The Association Between Ocular Rigidity and Neuroretinal Damage in Glaucoma

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Purpose. Ocular rigidity (OR) is an important biomechanical property, thought to be relevant in the pathophysiology of open-angle glaucoma (OAG). This study aims to evaluate the relationship between OR and neuroretinal damage caused by glaucoma.

Methods. One hundred eight subjects (22 with healthy eyes, 23 with suspect discs, and 63 with OAG) were included in this study. OR was measured using a noninvasive optical coherence tomography (OCT)-based method developed by our group. We also measured central corneal thickness (CCT), corneal hysteresis (CH), and corneal resistance factor (CRF). Pearson and partial correlations were performed to evaluate the relationship between OR and glaucomatous damage represented by ganglion cell complex (GCC), retinal nerve fiber layer (RNFL) thicknesses, and neuroretinal rim area.

Results. Significant positive correlations were found between OR and minimum GCC thickness ($r = 0.325$, $P = 0.001$), average GCC thickness ($r = 0.320$, $P = 0.002$), rim area ($r = 0.344$, $P < 0.001$), and RNFL thickness in the superior ($r = 0.225$, $P = 0.023$), and inferior ($r = 0.281$, $P = 0.004$) quadrants. These correlations were generally greater than those found for CCT, CH, and CRF. Furthermore, no correlation was found between OR and corneal biomechanical parameters. After adjusting for age, sex, and ethnicity, significant correlations were found between OR and minimum and average GCC thickness ($r = 0.357$, $P = 0.001$ and $r = 0.344$, $P = 0.001$, respectively), rim area ($r = 0.327$, $P = 0.001$), average RNFL thickness ($r = 0.331$, $P = 0.001$), and RNFL thickness in the superior ($r = 0.296$, $P = 0.003$) and inferior ($r = 0.317$, $P = 0.001$) quadrants.

Conclusions. In this study, we found a positive correlation between structural OCT-based parameters and OR, indicating more neuroretinal damage in eyes with lower OR. These findings could provide insight into the pathophysiology of OAG.

Keywords: ocular rigidity, glaucoma, corneal biomechanics, retinal nerve fiber layer, optical coherence tomography

Glaucoma is the leading cause of irreversible blindness worldwide, resulting in damage to the retinal ganglion cells (RGCs) that form the optic nerve, and in visual field loss. Elevated intraocular pressure (IOP) was traditionally associated with the pathogenesis of open-angle glaucoma (OAG), the main form of glaucoma. Evidence has since shown that factors other than IOP must underlie the susceptibility of the optic nerve head (ONH) to glaucomatous injury. This conclusion is corroborated by the existence of OAG with IOP in the normal range, and the absence of OAG in most patients with elevated IOP.[1] Recent biomechanical modeling has suggested that scleral stiffness, the main contributor to ocular rigidity (OR), is the greatest factor to influence strain (deformation) at the ONH in glaucoma, perhaps more so than IOP. A more compliant sclera would lead to increased ONH strain levels[2,3] and more neuronal damage.

Over the last 80 years, the role of OR in the pathophysiology of glaucoma has been scrutinized.[4–10] Despite this, the association between OR and glaucoma is not well established. On one side, OR is thought to be higher in glaucomatous eyes, producing higher IOP fluctuations due to rigid ocular walls, and hence more stress at the ONH and lamina cribrosa levels.[7–9,11] Inflation studies in cadaver eyes, and in vivo studies using indirect measurements showed higher OR in eyes with established glaucoma.[7–9] On the other hand OR is thought to be lower in early glaucoma, leading to axonal stretching and damage.[2,5,6,10] According to this theory, increased OR would occur at later stages of the disease.[10]Studies have reported low OR in OAG,[5,6,10] and highest OR in ocular hypertensives with no glaucomatous damage.[10] However, another study using intraoperative cannulation showed no difference in OR between diseased and healthy eyes.[12]

Despite limitations owing to the lack of an accurate, noninvasive measurement method, a growing body of evidence, including clinical and experimental studies, as well as computational models, seems to indicate that low OR may be a risk factor for glaucoma due to increased strain at the ONH.[2,3,5,6,10,13] This may further explain why myopia is as a risk factor for glaucoma[14–16] because elongated eyes were shown to have lower OR[10,17] (Sayah DN, et al. *IOVS* 2016;57:ARVO E-Abstract 3551). Biomechanical studies in monkeys, for example, have also demonstrated a hypercompliant deformation of the lamina cribrosa and peripapillary sclera with early experimental glaucoma.[18–20] Two in vivo studies reported contradictory results, an increased OR in OAG. They used indirect measurement techniques based on laser interferometry to assess the anterior to posterior expansion of the corneoscleral shell, which is itself dependent on OR,[7,8] and they did not account for changes in choroidal volume. Although reports show an increased OR with age,[4,21,22] our group previously hypothesized that increased stiffness may be a protective factor for OAG[10] and that stiffening of the peripapillary sclera could occur as an adaptive mechanism of the eye to elevated IOP.[23] However, this hypothesis remains to be fully assessed.

