol J Int Soc Matrix Biol 2018; 73:77–104.
24. Tschumperlin DJ, Lagares D. Mechano-therapeutics: targeting mechanical signaling in fibrosis and tumor stroma. Pharmacol Ther 2020; 212:107575. doi: 10.1016/j.pharmthera.2020.107575.
25. Humphrey JD. *Cardiovascular Solid Mechanics: Cells, Tissues, and Organs*. 2002nd ed. New York: Springer; 2002.
26. Ethier CR, By C. Ross Ethier – Introductory Biomechanics: From Cells to Organisms. 1st ed. Cambridge University Press; 2007.
27. Fung YC. Biomechanics: Mechanical Properties of Living Tissues. 2nd ed. New York: Springer; 1993.
28. Grant WM. Clinical measurements of aqueous outflow. AMA Arch Ophthalmol 1951; 46:113–131.
29. Mäepea O, Bill A. Pressures in the juxtacanalicular tissue and Schlemm's canal in monkeys. Exp Eye Res 1992; 54:879–883.
30. Johnson M, Shapiro A, Ethier CR, *et al.* Modulation of outflow resistance by the pores of the inner wall endothelium. Invest Ophthalmol Vis Sci 1992; 33:1670–1675.
31. Last JA, Pan T, Ding Y, *et al.* Elastic modulus determination of normal and glaucomatous human trabecular meshwork. Invest Ophthalmol Vis Sci 2011; 52:2147–2152.
32. Yemanyi F, Raghunathan V. Lysophosphatidic acid and IL-6 trans-signaling interact via YAP/TAZ and STAT3 signaling pathways in human trabecular meshwork cells. Invest Ophthalmol Vis Sci 2020; 61:29. doi: 10.1167/iovs.61.13.29.
33. ■■ Li G, Lee C, Read AT, *et al.* Antifibrotic activity of a rho-kinase inhibitor restores outflow function and intraocular pressure homeostasis. eLife 2021; 10:e60831. doi: 10.7554/eLife.60831.

The effects of the rho-kinase inhibitor, netarsudil, were studied in a mouse model of steroid-induced glaucoma. Netarsudil normalized conventional outflow facility, TM tissue stiffness, and TM fibrosis. A retrospective chart analysis similarly showed significant benefits of netarsudil treatment in a cohort of refractory steroid glaucoma patients.

34. Liu Z, Li S, Qian X, *et al.* RhoA/ROCK-YAP/TAZ axis regulates the fibrotic activity in dexamethasone-treated human trabecular meshwork cells. Front Mol Biosci 2021; 8:728932. doi: 10.3389/fmolb.2021.728932.
35. Dhamodaran K, Baidouri H, Sandoval L, *et al.* Wnt activation after inhibition restores trabecular meshwork cells toward a normal phenotype. Invest Ophthalmol Vis Sci 2020; 61:30. doi: 10.1167/iovs.61.6.30.
36. Wang K, Johnstone MA, Xin C, *et al.* Estimating human trabecular meshwork stiffness by numerical modeling and advanced OCT imaging. Invest Ophthalmol Vis Sci 2017; 58:4809–4817.
37. ■ Gao K, Song S, Johnstone MA, *et al.* Reduced pulsatile trabecular meshwork motion in eyes with primary open angle glaucoma using phase-sensitive optical coherence tomography. Invest Ophthalmol Vis Sci 2020; 61:21. doi: 10.1167/iovs.61.14.21.

TM motion (pulsation) was imaged in POAG and nonglaucomatous eyes using a novel OCT approach. Intriguingly, pulsatile TM motion was significantly less in POAG eyes, suggesting the potential of this imaging modality in clinical assessment of TM function.

38. Shim MS, Nettesheim A, Hirt J, *et al.* The autophagic protein LC3 translocates to the nucleus and localizes in the nucleolus associated to NUFIP1 in response to cyclic mechanical stress. Autophagy 2020; 16:1248–1261.
39. Youngblood H, Cai J, Drewry MD, *et al.* Expression of mRNAs, miRNAs, and lncRNAs in human trabecular meshwork cells upon mechanical stretch. Invest Ophthalmol Vis Sci 2020; 61:2. doi: 10.1167/iovs.61.5.2.
40. ■ Uchida T, Shimizu S, Yamagishi R, *et al.* Mechanical stretch induces Ca^{2+} influx and extracellular release of PGE2 through Piezo1 activation in trabecular meshwork cells. Sci Rep 2021; 11:4044. doi: 10.1038/s41598-021-83713-z.

