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Cornea and Glaucoma

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1. Introduction

Glaucoma is an acquired optic neuropathy in which destruction of ganglion cells and fibers leads to irreversible visual field loss. The prevalence of glaucoma, a leading cause of visual impairment and blindness worldwide [1,2], in the general population is about 2%. Increased intraocular pressure (IOP) is a primary risk factor for glaucoma development. IOP evaluation is used to assess disease control and treatment response, and lowering IOP has resulted in reducing the rates of disease progression over 5 years [3-7]. These data confirmed that elevated IOP is a pathophysiologic basis for glaucoma; therefore, accurate IOP measurement is critical in glaucoma.

Goldmann applanation tonometry (GAT), the gold standard for measuring IOP, estimates the IOP based on the force needed to flatten the corneal apex to a diameter of 3.06 mm. This area was chosen empirically to offset the surface tension of the tear film, which tends to draw the tonometry tip toward the eye, and the corneal and ocular rigidity, which affect the applanation force needed independent of the IOP level. When applanating this area, a gravitational force of 0.1 g corresponds to an IOP of 1 mmHg. Goldmann and Schmidt [8] found that when large variations in the central corneal thickness (CCT) occur, the accuracy of the GAT values can be affected.

The corneal rigidity affects the IOP measurements. The corneal biomechanics are more complex than central pachymetry alone and include viscosity, bioelasticity, hydration, regional pachymetry, and likely other as yet undetermined factors [9,10].

2. Corneal anatomy and histology

The cornea, the primary refractive ocular structure that contributes to focusing the external images on the retina, measures 11 to 12 mm horizontally, 10 to 11 mm vertically, and is about 0.5 mm thick centrally. The corneal thickness increases gradually toward the periphery to about 0.7 mm. Corneal nutrition depends on both glucose diffusing from the aqueous humor and oxygen supplied from the air through the tear film and in the peripheral cornea from the limbal blood vessels [11]. The cornea accounts for more than two thirds of the total ocular refractive power. Any slight change in the corneal contour can cause a substantial change in the ocular refractive power. The corneal optical properties are determined by its transparency, surface smoothness, contour, and refractive index.

The cornea is comprised of five layers: the epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. The epithelium, the most anterior layer, is comprised of non-keratinizing stratified squamous epithelial cells. The epithelium and tear film form an optically smooth surface. The Bowman's layer is the most anterior part of the corneal stroma, and is adjacent to the epithelial basement membrane.

The structural and optical features depend mainly on the structure and composition of the corneal stroma, which represents up to 90% of the corneal thickness. Corneal transparency basically depends on the regular spacial distribution of the stromal cells and the stromal lamellae, and also on the water content of the stroma, that must be kept at a constant level of about 78%. The keratocytes are highly scattered and do not affect transparency. The lattice structure of the corneal collagen fibers, within a distance of 0.5 microns of the visible wavelength, is responsible for corneal transparency. Any decrease (dehydration) or increase (edema) in this distance results in a loss of transparency. Fibrillar collagen types I and V, which are intertwined with type VI collagen filaments (collagen types III, XII, and XIV have also been found in the stroma) and corneal proteoglycans (mainly decorin associated with dermatan sulfate and lumican associated with keratan sulfate), are the fundamental components of the extracellular matrix (ECM).

Negatively charged stromal glycosaminoglycans tend to repel each other, producing the corneal swelling pressure (SP) (of about 50 mmHg in the excised cornea), and can absorb and retain large amounts of water. The keratocytes lie between the corneal lamellae and synthesize both collagen and proteoglycans.

The diameter of each collagen fiber and the distance between the collagen fibers are homogeneous and measure less than half of the wavelength of the visible light (400-700 nm). This anatomic distribution of fibers is responsible for the fact that the incident light rays scattered by each collagen fiber are cancelled by the interference of other scattered rays, which allows the incident light to pass through the cornea without optical disruption.

Descemet's membrane, the basement membrane of the endothelium, is highly elastic and can withstand high pressure. When injured, it can regenerate.