There is significant evidence that biomechanical properties of the cornea, such as central corneal thickness (CCT), corneal hysteresis (CH), and corneal resistance factor (CRF), are risk factors for glaucoma.[1,24–33] In the Ocular Hypertension Treatment Study, CCT was an important risk factor for progression from ocular hypertension (OHT) to OAG.[1] The importance of CCT as an independent risk factor and predictor for the development of OAG[1,24] and visual field loss[25] was later demonstrated. Similarly, CH was found to be significantly lower in POAG compared with controls.[26–29] Numerous studies also associated a lower CH with an increased risk of glaucoma progression,[30–33] with a higher predictive value of glaucoma progression than CCT.[30,31] The link between corneal biomechanical properties and the optic nerve's susceptibility to glaucomatous damage is not well understood, but it has been postulated that it is via the globe's biomechanical properties.[34] However, the relationship between OR and corneal biomechanical properties remains unclear, with a few studies showing at best a weak correlation[10,22] (Lin SC, et al. *IOVS* 2015;56:ARVO E-Abstract 6137).

A plethora of challenges and confounding factors have made these questions difficult to resolve,[35] including the ability to quantify OR in living human eyes using a reliable, direct, and noninvasive method. Such a method has only recently become available.[17,36] It estimates the OR coefficient using Friedenwald's equation,[4] in which the pulsatile ocular volume change is measured from video-rate OCT imaging coupled with automated choroidal segmentation, and the pulsatile IOP change is measured using Pascal dynamic contour tonometry (DCT).

To test the hypothesis that low OR is correlated with more glaucomatous damage, this study will evaluate the relationship between OR and glaucomatous structural damage such as the ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL) thicknesses. The association between CCT, CH, and CRF, known risk factors for OAG accounting for the biomechanics of the cornea, was also examined in relation to OR, which is a global biomechanical parameter of the eye.

Methods

This study followed the tenets of the Declaration of Helsinki and was approved by the Maisonneuve-Rosemont Hospital (HMR) institutional review board. Informed consent was obtained from all participants prior to testing.

Adult subjects with suspect discs or primary OAG were recruited from the HMR Ophthalmology Glaucoma Clinic. Healthy volunteers were recruited from older subjects consulting in the HMR Ophthalmology clinic for disorders such as blepharitis, which are not thought to be related to altered OR. Recruitment was carried out sequentially and directly by the research team from patients consulting in the clinic. A complete ocular examination was performed for all participants. Normal subjects had IOP less than 21 mm Hg under no pharmacologic treatment, normal optic nerve appearance on fundus examination, normal visual fields, and no other ocular disease. Subjects with suspect discs had increased cup-to-disc ratio or asymmetry of optic nerve appearance, with no detectable functional or structural damage. IOP in this group could be within normal range or elevated, and if there was a history of elevated IOP, could be treated with topical IOP-lowering agents. Subjects with OAG had open (nonoccludable) angles on gonioscopy, a glaucomatous optic nerve appearance, as well as repeatable structural and/or functional findings with optical coherence tomography (OCT) imaging and/or Humphrey visual field (VF; Zeiss Humphrey Systems, Dublin, CA, USA) testing (SITA standard threshold 24–2 strategy). Preperimetric glaucoma patients with confirmed neuroretinal damage were included in the glaucoma group. Participants were required to have clear media, steady fixation, and the ability to fixate a target light with the study or contralateral eye. Patients with a previous history of intraocular surgery (except cataract extraction) including trabeculectomy, tube shunt, and refractive surgery were excluded. Other exclusion criteria included secondary glaucoma, nonglaucomatous optic neuropathy, any retinopathy, and documented systemic collagen disease, as well as concomitant pathologies, which could affect the visual field. Subjects with diabetes mellitus (DM) were also excluded from the study because DM could have an effect on OR. Although not corroborated in clinical studies in which OR was measured in vivo,[22,37] DM was shown to increase and accelerate scleral stiffening with age in inflation studies[38] owing to the accumulation of advanced glycation end-product cross-links of collagen in various tissues of the eye.[39,40]

OR was measured using a noninvasive method involving video-rate OCT imaging and Pascal DCT.[17,36] This method is based on Friedenwald's equation,[4,36] which permits the OR coefficient to be estimated as the following pressure-volume relationship:

$$ln\frac{IOP}{IOP_0} = OR \times (V - V_0).$$

The OR coefficient thus obtained is a single value for the overall OR of the corneoscleral shell.

