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https://doi.org/10.1007/s00417-021-05212-1

GLAUCOMA

Synergic effect of corneal hysteresis and central corneal thickness in the risk of early-stage primary open-angle glaucoma progression

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Received: 2 September 2020 / Revised: 9 March 2021 / Accepted: 19 April 2021
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Abstract

Purpose To evaluate corneal hysteresis (CH), acquired with ocular response analyzer (ORA), as a risk factor for glaucoma progression in early-stage primary open-angle glaucoma (POAG).

Methods In a historical cohort study, patients diagnosed in 2011 with early-stage POAG according to the Hodapp, Parrish and Anderson classification modified for Octopus perimetry and followed up until glaucomatous progression development; otherwise, observations were censored in October 2018. Cox regression was used to obtain hazard ratios (HR) to evaluate baseline variables (CH, central corneal thickness, gender, age IOP and glaucoma family history) as risk factors for perimetric glaucoma progression. A likelihood ratio test for interaction was performed in order to assess the effect of the combination of CH and CCT on the risk of progression.

Results Of the cohort of 1573 patients, 11.38% developed early-stage POAG progression during the follow-up. The mean follow-up time was 3.28 ± 1.92 years. Patients without progression had a higher CH (11.35 ± 1.43 vs 9.07 ± 1.69 mmHg; $p < 0.001$) and CCT (570.75 ± 17.71 vs 554.51 ± 23.20; $p < 0.001$). In the multivariate analysis, each 1 mmHg of lower CH was associated with an increase of 2.13 times in the HR of progression (95% CI: 1.92–2.32; $p < 0.001$). CH hazard ratio was modified by CCT, with higher values of CCT and CH resulting in a higher HR of early glaucoma progression ($p < 0.001$).

Conclusions CH can be considered as a risk factor of progression in early-stage POAG. The risk associated with CH changed depending on CCT values, acting synergistically slowing the risk of glaucoma progression with higher values.

Key message:

- Corneal hysteresis (CH) is a risk factor for developing perimetric progression in patients with early-stage primary open angle glaucoma (POAG).
- CH play a role and can be considered as a risk factor of progression in early stage POAG, and corneal biomechanical properties should be considered together when evaluating glaucoma patients.
- It is essential to incorporate CH to evaluate the influence of corneal risk factors in clinical practice in a way to improve risk assessment in glaucoma.

Keywords Perimetry · Primary open-angle glaucoma · Progression · Corneal hysteresis · Risk factors

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Published online: 07 May 2021

Introduction

Glaucoma is an optic neuropathy defined by progressive degeneration of retinal ganglion cells and their axons which constitute the optic nerve head (ONH). The disease is characterized by progressive ONH damage associated with functional losses over time, but the rate of deterioration can be markedly variable amongst patients [1]. In the last decade, increasing attention has been focused on the impact of corneal features, particularly central corneal thickness (CCT) and biomechanical properties, such as corneal hysteresis (CH) and corneal resistant factor (CRF) because they may affect not only the accuracy of IOP measurements but also the glaucoma risk management [2]. Corneal tissue, as a biological material, exhibits inherent viscoelastic properties, which are characterized by a nonlinear stress-versus-strain response with gradual stiffening at higher strains [3]. Viscoelastic systems are often identified by hysteresis, and CH as measured by the ocular response analyzer (ORA) reflects the ability of corneal tissue to absorb and dissipate energy in response to a transient deformation of the cornea [4]. An eye with a lower CH correlates to a more stiffened cornea and is supposed to be more susceptible to glaucoma damage from raised IOP [6–8].

Ocular response analyzer (ORA) is based on non-contact tonometry and determines corneal biomechanical properties accurately and reproducibly using an applied force–displacement relationship [5]. A short-duration air pulse is directed to the cornea and produces a measurable corneal deformation (in the form of corneal applanation) while some energy is lost as heat during the rapid loading/unloading of the cornea. CH is calculated as the difference in internal air pulse pressures between force-in applanation and force out.

There have been multiple studies that have found CH to be lower in glaucomatous compared to healthy eyes [9, 10], and patients with lower CH have been identified to be at higher risk of progressive visual field loss [2, 10–12]. Although those studies have provided strong evidence for the role of CH in predicting progression, they have focused on different groups of glaucoma or glaucoma suspects and have not targeted the impact of CH on the risk of early-POAG progression. There have been conflicting reporting on the association between corneal biomechanical properties and glaucoma severity by visual field damage [13, 14] so it is possible that CH, being a glaucoma progression predictor, can carry different weight in early-stage POAG than when predicting conversion, further disease damage or when studied in different glaucoma types.