The endothelium, the innermost corneal layer, is a monolayer of hexagonally shaped endothelial cells arranged in a mosaic pattern. The integrity of this layer and the correct function

of the endothelial pump, which is linked to the ion-transport system controlled by enzymes such as Na^+, K^+-ATPase, are necessary to maintain the stability of the corneal water content. Therefore, the endothelium prevents corneal edema by both the barrier and the pump functions. The pump function generates the so-called corneal imbibition pressure (IP), a negative pressure that draws fluid into the cornea. The IP is equal to the SP in the excised cornea. In vivo, however, the IP is lower than the SP because of the compressive effect of the IOP on the cornea. The relationship between these three parameters is described by the equation:

$$IP = IOP - SP \tag{1}$$

Although the regulation of the corneal hydration is maintained largely by the function of the endothelial pump, the epithelial barrier effect, the surface evaporation, the IOP level, and the SP also play a role.

3. Impact of CCT on tonometry

The Ocular Hypertension Treatment Study (OHTS) [13] was a multicenter, randomized, prospective clinical trial of the efficacy of topical ocular hypotensive medications in delaying or preventing glaucoma onset in patients with ocular hypertension (OHT). Based on the OHTS, the CCT measured by pachymetry (Figure 1) has become important in glaucoma, and the study showed that the CCT is a significant predictor of the patients with OHT who are at higher risk of developing glaucoma, with a hazard ratio of 1.82 for each 40-μm thinning of the CCT.

Figure 1. Ultrasound Pachymeter DGH 500 (Pachette™)

Eyes with a CCT of 555 μm or less had a three-fold greater risk of developing glaucoma compared with eyes that had a CCT exceeding 588 μm. In the multivariate model of baseline characteristics predictive of conversion oh OHT to glaucoma, the CCT had the greatest impact on the risk. These findings were confirmed in the European Glaucoma Prevention Study [14].

The CCT can be easily and accurately measured, it remains quite constant over a patient's lifetime, and, thus, just one CCT measurement is adequate in most patients. It is not clear why the CCT is such a strong predictor of the development of primary open-angle glaucoma (POAG) in OHT patients. In a multivariable model including age, baseline GAT IOP, optic disc topography (cup to disc [c/d] ratio), and visual field (pattern standard deviation [PSD]), although the CCT and IOP have independent effects on the risk of developing POAG, the two factors interact. Nevertheless, because GAT measurements depend on the CCT, it was impossible in the original model to completely disassociate the effects of both. These findings prove that CCT is an independent risk factor for glaucoma development. The CCT artifacts the GAT, so the IOP may be overestimated or underestimated in thick or thin corneas, respectively.

In 1975, Ehlers cannulated 29 eyes undergoing cataract surgery and found differences between the cannulated IOP and GAT IOP that were related to the CCT [15]; the GAT IOP was most accurate when the CCT was 520 μm. These results indicated that the CCT varies among individuals, and that this variations significantly affect the GAT IOP (Figure 2); therefore, deviations from the 520-μm reference value produced under- and overestimates of 7 mmHg for every 100 μm of deviation.

Figure 2. Goldmann applanation tonometer on a slit-lamp.

Investigators have attempted to design nomograms or correction formulas to account for the effect of CCT on GAT-IOP measurement [15-18], but none has been satisfactory.

The use of the available formulas to obtain a CCT-corrected GAT IOP does not improve the accuracy of the models to predict the risk of glaucoma development [19]. The predictive abilities were similar between the original OHTS model that included CCT, and other models that did not include the CCT but only the CCT-corrected IOP. This may mean that the CCT is relatively unimportant in the final predictive ability of the multivariable model as long as the CCT-corrected IOP is included. For example, a model including the IOP values corrected by the Ehlers formula [15] (a commonly used CCT correction formula that excluded the CCT) had a predictive ability almost identical to the original OHTS model. Such a re-

sult could hardly indicate a major true independent contribution of CCT as a prognostic factor of glaucoma development.