The stretch-sensitive ion channel Piezo1 is identified as a putative homeostatic regulator of IOP in TM cells. Its activation by mechanical stretch triggers cell signaling pathways that regulate cell contraction.

41. Zhu W, Hou F, Fang J, *et al.* The role of Piezo1 in conventional aqueous humor outflow dynamics. iScience 2021; 24:102042. doi: 10.1016/j.isci.2021.102042.
42. Yarishkin O, Phuong TTT, Baumann JM, *et al.* Piezo1 channels mediate trabecular meshwork mechanotransduction and promote aqueous fluid outflow. J Physiol 2021; 599:571–592.
43. Morozumi W, Aoshima K, Inagaki S, *et al.* Piezo 1 is involved in intraocular pressure regulation. J Pharmacol Sci 2021; 147:211–221.
44. Lakk M, Križaj D. TRPV4-Rho signaling drives cytoskeletal and focal adhesion remodeling in trabecular meshwork cells. Am J Physiol Cell Physiol 2021; 320:C1013–C1030.
45. Shim MS, Nettesheim A, Dixon A, *et al.* Primary cilia and the reciprocal activation of AKT and SMAD2/3 regulate stretch-induced autophagy in trabecular meshwork cells. Proc Natl Acad Sci USA 2021; 118:e2021942118. doi: 10.1073/pnas.2021942118.
46. Madekurozwa M, Stamer WD, Reina-Torres E, *et al.* The ocular pulse decreases aqueous humor outflow resistance by stimulating nitric oxide production. Am J Physiol Cell Physiol 2021; 320:C652–C665.
47. McDonnell F, Perkumas KM, Ashpole NE, *et al.* Shear stress in Schlemm's canal as a sensor of intraocular pressure. Sci Rep 2020; 10:5804. doi: 10.1038/s41598-020-62730-4.
48. Reina-Torres E, De Ieso ML, Pasquale LR, *et al.* The vital role for nitric oxide in intraocular pressure homeostasis. Prog Retin Eye Res 2021; 83:100922. doi: 10.1016/j.preteyeres.2020.100922.
49. Bertrand JA, Schicht M, Stamer WD, *et al.* The 4-subunit of the large-conductance potassium ion channel KCa1.1 regulates outflow facility in mice. Invest Ophthalmol Vis Sci 2020; 61:41. doi: 10.1167/iovs.61.3.41.
50. Patel PD, Chen Y-L, Kasetti RB, *et al.* Impaired TRPV4-eNOS signaling in trabecular meshwork elevates intraocular pressure in glaucoma. Proc Natl Acad Sci USA 2021; 118:e2022461118. doi: 10.1073/pnas.2022461118.
51. Lee J, Choi JA, Ju H-H, *et al.* Role of MCP-1 and IL-8 in viral anterior uveitis, and contractility and fibrogenic activity of trabecular meshwork cells. Sci Rep 2021; 11:14950. doi: 10.1038/s41598-021-94391-2.
52. Sugali CK, Rayana NP, Dai J, *et al.* The canonical Wnt signaling pathway inhibits the glucocorticoid receptor signaling pathway in the trabecular meshwork. Am J Pathol 2021; 191:1020–1035.
53. Tie J, Chen D, Guo J, *et al.* Transcriptome-wide study of the response of human trabecular meshwork cells to the substrate stiffness increase. J Cell Biochem 2020; 121:3112–3123.
54. Maddala R, Rao PV. Global phosphotyrosinylated protein profile of cell-matrix adhesion complexes of trabecular meshwork cells. Am J Physiol Cell Physiol 2020; 319:C288–C299.
55. ■ Li H, Bagué T, Kirschner A, *et al.* A tissue-engineered human trabecular meshwork hydrogel for advanced glaucoma disease modeling. Exp Eye Res 2021; 205:108472. doi: 10.1016/j.exer.2021.108472.

A novel biomimetic hydrogel for 3D TM cell culture is introduced as a laboratory system to interrogate interactions between TM cells and extracellular matrix. The tunable mechanical properties of this hydrogel allow it to mimic important aspects of glaucomatous TM physiology.