Through dynamic OCT imaging (Spectralis SD-OCT; Heidelberg Engineering GmbH, Heidelberg, Germany) with enhanced depth imaging coupled with automated choroidal segmentation, we obtain a direct measurement of the volume of blood pumped into the choroid with each heartbeat—the pulsatile ocular volume change (ΔV, or $V - V_0$). The method is described in detail in our previous articles.[17,36] Briefly, the

choroidal segmentation algorithm is based on graph theory using an edge-probability weighting scheme that enables the precise detection of the choroid's boundaries, and has been shown to be more robust in detecting the choroid-sclera interface compared with existing algorithms.[17,41] It measures the choroidal thickness change (ΔCT) associated with the cardiac cycle through the time-series. To ensure that CT fluctuations in the time-series are owing to the pulsatile blood flow, high-frequency components from the spectral analysis must coincide with the first and second harmonics of the heart rate frequency, which was measured simultaneously using an oximeter.

Considering that the choroid represents approximately 90% of the blood flow in the eye,[42] ΔV can be estimated from the measured ΔCT. The ΔV is calculated according to the following equation: $\Delta V = (\pi/2)(AL_{adj} + CT)^2 \Delta CT$, where AL_{adj} is the ocular axial length (AL) measured using the IOL Master 500 (Carl Zeiss Meditec AG, Dublin, CA, USA) and adjusted for the anterior chamber depth.[36] The pulsatile pressure change was measured using the Pascal DCT (Ziemer Ophthalmic Systems AG, Port, Switzerland). This tonometer provides an IOP reading corresponding to the diastolic IOP, as well as the ocular pulse amplitude, which is the change in IOP between the systole and diastole. This noninvasive methodology has been previously validated and was also shown to have good repeatability.[36]

Structural OCT-based parameters such as GCC, RNFL thicknesses, and neuroretinal rim area were acquired using the Cirrus 5000 OCT (Carl Zeiss Meditec AG). These parameters characterize and quantify the retinal layers that contain neuronal structures that form the optic nerve. The GCC corresponds to the ganglion cell layer and inner plexiform layer thicknesses combined. These structural parameters can be presented as average, minimum, and sectoral thicknesses. The neuroretinal rim area, average and minimum GCC thicknesses, average RNFL thickness, and RNFL thickness in the superior, temporal, and inferior quadrants were considered.

Additional measurements were acquired including IOP by Goldmann applanation (GAT-IOP), CCT using optical pachymetry, and CH and CRF using the Ocular Response Analyzer (ORA; Reichert Technologies, Depew, NY, USA).[43] The ORA measures CH and CRF by analyzing the deformation of the cornea in response to a rapid air jet pulse.[43] CH represents the cornea's ability to absorb and dissipate energy, and is defined as the difference between P1 and P2, the inward and outward applanation pressures, respectively. CRF provides information about the elastic properties of corneal tissue or their resistance to stress, and is defined as P1-kP2 where k is a constant derived empirically from CCT.[44] ORA measurements were repeated at least twice and up to four times if the waveform score was below 6.0, in which case the acquisition with the highest waveform score was considered. Maximum historic IOP (Tmax) and glaucoma medications were also recorded for each participant.

Statistical analyses were performed using SPSS statistical software version 23 (IBM Inc., Armonk, NY, USA). Descriptive statistical analysis of baseline demographics was carried out and presented as the mean ± SD. The normality of data were verified with the Kolmogorov-Smirnov test. Correlations between neuroretinal damage and OR in all eyes were assessed and compared with correlations obtained between neuroretinal damage and known risk factors such as CCT, CH, CRF, and Tmax. The correlation between OR itself and corneal biomechanical parameters were also assessed. Partial correlations were calculated to adjust for potential covariates. Depending on data normality, the Pearson correlation coefficient or Spearman rank correlation coefficient was used to investigate correlations between OR and the other variables. A sensitivity analysis was carried out to verify the impact of the assumptions of normality on the results. If the results were robust to both statistical methods, the Pearson correlation coefficient was reported. Student's *t*-test or the Mann-Whitney *U* test was used to compare the effect of topical hypotensive medications on OR between the users and nonusers for each drug. For all statistical tests, a *P* value inferior to 0.05 was considered significant.