The fundamental concept supporting this correction formula is that as corneas become thinner, the GAT measurements become too low. If the CCT is an average value, the GAT value is essentially correct, and if the cornea is thicker than average, the GAT overvalues the true manometric IOP. Although the Ehlers formula was based on manometric data, the weakness of the formula arises from the small number of subjects studied and the high degree of variability among the subjects. Ehler's data showed a tendency for the Goldmann IOP to increase with increasing CCTs; however, a close look at that data indicates that many subjects clearly defy that trend, i.e., the Goldmann values were too low in some subjects with thick corneas and too high in some with thin corneas. The correlations between the IOP and CCT with Ehler's data and data from similar studies are too low to allow definitive clinical decision-making based on these formulas. However, adjusting the IOP using CCT-based formulas has resulted in poorer agreement with Pascal dynamic contour tonometry, a slit-lamp mounted tonometer for measuring IOP wich seems to be independent of the corneal properties (Figure 3), compared with unadjusted GAT IOP values [20]. It suggested that, although the CCT may be useful in population analyses, CCT-based correction formulas should not be applied to individuals.

Figure 3. Dinamic contour tonometer.

CCT correction formulas for GAT measurements are probably of little value in clinical practice [21]. It might be advantageous to incorporate the risk information from validated predictive models of glaucoma development or progression [19,21], so clinicians have to account for baseline older age, higher IOP, larger vertical c/d ratio, thinner CCT, and greater PSD in the visual field. The hypothesis that CCT is a true independent risk factor for glaucoma is currently not validated and requires further investigation.

In addition, the CCT is becoming more important clinically because of the large number of patients who undergo laser in situ keratomileusis (LASIK), which causes high IOP elevations intraoperatively [22] and a permanent corneal thinning, that, therefore, affects the IOP evaluation.

Because the IOP is an important risk factor for glaucoma, accurate measurement is important, and it can be achieved by intraocular manometry; however, this is an invasive method that obviously cannot be used in a clinical setting,

The only way to fully evaluate the possible independent role of CCT as a prognostic factor for glaucoma development is to include in the predictive model the IOP measurements obtained by a CCT-independent tonometer. The Pascal dynamic contour tonometer (DCT), is a slit-lamp-mounted, nonapplanation, digital contact tonometer that provides continuous tonometry recordings that measure the IOP and the ocular pulse amplitude, which is the difference between the minimal and maximal values of the pulsatile IOP wave contour, and does not require corneal applanation and the DCT IOP measurements seem to agree closely with manometric measurements [23]. Therefore, including DCT measurements with the CCT in a predictive model for glaucoma might better assess the true independent value of CCT compared with use of only the CCT-corrected GAT values. This has been investigated in patients undergoing phacoemulsification, that had the anterior chamber cannulated in a closed system and the IOP was set to 15, 20, and 35 mmHg by a water column. The IOP measurements then were taken by DCT. The results showed that the DCT agree well with the intracameral IOP. Interestingly, the CCT had a low but significant effect on the DCT measurements [23].

The DCT measurement principle is based on contour matching, which assumes that if the eye were enclosed by a contoured, tight-fitting shell, the forces generated by IOP would act on the shell wall. Replacing part of the shell wall with a pressure sensor would enable measurement of these forces and therefore the IOP. The DCT has a central gauge surrounded by a contoured plastic tip that is in contact with the cornea and creates a tight-fitting shell. The DCT compensates for all forces exerted on the cornea and an electronic sensor measures IOP independent of the corneal properties.

4. Corneal thickness and glaucoma

Most of the knowledge regarding the impact of corneal thickness in glaucoma is referred to CCT; however, Jordan et al. [24] found differences between the OHT and normal tension glaucoma (NTG) groups in central and paracentral corneal thicknesses measured by optical slip scan pachymetry. The study corroborated differences in CCT between OHT and NTG but also found that the corresponding paracentral quadrants differed significantly between groups. Patients with NTG had overall thinner corneas and those with OHT had overall thicker corneas. Is the corneal thickness an independent risk factor for glaucoma?

Goldmann first suggested in 1957 that the IOP measured by applanation tonometry might be affected by the CCT [25]. He found that IOP measurements in patients with thin corneas tended to be underestimated but overestimated in those with thick corneas.