56. Yemanyi F, Vranka J, Raghunathan V. Generating cell-derived matrices from human trabecular meshwork cell cultures for mechanistic studies. Methods Cell Biol 2020; 156:271–307.
57. Hocaoğlu M, Kara C, en EM, *et al.* Relationships between corneal biomechanics and the structural and functional parameters of glaucoma damage. Arq Bras Oftalmol 2020; 83:132–140.
58. Jung Y, Park H-YL, Oh S, *et al.* Corneal biomechanical responses detected using Corvis ST in primary open angle glaucoma and normal tension glaucoma. Medicine (Baltimore) 2020; 99:e19126. doi: 10.1097/MD.0000000000019126.
59. Matsuura M, Murata H, Fujino Y, *et al.* Relationship between novel intraocular pressure measurement from Corvis ST and central corneal thickness and corneal hysteresis. Br J Ophthalmol 2020; 104:563–568.
60. Fujino Y, Murata H, Matsuura M, *et al.* The relationship between corneal hysteresis and progression of glaucoma after trabeculectomy. J Glaucoma 2020; 29:912–917.
61. ■■ Sayah DN, Mazzaferri J, Descovich D, *et al.* The association between ocular rigidity and neuroretinal damage in glaucoma. Invest Ophthalmol Vis Sci 2020; 61:11. doi: 10.1167/iovs.61.13.11.

This paper focuses on investigating the correlation between ocular rigidity and neuroretinal damage measured by OCT, finding that lower ocular rigidity is associated with more neuroretinal damage. This association may eventually have clinical utility.