Table 1. Baseline Characteristics of Participants

Age (y)	65 ± 11
AL (mm)	24.35 ± 1.36
GAT-IOP (mm Hg)	17 ± 5
DCT-IOP (mm Hg)	18.8 ± 4.2
Ocular pulse amplitude (mm Hg)	3.2 ± 1.2
Tmax (mm Hg)	22 ± 6
CCT (µm)	534 ± 40
CH (mm Hg)	8.9 ± 2.0
CRF (mm Hg)	9.5 ± 1.9
OR (μL^{-1})	0.026 ± 0.013
Neuroretinal rim area (mm^2)	0.99 ± 0.28
Minimum GCC thickness (µm)	67 ± 11
Average GCC thickness (µm)	72 ± 9
Average RNFL thickness (µm)	79 ± 12
Superior quadrant RNFL thickness (µm)	95 ± 18
Temporal quadrant RNFL thickness (µm)	58 ± 12
Inferior quadrant RNFL thickness (µm)	98 ± 20
Glaucoma medications	
Number of treated subjects	59
Number of medications per subject	1.2 ± 1.4
Prostaglandin analog	51
Beta-adrenergic antagonist	40
Alpha 2-adrenergic agonist	6
Carbonic anhydrase inhibitor	28
Cholinergic agonist	2

Data are presented as the mean ± SD. GAT-IOP, IOP measured by Goldmann applanation tonometry; DCT-IOP, IOP measured using Pascal dynamic contour tonometry; Tmax, maximum historical IOP.

Results

One hundred eight subjects (22 with healthy eyes, 23 with suspect discs, and 63 with early to advanced OAG) were recruited. One eye per subject was included in the study; 57 (53%) were right eyes. Of the 108 participants, 59 (55%) were female, 91 (84%) were Caucasian, 10 (9%) were from African origins, 4 (4%) were Hispanic, and 3 (3%) were from another ethnic origin. A description of their baseline characteristics is presented in Table 1. In the OAG group, the average visual field mean defect was −2.51 ± 4.44 dB. Correlations between OR, CCT, CH, CRF, and Tmax, and OCT measurements of structural glaucomatous damage are shown in Table 2. Significant positive correlations were found between OR and the minimum and average GCC thicknesses (r = 0.325, $P = 0.001$ and r = 0.320, $P = 0.002$, respectively). Direct correlations were also found between OR and rim area (r = 0.344, $P < 0.001$), as well as OR and the RNFL thickness in the superior and inferior quadrant (r = 0.225, $P = 0.023$ and r = 0.281, $P = 0.004$, respectively). These correlations were generally greater than

Table 2. Comparison of the Association Between Parameters of Structural Damage in Glaucoma and OR, as well as With Other Known Risk Factors. Pearson Correlation Coefficients and Significance Values are Shown (in bold, if $P < 0.05$)

	OR	CCT	CH	CRF	Tmax
Rim area	**0.344 (<0.001)**	**0.227 (0.027)**	**0.291 (0.005)**	**0.226 (0.031)**	**−0.228 (0.034)**
Minimum GCC thickness	**0.325 (0.001)**	0.160 (0.145)	**0.265 (0.018)**	0.168 (0.136)	**−0.504 (<0.001)**
Average GCC thickness	**0.320 (0.002)**	0.116 (0.291)	0.167 (0.139)	0.053 (0.638)	**−0.399 (<0.001)**
Average RNFL thickness	**0.266 (0.005)**	**0.206 (0.043)**	0.159 (0.125)	0.115 (0.269)	**−0.387 (<0.001)**
Superior quadrant RNFL thickness	**0.225 (0.023)**	0.069 (0.512)	0.048 (0.657)	−0.066 (0.541)	**−0.298 (0.006)**
Temporal quadrant RNFL thickness	0.105 (0.292)	**0.226 (0.030)**	0.147 (0.171)	0.204 (0.057)	**−0.242 (0.026)**
Inferior quadrant RNFL thickness	**0.281 (0.004)**	0.150 (0.154)	0.189 (0.077)	0.096 (0.375)	**−0.478 (<0.001)**