In the OHTS, the GAT IOP was used to determine participant eligibility, guide treatment decisions, and construct a model predictive of POAG development. Had the OHTS been carried out with a perfectly accurate, cornea-independent tonometer, which does not exist, the IOP might have been a more powerful predictor of POAG development and the CCT might

have been a less powerful predictor. Some investigators interpreted the OHTS results to in-
dicate that the CCT is an independent risk factor for glaucoma development. Because the
GAT measurements ultimately depend on the CCT, Medeiros and Weinreb [26] stated that it
is impossible, based on the original model, to disassociate the effects of both. Some groups
have evaluated [19,27,28] whether the OHTS prediction model could be improved using
CCT-corrected IOP using previously published formulas (Table 1), evaluated using the c sta-
tistics (a measure of concordance), and calibration chi-squares. The c statistic is the fraction
of patients with an outcome among pairs of patients, in which one has the outcome and one
does not; the patient with the higher predictive value is classified as the one with the out-
come. The c statistic varies between 0.5 when a model provides no information and 1.0 in
sensible models. The CCT also remained a significant predictor of glaucoma development in
a multivariable model that included the CCT-corrected IOP.

CCT in microns	IOP correction in mm Hg
445	7
455	6
465	6
475	5
485	4
495	4
505	3
515	2
525	1
535	1
545	0
555	-1
565	-1
575	-2
585	-3
595	-4
605	-4
615	-5
625	-6
635	-6
645	-7

Table 1. Correction values for IOPs based on CCT [8,17].

Medeiros and Weinreb [26] argued that other factors besides corneal thickness such as corneal elasticity and viscoelasticity might affect tonometric readings and the formulas to correct the GAT IOP [19] do not fully consider these factors [19, 27, 28]. The DCT measurements have been proposed and agree closely with the manometric measurements [20]. Therefore, the inclusion of DCT measurements along with corneal thickness in a model predictive of glaucoma might better assess the true independent value of IOP. A biologic link might exist between some corneal parameters such as the thickness or the viscoelastic properties and the structure/deformability/physiology of the lamina cribosa and peripapillary sclera.

It is noteworthy that in the Early Manifest Glaucoma Trial (EMGT) the IOP was not used to determine patient eligibility or treatment decisions, and thus the possible effect of the CCT on GAT measurements was less likely to affect the incidence of glaucoma progression. In the EMGT, the CCT was an independent factor predictive of POAG progression [29]. In the population-based, longitudinal Barbados Eye Studies, the CCT (measured 9 years after the recruitment) was an independent risk factor for development of glaucoma [30]. In the population-based Los Angeles Latino Eye Study (LALES), the prevalence of glaucoma was higher among individuals with thin CCTs than among individuals with normal or thick CCTs across all IOP levels [31]. The LALES, which investigated whether adjusting each IOP individually for CCT using the Doughty and Zaman algorithm [16] changed this relationship, reported almost no change in the association between a thin CCT and a higher prevalence of glaucoma. This algorithm showed that 2.5 mmHg was correlated with a 50-μm difference from the baseline CCT. Each of these corrective factors had proponents, and the use of algorithms to correct for the IOP based on the CCT became popular. The LALES concluded that the CCT is an independent factor itself [31]. The findings of the EMGT, Barbados Eye Studies, and LALES suggest that the effect of CCT on the glaucoma development risk is caused by more than just a tonometry artifact.

5. Corneal biomechanics

Ocular biomechanics is an increasingly important field. Overt corneal biomechanical problems have long been seen in keratoconus and corneal ectasia after corneal refractive surgery [32].

In keratoconus, there are clear changes in the corneal collagen, and the cornea loses rigidity over time and becomes ectatic; in corneal ectasia, the ablation of some corneal stroma can weaken the cornea and result in progressive corneal deformation [33]. In refractive surgical practice, patients with preexisting ectasia usually are excluded from treatment. However, individual variations in biomechanical integrity and postoperative wound healing preclude preoperative identification of all potentially vulnerable patients. There is considerable but mostly indirect evidence suggesting that the biomechanical corneal properties vary with age. Quantifying the biomechanical corneal properties is difficult, but the available evidence supports corneal stiffening with age; in other words, there is an increment in Young's modulus [34], the ocular rigidity coefficient, that expresses the elastic properties of the globe [35,36], the cohesive tensile strength, and the breaking force of a tissue [37].