62. Chan E, Yeh K, Moghimi S, *et al.* Changes in corneal biomechanics and glaucomatous visual field loss. J Glaucoma 2021; 30:e246–e251.
63. Radcliffe NM, Tracer N, De Moraes CGV, *et al.* Relationship between optic disc hemorrhage and corneal hysteresis. Can J Ophthalmol J Can Ophtalmol 2020; 55:239–244.
64. Katiyar S, Tong J, Pensyl D, *et al.* Corneal biomechanical changes caused by acute elevation of IOP in eyes with and without glaucoma. Optom Vis Sci 2021; 98:367–373.
65. Burgoyne CF, Downs JC, Bellezza AJ, *et al.* The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. Prog Retin Eye Res 2005; 24:39–73.
66. Sigal IA, Ethier CR. Biomechanics of the optic nerve head. Exp Eye Res 2009; 88:799–807.
67. Anderson DR, Hendrickson A. Effect of intraocular pressure on rapid axoplasmic transport in monkey optic nerve. Invest Ophthalmol 1974; 13:771–783.
68. Sigal IA, Flanagan JG, Tertinegg I, *et al.* Predicted extension, compression and shearing of optic nerve head tissues. Exp Eye Res 2007; 85:312–322.
69. Quigley Ha, Addicks EM. Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. Arch Ophthalmol 1981; 99:137–143.
70. Kirwan RP, Fenerty CH, Crean J, *et al.* Influence of cyclical mechanical strain on extracellular matrix gene expression in human lamina cribrosa cells in vitro. Mol Vis 2005; 11:798–810.
71. Kirwan RP, Crean JK, Fenerty CH, *et al.* Effect of cyclical mechanical stretch and exogenous transforming growth factor-beta1 on matrix metalloproteinase-2 activity in lamina cribrosa cells from the human optic nerve head. J Glaucoma 2004; 13:327–334.
72. Rogers R, Dharsee M, Ackloo S, *et al.* Proteomics analyses of activated human optic nerve head lamina cribrosa cells following biomechanical strain. Invest Ophthalmol Vis Sci 2012; 53:3806–3816.
73. Rogers RS, Dharsee M, Ackloo S, *et al.* Proteomics analyses of human optic nerve head astrocytes following biomechanical strain. Mol Cell Proteomics MCP 2012; 11:. M111.012302, doi: 10.1074/mcp.M111.012302.
74. Sigal IA, Flanagan JG, Tertinegg I, *et al.* Finite element modeling of optic nerve head biomechanics. Invest Ophthalmol Vis Sci 2004; 45:4378–4387.
75. Norman RE, Flanagan JG, Sigal IA, *et al.* Finite element modeling of the human sclera: influence on optic nerve head biomechanics and connections with glaucoma. Exp Eye Res 2011; 93:4–12.
76. Sigal IA, Flanagan JG, Ethier CR. Factors influencing optic nerve head biomechanics. Invest Ophthalmol Vis Sci 2005; 46:4189–4199.
77. Burgoyne CF, Downs JC. Premise and prediction-how optic nerve head biomechanics underlies the susceptibility and clinical behavior of the aged optic nerve head. J Glaucoma 2008; 17:318–328.
78. Iomdina EN, Tikhomirova NK, Bessmertny AM, *et al.* Alterations in proteome of human sclera associated with primary open-angle glaucoma involve proteins participating in regulation of the extracellular matrix. Mol Vis 2020; 26:623–640.
79. Wang X, Tun TA, Nongpiur ME, *et al.* Peripapillary sclera exhibits a v-shaped configuration that is more pronounced in glaucoma eyes. Br J Ophthalmol 2020. doi: 10.1136/bjophthalmol-2020-317900.
80. Grytz R, Yang H, Hua Y, *et al.* Connective tissue remodeling in myopia and its potential role in increasing risk of glaucoma. Curr Opin Biomed Eng 2020; 15:40–50.
81. Grytz R, Girkin CA, Libertiaux V, *et al.* Perspectives on biomechanical growth and remodeling mechanisms in glaucoma. Mech Res Commun 2012; 42:92–106.
82. Grytz R, Sigal IA, Ruberti JW, *et al.* Lamina cribrosa thickening in early glaucoma predicted by a microstructure motivated growth and remodeling approach. Mech Mater Int J 2012; 44:99–109.
83. Grytz R, Meschke G, Jonas JB. The collagen fibril architecture in the lamina cribrosa and peripapillary sclera predicted by a computational remodeling approach. Biomech Model Mechanobiol 2011; 10:371–382.
84. Cone-Kimball E, Nguyen C, Oglesby EN, *et al.* Scleral structural alterations associated with chronic experimental intraocular pressure elevation in mice. Mol Vis 2013; 19:2023–2039.
85. Jonas RA, Holbach L. Peripapillary border tissue of the choroid and peripapillary scleral flange in human eyes. Acta Ophthalmol 2020; 98:e43–e49.
86. Geraghty B, Abass A, Eliasy A, *et al.* Inflation experiments and inverse finite element modelling of posterior human sclera. J Biomech 2020; 98:109438. doi: 10.1016/j.jbiomech.2019.109438.
87. Bianco G, Levy AM, Grytz R, *et al.* Effect of different preconditioning protocols on the viscoelastic inflation response of the posterior sclera. Acta Biomater 2021; 128:332–345.
88. Kokott W. Über mechanisch-funktionelle Strukturen des Auges. Albrecht Von Graefes Arch Für Ophthalmol 1938; 138:424–485.
89. Kokott W. Das Spaltlinienbild der Sklera [The slit-lamp study of the sclera]. Klin Monatsblätter Für Augenheilkd 1934; 92:177–185.
90. Boote C, Sigal IA, Grytz R, *et al.* Scleral structure and biomechanics. Prog Retin Eye Res 2020; 74:100773. doi: 10.1016/j.preteyeres.2019.100773.
91. Norman RE, Flanagan JG, Rausch SMK, *et al.* Dimensions of the human sclera: thickness measurement and regional changes with axial length. Exp Eye Res 2010; 90:277–284.
92. Eilaghi A, Flanagan JG, Simmons CA, *et al.* Effects of scleral stiffness properties on optic nerve head biomechanics. Ann Biomed Eng 2010; 38:1586–1592.
93. Boazak EM, King R, Wang J, *et al.* Smarce1 and tensin 4 are putative modulators of corneoscleral stiffness. Front Bioeng Biotechnol 2021; 9:596154. doi: 10.3389/fbioe.2021.596154.