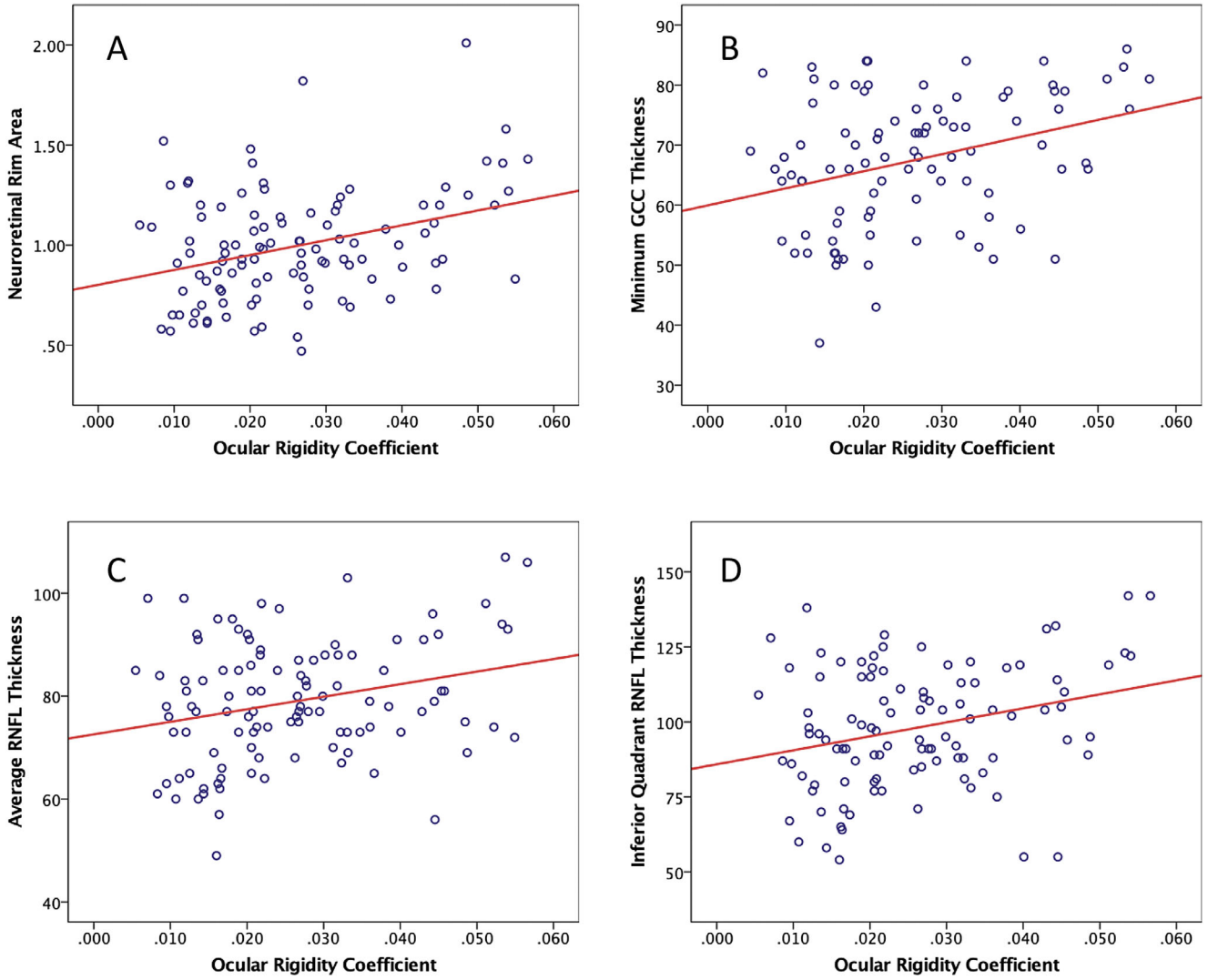

Figure. Scatter plots showing significant correlations between OR coefficients and the (**A**) neuroretinal rim area (r = 0.344, $P < 0.001$; rim area = 0.8 + 7.43*OR); (**B**) minimum GCC thickness (r = 0.325, $P = 0.001$; GCC = 59.96 + 284*OR); (**C**) average RNFL thickness (r = 0.266, $P = 0.005$; average RNFL = 72.58 + 244*OR); and (**D**) RNFL thickness in the inferior quadrant (r = 0.281, $P = 0.004$; inferior quadrant RNFL = 85.86 + 467*OR).

those found for CH, CRF, and CCT, albeit usually lower than those found for Tmax. To illustrate the association between OR and some of these parameters, the Figure displays the scatter plots for OR and the rim area, the minimum GCC thickness, the average RNFL thickness, and the RNFL thickness in the inferior quadrant. After adjusting for age, sex, and ethnicity, Pearson correlation coefficients between OR and each OCT-based parameter are shown in Table 3. Rim area was also adjusted for disc area. Significant correlations were found between OR and minimum and average GCC thickness (r = 0.357, $P = 0.001$ and r = 0.344, $P = 0.001$, respectively), rim area (r = 0.327, $P = 0.001$), average RNFL thickness (r = 0.331, $P = 0.001$), and RNFL thickness in the superior (r = 0.296, $P = 0.003$) and inferior (r = 0.317,