Young's modulus, also known as the tensile modulus, is a measure of the stiffness of an elastic material and is a parameter used to characterize elastic materials. Perhaps the single best descriptor of a given material's biomechanical properties at low strain is its Young's modulus (E), which is defined as the ratio of stress to strain or

$$Young\text{'}s\,modulus(E)=stress\,/\,strain$$

where stress is an applied force (load/unit area), and strain is the deformation of the material to which stress has been applied (displacement/unit length). This parameter depends on the material's physical properties and dimensions. Importantly, when stress is applied and removed, elastic materials follow the same path during deformation and relaxation and ultimately recover the original shape. Viscoelastic materials, such as the cornea, also can recover the original shape after stress is removed, but the relaxation path differs from the deformation path; therefore, the relationship between stress and strain is nonlinear, and stiffening occurs as strain increases [38-40] (Figure 4). This behavior, referred to as corneal hysteresis (CH), results from dissipation of energy as heat in the material.
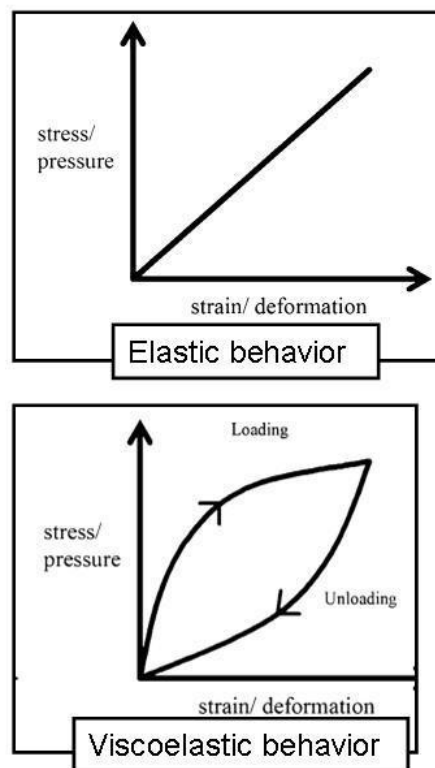

Figure 4. Here, it can be seen the relationship between stress and strain is linear in an elastic behaviour and nonlinear in a viscoelastic behaviour.

The GAT IOP measurement, obtained from the force needed to applanate the cornea, is based on a number of assumptions about corneal deformability. The corneal mix of collagen

types, corneal hydration, collagen fibril density, ECM, and other factors vary among individuals. In some patients, these factors dwarf the effect of the CCT on the accuracy of the GAT IOP value. In fact, the effect of the corneal thickness on GAT measurements may be less important than the effect of variations in corneal elasticity [41].

CH is a measure of the viscoelastic properties of the corneal tissue together with the corneal resistance factor (CRF), i.e., the "energy absorption capability" of the cornea, and indicates the biomechanical integrity. The Ocular Response Analyzer (ORA) (Reichert Ophthalmic Instruments, Inc., Buffalo, NY) provides both parameters (Figure 5).

Figure 5. Ocular response analyzer.

The ORA, which measures some of the corneal biomechanical properties in vivo, uses a 25-millisencond (ms) air pulse to apply pressure to the cornea. The air pulse causes the cornea to move inward, past applanation and into a slight concavity, before returning to the normal curvature. Corneal deformation is recorded via an electro-optical infrared detection system similar to classic air-puff tonometry. The ORA acquires corneal biomechanical data by quantifying this differential inward and outward corneal response to the air pulse over about 20 ms (Figure 6).
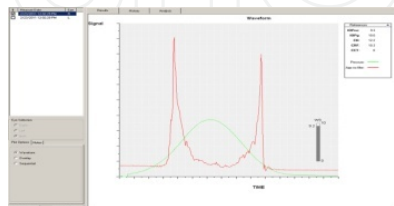

Figure 6. This picture shows the measurements done by ORA.

Because of the dynamic nature of the measurement process, viscous damping in the cornea causes delays in the inward and outward applanation events (energy absorption). Milliseconds after the first applanation, the air pump that generated the air pulse also shuts down,

and the air pressure applied to the eye decreases in an inverse-time symmetric fashion. However, before that decrease, the cornea is indented substantially as the air pressure peaks about 3 ms after applanation. As the pressure decreases from its peak, the cornea passes through a second applanated state while returning to the normal convex curvature. This allows detection of a second applanation point. Using the first applanation pressure point (P1) and the second applanation pressure point (P2) [42,43] (Figure 7), the ORA generates two separate IOP output parameters, and the difference between the two pressures is CH.
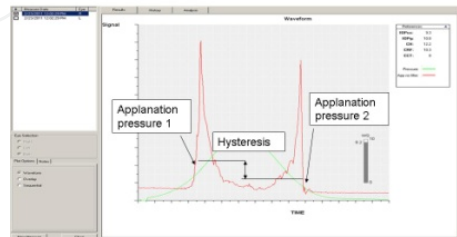

Figure 7. This picture shows de P1 and P2 points. Hysteresis is also showed.