94. Coudrillier B, Tian J, Alexander S, *et al.* Biomechanics of the human posterior sclera: age- and glaucoma-related changes measured using inflation testing. Invest Ophthalmol Vis Sci 2012; 53:1714–1728.
95. Pijanka JK, Coudrillier B, Ziegler K, *et al.* Quantitative mapping of collagen fiber orientation in nonglaucoma and glaucoma posterior human sclerae. Invest Ophthalmol Vis Sci 2012; 53:5258–5270.
96. Coudrillier B, Pijanka JK, Jefferys JL, *et al.* Collagen structure and mechanical properties of the human sclera: analysis for the effects of age. J Biomech Eng 2014; 137:041006. doi: 10.1115/1.4029430.
97. ■ Hua Y, Voorhees AP, Jan N-J, *et al.* Role of radially aligned scleral collagen fibers in optic nerve head biomechanics. Exp Eye Res 2020; 199:108188. doi: 10.1016/j.exer.2020.108188.
Collagen fibers in the peripapillary sclera are preferentially aligned around the scleral canal. This computational engineering study determines radially aligned fibers affects optic nerve head biomechanics, finding a combination of radial and circumferential fibers is optimal.
98. Wang B, Hua Y, Brazile BL, *et al.* Collagen fiber interweaving is central to sclera stiffness. Acta Biomater 2020; 113:429–437.
99. Murienne BJ, Jefferys JL, Quigley HA, *et al.* The effects of glycosaminoglycan degradation on the mechanical behavior of the posterior porcine sclera. Acta Biomater 2015; 12:195–206.
100. Hatami-Marbini H, Pachenari M. Tensile viscoelastic properties of the sclera after glycosaminoglycan depletion. Curr Eye Res 2021; 46:1299–1308.
101. Murienne BJ, Chen ML, Quigley HA, *et al.* The contribution of glycosaminoglycans to the mechanical behaviour of the posterior human sclera. J R Soc Interface 2016; 13:20160367. doi: 10.1098/rsif.2016.0367.
102. Hatami-Marbini H, Pachenari M. The contribution of sGAGs to stress-controlled tensile response of posterior porcine sclera. PloS One 2020; 15:e0227856. doi: 10.1371/journal.pone.0227856.
103. ■■ Szeto J, Chow A, McCrea L, *et al.* Regional differences and physiologic behaviors in peripapillary scleral fibroblasts. Invest Ophthalmol Vis Sci 2021; 62:27. doi: 10.1167/iovs.62.1.27.
The sclera is critical in ocular biomechanics, yet we know relatively little about scleral fibroblasts. This intriguing study reveals patterns of scleral fibroblast density and nuclear morphology in the posterior eye, and how local strain and topography alter cellular response.
104. Gawargious BA, Le A, Lesgart M, *et al.* Differential regional stiffening of sclera by collagen cross-linking. Curr Eye Res 2020; 45:718–725.
105. Rahman N, O'Neill E, Irnaten M, *et al.* Corneal stiffness and collagen cross-linking proteins in glaucoma: potential for novel therapeutic strategy. J Ocul Pharmacol Ther 2020; 36:582–594.
106. Hannon BG, Luna C, Feola AJ, *et al.* Assessment of visual and retinal function following in vivo genipin-induced scleral crosslinking. Transl Vis Sci Technol 2020; 9:8. doi: 10.1167/tvst.9.10.8.
107. Blackburn BJ, Rollins AM, Dupps WJ. Biomechanics of ophthalmic cross-linking. Transl Vis Sci Technol 2021; 10:8. doi: 10.1167/tvst.10.5.8.
108. ■ Gerberich BG, Hannon BG, Hejri A, *et al.* Transpupillary collagen photocrosslinking for targeted modulation of ocular biomechanics. Biomaterials 2021; 271:120735. doi: 10.1016/j.biomaterials.2021.120735.
Spatially targeted scleral stiffening could be useful in myopia and glaucoma, yet is challenging to achieve. This paper shows preclinical *in vivo* data demonstrating successful scleral cross-linking using a spatial patterning approach.
109. Norman RE, Flanagan JG, Sigal IA, *et al.* Finite element modeling of the human sclera: Influence on optic nerve head biomechanics and connections with glaucoma. Exp Eye Res 2011; 93:4–12.
110. Nguyen C, Cone FE, Nguyen TD, *et al.* Studies of scleral biomechanical behavior related to susceptibility for retinal ganglion cell loss in experimental mouse glaucoma. Invest Ophthalmol Vis Sci 2013; 54:1767–1780.
111. Quigley HA, Cone FE. Development of diagnostic and treatment strategies for glaucoma through understanding and modification of scleral and lamina cribrosa connective tissue. Cell Tissue Res 2013; 353:231–244.
112. Steinhart MR, Cone FE, Nguyen C, *et al.* Mice with an induced mutation in collagen 8A2 develop larger eyes and are resistant to retinal ganglion cell damage in an experimental glaucoma model. Mol Vis 2012; 18:1093–1106.
113. Wang J, Freeman EE, Descovich D, *et al.* Estimation of ocular rigidity in glaucoma using ocular pulse amplitude and pulsatile choroidal blood flow. Invest Ophthalmol Vis Sci 2013; 54:1706–1711.
114. Quigley HA. Can diabetes be good for glaucoma? Why can't we believe our own eyes (or data)? Arch Ophthalmol 2009; 127:227–229.
115. Kimball EC, Nguyen C, Steinhart MR, *et al.* Experimental scleral cross-linking increases glaucoma damage in a mouse model. Exp Eye Res 2014; 128:129–140.
116. Yan D, McPheeters S, Johnson G, *et al.* Microstructural differences in the human posterior sclera as a function of age and race. Invest Ophthalmol Vis Sci 2011; 52:821–829.
117. Morris HJ, Tang J, Cruz Perez B, *et al.* Correlation between biomechanical responses of posterior sclera and IOP elevations during micro intraocular volume change. Invest Ophthalmol Vis Sci 2013; 54:7215–7222.