The purpose of the present study was to measure and evaluate corneal hysteresis as an anatomic independent risk factor for glaucoma progression in a set of patients diagnosed with early-stage primary open-angle glaucoma (POAG).

Methods

Population source

This retrospective (historical) cohort study was approved by the Institutional Review Board at the Hospital Clínico San Carlos, and informed consent to access their clinical records was obtained from all patients. The research was carried out in accordance with the principles of the Helsinki Declaration for medical research involving human subjects.

This study was carried on a cohort of patients diagnosed with early-stage POAG who were recruited from the Glaucoma Department of Hospital Clinico San Carlos from January 2011 to the development of progression or to October of 2018 when the observations were censored in case the event had not developed during the follow-up. These subjects were followed every 4 months, and if their follow-up was lost, their observations were censored at the last visit time.

At each visit during the 94 months of follow-up, the patients underwent a comprehensive ophthalmological examination including IOP measured with Goldmann applanation tonometry (GAT; Haag-Streit, Konig, Switzerland), Octopus TOP perimetry (Haag-Streit, Konig, Switzerland) and spectral-domain OCT peripapillary retinal nerve fibre layer assessment (Software version 5.4.7.0, Heidelberg Engineering, Dossenheim, Germany). All patients had central corneal thickness (CCT) measurements obtained using pupil-centred optical pachymetry with Pentacam (Oculus GmbH, Wetzlar, Germany). Corneal hysteresis (CH) was determined using the ocular response analyzer (ORA, Reichert Instruments, Depew, NY, USA).

Patient selection

Data were collected from the patients' medical records and, in particular, information regarding their ocular history. The data collected at baseline (January 2011) included basic demographics, such as age, gender or race, prior medical history, topical eye treatments, concomitant ocular eye diseases, complications related to the treatment, best-corrected visual acuity and family history of glaucoma (dichotomous: first-degree relative suffering from POAG or not). Subjects included in the study had a well-established diagnosis of early-stage POAG so all of them were under medical glaucoma treatment. The type of glaucoma medication was registered and categorized accordingly in the following groups: β-blockers, prostaglandin (PG) analogues, carbonic anhydrase inhibitors (CAI), α-agonists, combination of β-blockers with prostaglandin analogues, combination of β-blockers with carbonic anhydrase inhibitors and combination of β-blockers with α-agonists.

Non-inclusion criteria (only one criterion necessary for non-inclusion) were best-corrected visual acuity less than 20/25, astigmatism higher than ± 1.5 diopters (D), mean spherical equivalent higher ± 5 D, media opacities impairing optic nerve head visualization or variations in optic nerve head morphology, such as oblique discs or peripapillary atrophy. Patients with prior eye surgery or any other ocular or systemic disease that could affect the optic nerve or the visual fields were automatically excluded. Only subjects with open angles on gonioscopy were considered to be included. Any other type of glaucoma different from POAG was also an exclusion criterion. Patients who refused to comply with the follow-up visits or with non-controlled IOP were also excluded.

If both eyes of a single patient met the inclusion and non-inclusion criteria, only one eye per individual was chosen to be included because ocular variables could not be independent due to within-subject correlation. If both eyes fulfilled the inclusion and exclusion criteria, the eye to be analyzed was determined according to an automatic procedure www.randomization.com.

Main outcome measurement

The early-stage POAG progression was defined according to the Hodapp, Parrish and Anderson classification [14], modified for Octopus perimetry [15].

The presence of progression was stated if one of the following criteria were present in one visual field and confirmed on three consecutive further tests: (1) development of at least 3 non-edged points with depression of ≥ 5 dB or one non-edged point with depression ≥ 10 dB in a previously normal area; (2) development of a cluster of 3 or more non-edged points with ≥ 10 dB worsening in the area of a pre-existing scotoma; (3) development of a cluster of 3 or more previously normal points depressed by ≥ 10 dB within 15 degrees of a previously existing scotoma; (4) worsening of MD by ≥ 2 dB/year.