The Goldmann-correlated IOP (IOPg) is the average of the inward (P1) and outward (P2) applanation pressures. This parameter is closely correlated with the GAT IOP.

The CH measurement also provides a basis for two additional new parameters: the corneal-compensated IOP (IOPcc), an IOP measurement that is less affected by corneal properties than other tonometric methods, such as GAT, and CRF, an index of corneal resistance to deformation derived from the formula P1 x kP2, where k is the constant determined from empirical analysis of the relationship between both P1 and P2 and CCT to develop a corneal parameter more strongly associated with CCT than CH [44].

The CH in patients with glaucoma and in those with acquired optic nerve head (ONH) pits is lower than in normal controls [43, 45]. Other authors also have found that the CH predicts visual field damage progression. However, other studies using the ORA have reported that the CRF and CH did not change significantly when the IOP was lowered using topical anti-glaucoma drugs and that the relationship between the GAT IOP and CRF or CH is weak and unchanged by ocular hypotensive drugs [46].

6. Corneal and refractive surgeries

The changes in the GAT IOP after corneal refractive surgery have been studied because of the large number of patients who undergo laser refractive procedures. In corneal laser excimer refractive surgery, the cornea becomes thinner and, therefore, the IOP measurement is affected [47,48]. Because most patients undergoing laser refractive surgery are myopic and

at increased risk for glaucoma [28], the effect of these procedures on glaucoma management should be determined.

After laser ablation, the corneal thickness and shape change, so the mathematical assumptions used in existing models for IOP measurement cannot be satisfied [49]. In lamellar procedures, creation of a corneal flap changes the corneal biomechamical stability. The depth-dependent tensile strength of the cornea, also have been reported [50,51], with the anterior 40% of stroma having a significantly higher tensile strength than the posterior 60%; therefore, a corneal flap can have viscoelastic properties that differ from the underlying stroma and further affect the GAT IOP readings. Patients who underwent LASIK and laser-assisted subepithelial keratomileusis seem to have a postoperative decrease in CH [52,53].

In some cases, LASIK is associated with the interface fluid syndrome (IFS), first described by Rehany et al. [54], that is characterized by fluid collection in the flap interface due to a marked IOP increase. The resultant GAT IOP value is falsely lower [48]. In normal corneas with intact functioning membranes and avascular compact corneal stroma, the stroma bears the acute IOP increases, and the fluid flows from the stroma to the epithelium, which has lower pressure, resulting in epithelial edema. After LASIK, there is a virtual space between the flap and the stromal bed, with fluid accumulating in the flap interface [55].

7. Cornea, lamina cribrosa, and glaucoma

The lamina cribrosa is a sieve-like fenestrated structure in the posterior sclera through which the optic nerve fibers and the retinal vessels enter and exit the eye. The glial segment of the optic nerve and lamina cribrosa derive from the neuroectoderm, and the mesenchyme originates from the neural crest. Because the corneal stroma and the corneal endothelium also derive from the neural crest, they are related embryologically. The lamina cribrosa is believed to be the site at which the neural damage induced by glaucoma occurs.

The CCT may reflect the scleral and lamina cribrosa properties associated with glaucomatous optic neuropathy. In fact, the CCT is correlated with the anterior scleral thickness in patients with POAG [56]. Several studies have assessed the relationship between the CCT and objectively measured optic disc parameters, but they provide inconsistent results. Using the confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph, Heidelberg Engineering, Heidelberg, Germany), several hospital-based studies of patients with glaucoma have suggested that the CCT is correlated with the optic disc area and nasal rim volume [57], while another population-based study [58] did not identify these correlations. In another population-based survey [59], no significant relationship was found between the CCT and ONH parameters obtained with retinal tomography.