Table 3. Partial Correlation Between OR, Rim Area, GCC, and RNFL Thicknesses in the Superior, Temporal, and Inferior Quadrants. Pearson Correlation Coefficients Adjusted for Age, Sex, and Ethnicity (and Disc Area for the Correlation With the Rim Area) and Significance Values are Shown (in bold, if $P < 0.05$)

	Correlation with OR
Neuroretinal rim area	**0.327 (0.001)**
Minimum GCC thickness	**0.357 (0.001)**
Average GCC thickness	**0.344 (0.001)**
Average RNFL thickness	**0.331 (0.001)**
Superior quadrant RNFL thickness	**0.296 (0.003)**
Temporal quadrant RNFL thickness	0.108 (0.288)
Inferior quadrant RNFL thickness	**0.317 (0.001)**

$P = 0.001$) quadrants. Because OR is correlated with AL, we also looked at the correlation between neuroretinal damage and AL in our cohort. Although AL was negatively correlated with the minimum GCC and average RNFL thicknesses (r = −0.263, $P = 0.011$ and r = −0.203, $P = 0.035$, respectively) for example, controlling for AL as a covariate in addition to age, sex, and ethnicity, still yielded significant correlations between OR and the same parameters of neuroretinal damage (r = 0.266, $P = 0.012$ and r = 0.259, $P = 0.008$, respectively).

The correlation between OR and the corneal biomechanical parameters is presented in Table 4. No multicollinearity was found among all variables. CH and CRF were positively correlated with each other (r = 0.663, $P < 0.001$), as well as with CCT (r = 0.476, $P < 0.001$ and r = 0.592, $P < 0.001$, respectively). No significant correlations were found between OR and CH (r = 0.190, $P = 0.066$), CRF (r = 0.133, $P = 0.203$), and CCT (r = 0.081, $P = 0.433$) in our cohort. After adjustment for covariates such as age, sex, ethnicity, GAT-IOP, and CCT, correlations between OR and corneal biomechanical parameters remained nonsignificant. Similarly, in subjects with OAG, no association was found between OR and CH, CRF, and CCT (r = 0.132, $P = 0.322$; r = 0.130, $P = 0.329$; and r = 0.035, $P = 0.786$, respectively), even after adjusting for age, sex, ethnicity, GAT-IOP, and CCT (r = 0.126, $P = 0.370$; r = 0.197, $P = 0.157$; and r = −0.050, $P = 0.720$, respectively).

Discussion

In this study, we found modest but positive correlations between OR and structural OCT-based parameters. This suggests that neuroretinal damage due to glaucoma, reflected by a thinner GCC or RNFL, is associated with less rigid eyes. Given the multifactorial nature of glaucoma, the modest correlations between OR and neuroretinal damage are expected. To further assess their relationship and interpret the findings adequately, correlations between OR and other risk factors for glaucoma, namely corneal biomechanical factors and Tmax, were computed. Comparison of the correlations and P values further affirm our findings and the strength of the evidence that exists in our sample for the association between OR and structural parameters of neuroretinal damage.

The strength of the correlations obtained with OR are comparable to or greater than the ones obtained with CCT, CH, and CRF, parameters that have been extensively investigated and are recognized as important risk factors for the development and progression of glaucoma.[1,24,25,30–33,45] Various studies have found associations between these parameters and optic nerve parameters, including rim area.[27,31,34,46–51] More specifically, Jonas et al.[51] found a significant correlation between CCT and the neuroretinal rim area (r = 0.13, $P < 0.001$) as measured from stereo optic disc slides in a cohort regrouping normal, OAG, and OHT eyes. Park et al.[49] showed that low CCT, CH, and CRF were associated with a smaller rim area (r = 0.256, $P = 0.012$; r = 0.347, $P = 0.001$; and r = 0.227, $P = 0.027$, respectively), as measured using the HRT (Heidelberg Retina Tomograph), in eyes with normotensive glaucoma (NTG) but not in normal eyes. After adjusting for covariates, only the association between CH and the rim area remained significant ($P = 0.012$). Wu et al.[50] showed an association between CCT and rim area in the POAG group, but not in the normal group, or both groups combined. Correspondingly, in our cohort, we found a positive correlation between CCT, CH, and CRF and the rim area. Limited evidence of a relationship between corneal biomechanical parameters and RNFL has been shown in the literature.[49,52–54] Park et al.[49] report no significant association between CCT, CH, or CRF with the mean RNFL thickness, although after adjustment, CH and RNFL were directly associated (ß = 0.013, $P = 0.043$) in NTG patients. In studies measuring RNFL using OCT, no association was found between CH and CRF, and RNFL thickness in suspect or confirmed OAG, as well as in healthy myopic eyes,[52,53] except for one study in which the relationship between CH and RNFL thickness was significant (ß = 0.2, $P = 0.001$) in OAG.[54] The results of our study did not find a significant correlation between the average RNFL thickness and CH or CRF, but did find a correlation with CCT, as shown in Table 2.