118. Hannon BG. Stiffening the posterior rat sclera to provide neuroprotection in glaucoma. July 2020. Available at: https://smartech.gatech.edu/handle/1853/63648 [Accessed October 4, 2021].

119. Xiao C, Huang X, Li M, *et al.* Evaluation of the biomechanical properties of the posterior eye using shear wave elastography in patients with increased intracranial pressure. Med Ultrason 2021; 23:305–310.

120. Qian X, Li R, Lu G, *et al.* Ultrasonic elastography to assess biomechanical properties of the optic nerve head and peripapillary sclera of the eye. Ultrasonics 2021; 110:106263. doi: 10.1016/j.ultras.2020.106263.

121. Ma Y, Pavlatos E, Clayson K, *et al.* Three-dimensional inflation response of porcine optic nerve head using high-frequency ultrasound elastography. J Biomech Eng 2020; 142:051013. doi: 10.1115/1.4045503.

122. Girard MJA, Dupps WJ, Baskaran M, *et al.* Translating ocular biomechanics into clinical practice: current state and future prospects. Curr Eye Res 2014; 40:1–18.

123. Du Z, Li R, Qian X, *et al.* Quantitative confocal optical coherence elastography for evaluating biomechanics of optic nerve head using Lamb wave model. Neurophotonics 2019; 6:041112. doi: 10.1117/1.NPh.6.4.041112.

124. Zaitsev VY, Matveyev AL, Matveev LA, *et al.* Strain and elasticity imaging in compression optical coherence elastography: the two-decade perspective and recent advances. J Biophotonics 2021; 14:e202000257. doi: 10.1002/jbio.202000257.

125. ■ Zhang L, Beotra MR, Baskaran M, *et al.* In vivo measurements of prelamina and lamina cribrosa biomechanical properties in humans. Invest Ophthalmol Vis Sci 2020; 61:27. doi: 10.1167/iovs.61.3.27.

This work is an example of the successful combination of clinical OCT imaging and biomechanical analysis to investigate the mechanical properties of normal and diseased tissue in vivo.

126. Schwaner SA, Feola AJ, Ethier CR. Factors affecting optic nerve head biomechanics in a rat model of glaucoma. J R Soc Interface 2020; 17:20190695. doi: 10.1098/rsif.2019.0695.

127. Schwaner SA, Perry RN, Kight AM, *et al.* Individual-specific modeling of rat optic nerve head biomechanics in glaucoma. J Biomech Eng 2021; 143:041004. doi: 10.1115/1.4049157.

128. Chuangsuwanich T, Hung PT, Wang X, *et al.* Morphometric, hemodynamic, and biomechanical factors influencing blood flow and oxygen concentration in the human lamina cribrosa. Invest Ophthalmol Vis Sci 2020; 61:3. doi: 10.1167/iovs.61.4.3.