Thin corneas also can be associated with weak ONHs and this weakness may be related with a thin lamina cribrosa [60-62]. Further, the development and progression of glaucoma are correlated with the CCT [62]. Other studies have suggested that CH and not corneal thickness is correlated with the vulnerability of the ONH to sustain glaucomatous damage [63].

The correlation between CCT and ONH topographic changes in response to IOP reductions in patients with POAG also has been evaluated [64]. The hypothesis was that thinner CCTs might be associated with greater changes in ONH topography due to a more compliant lamina cribrosa. Nicolela et al. [65] found that patients with thinner corneas show significantly greater cup shallowing, which is a surrogate marker for lamina cribrosa displacement and compliance in response to IOP reduction. The investigators interrupted the medical treatment for 4 weeks (with an average increase of IOP of 5.4 mmHg), and when the medical treatment was restarted, the IOPs were remeasured after 4 weeks, and they found that the IOP decreased from a mean of 22.27±4.12 mmHg to a mean of 17.39±2.67 mmHg. This finding may support the hypothesis that eyes with a thinner CCT have an increased risk of developing glaucomatous ONH changes because the lamina cribrosa may be more prone to displacement in response to IOP changes. Nevertheless, the changes of the ONH topography were unconfirmed [65] for relatively moderate IOP changes of about 5 mmHg. In addition, the stage of the ONH glaucomatous damage and the disease duration might affect the degree of compliance of the lamina in response to IOP changes, so that for more advanced and long-standing damage less compliance of the lamina can be expected.

The differences in laminar thickness have been studied in different glaucoma types. Park et al. [66] reported that NTG was associated with a thinner lamina cribosa than OAG in patients with a similar disease stage; another study showed that patients with pseudoexfoliation syndrome have less stiffness compared with normal controls, which may reflect an inherent tissue weakness that makes these eyes more vulnerable to glaucomatous damage [67].

Researchers generally agree that the lamina cribrosa is important in glaucoma [68]. Nevertheless, in vivo clinical clues regarding the correlated parameters of the lamina cribrosa are limited [69, 70].

8. Effect of topical hypotensive drugs on the cornea

Some ocular hypotensive drugs, such as topical carbonic anhydrase inhibitors (CAIs) and F2α-prostaglandin analogs (PGAs), induce changes in the CCT [71].

The hypotensive effect of PGAs, first-line treatments of glaucoma and OHT, may be affected by some ocular characteristics, such as the axial length [72]. Eyes with a longer axial length have a worse response to PGAs treatment. If a patient had undergone a previous argon laser trabeculoplasty, there is a minimal response to a PGA [73]. In addition to its effectiveness in lowering IOP, PGAs have mild and local side effects that include changes in iris color in up to 70% of patients [74], especially in patients with mixed colors and in the irises of older patients [75]. The changes in iris pigmentation are related to increased melanin content of the iris melanocytes [76]. Other side effects are periocular hyperpigmentation and darkening and increased eyelash length. PGAs are highly efficient for lowering IOP, with few local and systemic side effects. Interestingly, most recent studies have shown that PGAs decrease the CCT, and Viestenz et al. [77] reported thinner CCTs in patients treated with topical prostaglandin F2-alpha, compared with topical CAIs. Harasymowycz et al. in a prospective study

[78] found a mean 6.9-micron CCT decrease after 6 weeks of travoprost treatment. Sen et al. [79] reported 1.9 ± 2.4% and 2.8 ± 1.8% CCT decreases over 24 months with latanoprost and bimatoprost, respectively. Hatanaka et al. [80] also reported that topical PGAs were associated with a CCT reduction over at least 8 weeks (the bimatoprost 0.03% group decreased from 544.41 ± 35.4 to 540.35 ± 35.9 µm; the travoprost 0.004% group decreased from 538.47 ± 32.0 to 532.25 ± 30.4 µm; the latanoprost 0.005% group decreased from 548.57 ± 32.4 to 543.88 ± 35.6 µm). Zhong et al. [81] reported CCT reductions in the latanoprost, travoprost, and bimatoprost groups of 14.95 ± 5.04, 15.73 ± 3.25, and 17.00 ± 6.23 mm, respectively, and no significant difference was seen in the CCT reductions between patients with 6 months or shorter treatment and patients with 6 months or longer treatment in the three groups.