Considering that elevated IOP leads to glaucomatous damage, an inverse correlation exists between Tmax and the thickness of the structural parameters, whereas a direct correlation is found with CCT, CH, and CRF, considering that their values are lower in glaucomatous eyes compared with controls.[26–29] Subjective assessment of our correlations suggests better correlations between OR and OCT parameters than between CCT, CH, or CRF and the same parameters as seen in Table 2, although we did not test this statistically. Comparison between the correlations of OR with neuroretinal damage parameters, as well as the correlations of CCT, CH, and CRF with neuroretinal damage parameters, implies that OR is at least as important as these widely recognized corneal biomechanical parameters for glaucoma. OR is correlated with AL because elongated eyes undergo scleral changes and are known to have a thinner sclera and lower

Table 4. Relationship Between OR and Corneal Biomechanical Parameters. Pearson Correlation Coefficients and Significance Values are Shown (in bold, if $P < 0.05$)

	Pearson Correlation Coefficient	Covariates	Adjusted Pearson Correlation Coefficient
OR and CCT	0.081 (0.433)	Age, sex, ethnicity, GAT-IOP, CRF	0.059 (0.591)
OR and CH	0.190 (0.066)	Age, sex, ethnicity, GAT-IOP, CCT	0.034 (0.759)
OR and CRF	0.133 (0.203)	Age, sex, ethnicity, GAT-IOP, CCT	0.108 (0.327)

OR.[10,55–57] The correlations between OR and neuroretinal damage are thus weaker, as expected, although still significant, when controlling for AL because of the correlation between OR and AL.

Furthermore, OR and corneal biomechanical properties were not found to be correlated in this study. These results demonstrate that corneal biomechanical factors do not appear to be a surrogate for OR. This is corroborated by similar findings from a previous study showing no significant correlation between CCT and OR obtained invasively ($r = 0.22$, $P = 0.12$).[22] Another study investigating the link between OR and acute IOP elevation following intravitreal injections also found IOP spikes to be strongly correlated with OR, whereas they were not significantly associated with CCT, CH, and CRF.[58] It is speculated that corneal biomechanical parameters could reflect glaucoma susceptibility in a given eye through similar properties of the extracellular matrix of the cornea, lamina cribrosa, and peripapillary sclera. In other words, this would mean that an eye with a more deformable cornea, or low CH, CRF, and CCT, may also be more vulnerable to IOP-induced ONH damage. Several experiments were carried out to better understand the link between CH, CRF, and CCT and posterior structures of the eye in glaucoma. However, the relationship between the biomechanics of the cornea and those of the globe remains unclear. Our study further indicates that the link between corneal and global biomechanical properties is indeed limited, suggesting that OR and corneal biomechanical parameters are not redundant parameters. This finding is important in improving our understanding of the biomechanics of the front and back of the eye. In research or clinical settings this could also mean that the measurement of OR, in addition to CCT, CH, or CRF, may provide useful information pertaining to OAG.

In our study population, which includes healthy eyes and others over the glaucoma spectrum, there was a correlation between rim area and OR that was similar to that obtained with Tmax. This could be further verified by assessing the strength of correlations between OR and Bruch's membrane opening-minimum rim width in future studies, as this parameter was found to have improved diagnostic capacity for early glaucoma.[59] However, correlations with GCC and RNFL parameters were lower (although often significant) for OR than for Tmax. These parameters are usually considered to be affected earlier in glaucoma than rim area. Further studies will be required to confirm and clarify the cause of this observation.

Unlike the recorded Tmax, which is most commonly the initial untreated IOP, OR evolves over the course of the disease, and this evolution may impact the strength of our correlations. If low OR contributes to the initiation of glaucomatous damage but subsequently the sclera becomes more rigid during the course of the disease and with aging,[4,5,9,10,21,22] correlations would be hard to observe except in the earliest glaucoma patients. In this study we attempted to include only relatively early glaucoma patients as evidenced by the OCT parameters shown in Table 1, but in general we recruited few patients ($n = 9$) with visual field mean defect worse than −6 dB. Since approximately half of the ONH axons are damaged before the standard visual field is affected, it is possible that stronger correlations between OCT parameters and OR would have been found if recruitment in the glaucoma group had been limited to patients with even earlier damage. Comparatively, Tmax may reflect the highest stress imposed on the ONH during the disease history.[60] It often does not change during the course of the disease but if it does it is because it *increases*. Such episodic increases are often associated with progression, further strengthening the correlation between Tmax and parameters of damage.