129. Quigley HA, Addicks EM. Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. Arch Ophthalmol 1981; 99:137–143.

130. Korneva A, Kimball EC, Jefferys JL, *et al.* Biomechanics of the optic nerve head and peripapillary sclera in a mouse model of glaucoma. J R Soc Interface 2020; 17:20200708. doi: 10.1098/rsif.2020.0708.

131. Voorhees AP, Hua Y, Brazile BL, *et al.* So-called lamina cribrosa defects may mitigate IOP-induced neural tissue insult. Invest Ophthalmol Vis Sci 2020; 61:15. doi: 10.1167/iovs.61.13.15.

132. Safa BN, Read AT, Ethier CR. Assessment of the viscoelastic mechanical properties of the porcine optic nerve head using micromechanical testing and finite element modeling. Acta Biomater 2021; 134:379–387.

133. Boazak EM, d'Humières J, Read AT, *et al.* Compressive mechanical properties of rat and pig optic nerve head. J Biomech 2019; 93:204–208.

134. Paula JS, O'Brien C, Stamer WD. Life under pressure: the role of ocular cribriform cells in preventing glaucoma. Exp Eye Res 2016; 151:150–159.

135. ■ Liou J-J, Drewry MD, Sweeney A, *et al.* Decellularizing the porcine optic nerve head: toward a model to study the mechanobiology of glaucoma. Transl Vis Sci Technol 2020; 9:17. doi: 10.1167/tvst.9.8.17.

A novel approach for developing a physiologically appropriate *ex vivo* platform to study ONH mechanobiology using a decellularized animal tissue explant, providing both the methodology and valuable quantitative parameters for future studies.

136. Clark RA, Suh SY, Caprioli J, *et al.* Adduction-induced strain on the optic nerve in primary open angle glaucoma at normal intraocular pressure. Curr Eye Res 2021; 46:568–578.

137. Wang X, Rumpel H, Baskaran M, *et al.* Optic nerve tortuosity and globe proptosis in normal and glaucoma subjects. J Glaucoma 2019; 28:691–696.

138. Park J, Shin A, Jafari S, *et al.* Material properties and effect of preconditioning of human sclera, optic nerve, and optic nerve sheath. Biomech Model Mechanobiol 2021; 20:1353–1363.

139. Shin A, Park J, Le A, *et al.* Bilaminar mechanics of the human optic nerve sheath. Curr Eye Res 2020; 45:854–863.

140. Lee C, Rohr J, Sass A, *et al.* In vivo estimation of optic nerve sheath stiffness using noninvasive MRI measurements and finite element modeling. J Mech Behav Biomed Mater 2020; 110:103924. doi: 10.1016/j.jmbbm.2020.103924.

141. Mao Y, Yang D, Li J, *et al.* Finite element analysis of trans-lamina cribrosa pressure difference on optic nerve head biomechanics: the Beijing Intracranial and Intraocular Pressure Study. Sci China Life Sci 2020; 63:1887–1894.

142. Berdahl JP, Allingham RR, Johnson DH. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. Ophthalmology 2008; 115:763–768.

143. Quigley HA, Silver DM, Friedman DS, *et al.* Iris cross-sectional area decreases with pupil dilation and its dynamic behavior is a risk factor in angle closure. J Glaucoma 2009; 18:173–179.

144. Wang B-S, Narayanaswamy A, Amerasinghe N, *et al.* Increased iris thickness and association with primary angle closure glaucoma. Br J Ophthalmol 2011; 95:46–50.

145. Friedman DS, Foster PJ, Aung T, *et al.* Angle closure and angle-closure glaucoma: what we are doing now and what we will be doing in the future. Clin Experiment Ophthalmol 2012; 40:381–387.

146. Zhu Y, Zhang Y, Shi G, *et al.* Quantification of iris elasticity using acoustic radiation force optical coherence elastography. Appl Opt 2020; 59:10739–10745.

147. Ye S, Zhou Y, Bao C, *et al.* In vivo noncontact measurement of human iris elasticity by optical coherence elastography. J Biophotonics 2021; 14:e202100116. doi: 10.1002/jbio.202100116.

148. Lee C, Li G, Stamer WD, *et al.* In vivo estimation of murine iris stiffness using finite element modeling. Exp Eye Res 2021; 202:108374. doi: 10.1016/j.exer.2020.108374.