The reason for the effect of the PGAs on the CCT is unknown, but it is widely accepted that PGAs seem to induce ECM remodeling due to a FP-receptor-mediated increased synthesis of matrix metalloproteinases (MMPs) [82]. The MMPs are a family of enzymes that degrade several components of the ECM, thus decreasing the levels of collagen types I, II, III, and IV. Published evidence suggests that the PGA-related activation of the MMPs activity takes place in the ciliary body, the trabecular meshwork [83], the conjunctiva, the sclera, and the zonular fibers-ciliary muscle complex [84]. Further, naturally occurring prostaglandins seem to play a relevant role in physiologic corneal conditions, i.e., repair after corneal injuries, and in pathologic corneal conditions, i.e., corneal ectasia. In fact, PGA treatment may be related to keratoconus progression [85]. Thus, there is enough evidence to suggest that topical PGAs might induce changes in the ECM of the corneal stroma via up-regulation of MMPs that may slightly change the CCT and perhaps the corneal viscoelastic properties. In fact, CH seems to be significantly lower in PGA-treated eyes [86]. PGAs also seem to increase the keratocyte density in the corneal stroma, which might also result in changes in the ECM [87].

Previous reports have suggested that chronic topical PGA treatment is associated with a slight decrease in the CCT [86,88] and an increase in the CH. We studied the response of CCT to increased IOP in rabbit eyes treated with travoprost for 1 month and in an untreated control group, and found that the decrease in CCT induced by a sudden increase in IOP was greater in the PGA-treated eyes than in the control eyes [88]. The changes in corneal thickness induced by IOP increases are believed to be a strain response and thus are probably a biomechanical response of the corneal tissue to the IOP changes. Then the differences in the CCT behavior between groups also suggest that PGAs induce changes in the corneal biomechanical properties, at least in rabbits.

Topical dorzolamide induces a 14.4% increase in CCT in patients with corneal guttata [89]. Patients with severe corneal guttata or a highly compromised endothelial function may have a higher risk of corneal decompensation after prolonged topical use of dorzolamide.

Dorzolamide is a potent cytosolic carbonic anhydrase inhibitor (CAI) isoenzyme II, and the corneal endothelium contains carbonic anhydrase (CA) II and the cytosolic CA I, which plays a major role in keeping the cornea relatively dehydrated. Dorzolamide has a high affinity for CA II and low affinity for CA I, and thus, it has the potential to interfere with the pump function of the corneal endothelium, which could theoretically lead to corneal edema. Changes in CCT have been used as an indirect indicator of the endothelial function. Some investigations have report-

ed a slight but significant increase in CCT in eyes treated with brinzolamide, another CAI inhibitor [90]. Another way to measure the endothelial function in vivo is to measure the intrastromal corneal pressure [91,92], formerly known as corneal intrastromal pressure, which has a negative value under physiologic conditions. The amount of negative pressure in the corneal stroma is likely to be correlated with the endothelial function, and topical dorzolamide significantly reduces the negative pressure in the corneal stroma in rabbits [91], suggesting that the drug affects the endothelial function in healthy rabbit corneas. This finding is consistent with the reported cases of dorzolamide-induced corneal edema in susceptible patients and with the finding that inhibiting CA in the corneal endothelium causes a 50% decrease in the endothelial fluid transport and some corneal swelling [92].

9. Conclusion

There is growing interest in the possible effect of some corneal parameters in glaucoma. There is sufficient evidence to suggest that CCT evaluation predicts the risk of conversion from OHT to glaucoma. The influence of the CCT on the GAT IOP is clear, so true IOP is higher than GAT IOP in patients with thinner corneas and true IOP is lower than GAT IOP in patients with thicker corneas. In addition, some data suggest that CCT may be an independent risk factor for glaucoma development, although there is no clear evidence to support this hypothesis.

Of special interest is the fact that GAT is affected by laser excimer refractive surgery, a popular procedure that changes some corneal properties that affect accurate IOP measurement. New tonometers with a lower relationship to the corneal thickness and viscoelastic properties need to be developed.

Finally, widely used topical antiglaucomatous medications can alter the corneal viscoelastic properties and thus affect the GAT readings. This also needs to be investigated further.

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