Some reports suggest topical hypotensive medications may have an effect on ocular biomechanics. Prostaglandin analogs (PGAs) have been shown to induce changes in metalloproteinase activity and collagen metabolism.[61] More specifically, PGAs were shown to alter CH, CRF, and CCT.[62–65] They were also shown to increase the permeability of the sclera and to reduce its collagen content.[66,67] However, their effect on scleral stiffness and OR remains unknown, and may not be equivalent between the anterior and posterior sclera given its topical administration. In our cohort, no difference was found in OR values ($P = 0.311$) between the 51 patients treated with a PGA (OR = 0.025 ± 0.012 μL^{-1}) and the other 57 patients (OR = 0.027 ± 0.013 μL^{-1}). Similarly, earlier reports also indicate that treatment with timolol maleate (0.25%) or miotics could lead to increased OR in confirmed glaucoma cases, bringing OR values closer to those of normal eyes.[6] In our cohort, 40 subjects were treated with a β-adrenergic antagonist agent and only two with pilocarpine, six with α2-adrenergic agonists, and 28 with carbonic anhydrase inhibitors. There were no differences in OR between users and nonusers of each type of medication ($P = 0.112$; $P = 0.972$; $P = 0.979$; $P = 0.416$), respectively. These findings suggest that the use of topical hypotensive medications does not seem to be a confounding factor for OR in this study.

To our knowledge, this study shows for the first time that across the spectrum of glaucoma the rigidity of the eye is correlated with OCT-based parameters that quantify neuroretinal damage. More specifically, a more compliant eye is found to be associated with thinner GCC, RNFL, and neuroretinal rim. The literature presents seemingly contradictory results on the relationship between OR and OAG. A study by Dastiridou et al.[12] estimating OR using an invasive method involving intraoperative cannulation found no difference in OR between glaucomatous and healthy eyes, however, their subjects were a decade older than ours and had more advanced glaucoma. Inflation studies in cadaver eyes and in vivo studies showed higher OR in glaucomatous eyes, including studies by Hommer et al.[7] and Ebneter et al.[8] using noninvasive, indirect measurement methods.[9] The age and stage of subjects, as well as methodological issues, need to be accounted for when comparing these studies to ours. However, our findings are in agreement with several other studies on the association between OR and OAG that show lower OR values in glaucoma patients compared with controls.[5,6,10] For example, Drance,[5] and later Agrawal et al.,[6] found reduced OR in untreated OAG compared with healthy eyes using differential tonometry techniques. Wang et al.[10] also reported lower OR values in OAG and highest OR in OHT using choroidal laser Doppler flowmetry to estimate ΔV and compute OR. Biomechanical studies in monkeys have also demonstrated a hypercompliant deformation of the lamina cribrosa and peripapillary sclera with early experimental glaucoma,[18–20] followed by later stiffening.[20,68] It was suggested that a strain of mice, CD1, characterized by a more compliant sclera showed an increased susceptibility to RGC loss with chronic IOP elevation.[69–71] In addition, finite element models also suggest that

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a more compliant sclera is associated with increased strain at the ONH.[2,3,13]

We could speculate that the association between eyes with lower rigidity and greater neuroretinal damage may be due to increased deformation (strain) of the load-bearing tissues of the ONH and peripapillary retina in eyes with lower OR. This deformation would occur with pulsatile, diurnal, or episodic changes in IOP and would lead to axonal deformation and stretching as well as to connective tissue changes, contributing to glaucomatous optic neuropathy. Early glaucomatous damage is thought to manifest in the macular region, where over 30% of the RGCs are located,[72] as well as in the inferior peripapillary region.[73,74] Perhaps our findings, which included stronger correlations in the macular GCC and inferior RNFL, could thus signify that OR may play a greater role in the early stages of glaucoma. Our analysis is complicated by the fact that OR changes with age as the sclera becomes more rigid, but also because it is possible that glaucoma itself eventually causes the sclera to become stiffer thereby erasing the relationship to low OR found early in the disease.[4,5,9,10,21,22] To show to what degree OR contributes primarily to glaucoma and is altered by the disease process, and to establish low OR as a risk factor for OAG would require longitudinal assessment of OR at all stages of the disease, but especially in very early disease. Although further investigation is warranted to confirm the role of OR in glaucoma, and to explore its value in detecting early glaucoma, our findings provide insight into the pathophysiology of OAG.

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