149. Zhang K, Qian X, Mei X, *et al.* An inverse method to determine the mechanical properties of the iris in vivo. Biomed Eng Online 2014; 13:66. doi: 10.1186/1475-925X-13-66.

150. Pant AD, Gogte P, Pathak-Ray V, *et al.* Increased iris stiffness in patients with a history of angle-closure glaucoma: an image-based inverse modeling analysis. Invest Ophthalmol Vis Sci 2018; 59:4134–4142.

151. Panda SK, Tan RKY, Tun TA, *et al.* Changes in Iris Stiffness and Permeability in Primary Angle Closure Glaucoma. Invest Ophthalmol Vis Sci 2021; 62:29.

152. Urbanczyk M, Layland SL, Schenke-Layland K. The role of extracellular matrix in biomechanics and its impact on bioengineering of cells and 3D tissues. Matrix Biol 2020; 85-86:1–14.

153. Guimarães CF, Gasperini L, Marques AP, *et al.* The stiffness of living tissues and its implications for tissue engineering. Nat Rev Mater 2020; 5:351–370.

154. ■■ Rashidi N, Pant AD, Salinas SD, *et al.* Iris stromal cell nuclei deform to more elongated shapes during pharmacologically-induced miosis and mydriasis. Exp Eye Res 2021; 202:108373. doi: 10.1016/j.exer.2020.108373.

An interesting *ex vivo* study using pharmacological stimulation of iris tissue to induce muscular activation, followed by measurements of the resulting cellular deformations, providing novel insights into the potential role of mechanobiological remodeling in the iris.

155. Szczesny SE, Mauck RL. The nuclear option: evidence implicating the cell nucleus in mechanotransduction. J Biomech Eng 2017; 139:. doi: 10.1115/1.4035350.

156. Imai K, Sawada H, Hatase T, *et al.* Iridocorneal contact as a potential cause of corneal decompensation following laser peripheral iridotomy. Jpn J Ophthalmol 2021; 65:460–471.

157. Kaushik S, Pandav SS. Ocular response analyzer. J Curr Glaucoma Pract 2012; 6:17–19.

158. Susanna CN, Diniz-Filho A, Daga FB, *et al.* A prospective longitudinal study to investigate corneal hysteresis as a risk factor for predicting development of glaucoma. Am J Ophthalmol 2018; 187:148–152.

159. ■ Uchida K, Himori N, Hashimoto K, *et al.* The association between oxidative stress and corneal hysteresis in patients with glaucoma. Sci Rep 2020; 10:545. doi: 10.1038/s41598-020-57520-x.

This is the first study to investigate the association between systemic oxidative stress and corneal biomechanical properties in glaucoma patients, both of which have been implicated in glaucoma pathogenesis.

160. Kaderli A, Demirok G, Tamer Kaderli S, *et al.* Effect of trabeculectomy and Ahmed glaucoma valve implantation surgery on corneal biomechanical changes. Int Ophthalmol 2020; 40:1941–1947.

161. Yang Y, Ng TK, Wang L, *et al.* Association of 24-hour intraocular pressure fluctuation with corneal hysteresis and axial length in untreated Chinese primary open-angle glaucoma patients. Transl Vis Sci Technol 2020; 9:25. doi: 10.1167/tvst.9.12.25.

162. ■■ Potop V, Coviltir V, Schmitzer S, *et al.* The relationship between corneal hysteresis and retinal ganglion cells – a step forward in early glaucoma diagnosis. Med Sci Monit 2020; 26:e924672. doi: 10.12659/MSM.924672.

This study highlights the potential of noninvasive corneal hysteresis measurements in glaucoma patients as a useful parameter to monitor disease progression, since corneal hysteresis was positively correlated with peripapillary retinal nerve fiber layer and ganglion cell complex thicknesses.

163. Gogola A, Jan N-J, Lathrop KL, *et al.* Radial and circumferential collagen fibers are a feature of the peripapillary sclera of human, monkey, pig, cow, goat, and sheep. Invest Ophthalmol Vis Sci 2018; 59:4763–4774.

164. Albon J, Farrant S, Akhtar S, *et al.* Connective tissue structure of the tree shrew optic nerve and associated ageing changes. Invest Ophthalmol Vis Sci 2007; 48:2134–2144.