Standard automatic perimetry

Standard automatic perimetry (SAP) visual fields were performed using the Octopus TOP G1 perimetry. All the visual fields with more than 33% fixation losses or false-negative errors or more than 15% false-positive errors were excluded. Visual fields were further reviewed for the following artefacts: lid and rim artefacts, fatigue effects, inappropriate fixation and evidence that the visual field results were due to a disease other than glaucoma. TOP strategy tests each point only once, but each point is affected by the responses of the surrounding points to reach the final threshold approximation. The program uses a mathematical algorithm to investigate the threshold through consecutive approximation, examining four intermingled grids. TOP requires 80% less presentation of stimuli than the standard strategy [16].

Corneal hysteresis measurement

CH measurements were acquired at the baseline using the ORA. A trained technician obtained three measurements for each eye, and the average of the measurements per eye was considered for analysis. The ORA determines corneal biomechanical properties using an applied force–displacement relationship [4]. During an ORA measurement, a precisely metered air pulse is delivered to the eye and, as the cornea moves inward and outward in response to the increasing and decreasing velocity of the air jet, its deformation is tracked by an electro-optical system. The two applanations take place within approximately 20 ms, a time sufficiently short to ensure eye position does not change during the measurement process. From these data, the pressure at which the cornea flattens inward (P1) and outward (P2) as the pressure rises and falls is derived. The average between P1 and P2 provides a Goldmann-correlated IOP value referred to as IOPg. The difference between P1 and P2 is the corneal hysteresis (CH), measured in mmHg, and is related to the viscous damping property of the cornea [17].

The device provides a waveform score to reflect the quality of the measurements. Only measurements associated with a waveform score higher than four were considered as apt for inclusion in the study.

Statistical analysis

Quantitative baseline characteristics (age, IOP, CH and CCT) have been presented as means and standard deviation (SD), and student *t*-test for independent samples was used to determine if significant statistical differences were present at baseline between the progressor group and non-progressors. Qualitative data (glaucoma family history and gender) and their differences between the two groups were analyzed through the χ^2 test. A *p*-value of less than 0.05 was considered statistically significant.

Initially, early-stage POAG progression rate was estimated, and Kaplan–Meier plots, depicting the cumulative probability of developing glaucoma over time, when considering a dichotomous status of CH (above or below its median), were provided and Mantel-Cox (log-rank test) was used to compare the cumulative probability of both curves.

The effect of baseline variables (IOP, age, gender, CH, CCT, type of glaucoma medication and family history of glaucoma) in the risk of progression of the disease was estimated by several univariate Cox proportional hazards regression models (one per each baseline variable).

After that, and factoring the results obtained in the univariate model that have been proved to influence glaucoma progression in multiple studies, a multivariate Cox proportional hazards model was constructed in order to obtain adjusted measures of association. The interaction between CH and CCT was ascertained through the likelihood ratio test. For quantitative covariates, a linear trend was also assessed.

Sample size calculation

We determined the sample size in order to provide 90% to detect a HR (for CH ≥ 1.20 [11] or ≤ 1/1.20), presuming a probability for progression of 5% [18], a standard deviation for the main explanatory variable (CH) of 2.3 mmHg [19] and potential losses of follow-up of 20%. The alpha level (type I error) was set at 0.05.

Statistical analyses were carried out using version 14 of the commercially available software Stata (StataCorp LP, College Station, Texas, USA).

Results

In order to comply with the sample size calculations requirements, 1494 subjects needed to be included in the study. Ultimately, a cohort of 1573 patients diagnosed with early-stage POAG in 2011 was incorporated in this historical cohort study. Mean follow-up time was 3.28 years (standard deviation (SD): 1.92 years), being 3.36 years (SD: 1.93) in the progressor group and 2.47 years (SD: 1.58) in the non-progressors. All the participants in this study were Caucasian. 11.38% of the patients developed early glaucoma progression during the follow-up, and the overall early-stage progression rate was 43.36 per 1000 person-years (95% CI: 36.65–51.30). The baseline characteristics of the patients according to the event status are depicted in Table 1. There was no statistically significant difference in sex between the progressors (55.87% were men) and non-progressors (49.14% χ^2; $p = 0.090$) and those who had early-stage glaucoma progression had a higher prevalence of glaucoma family history (17.07% vs 10.32%; $p = 0.002$). All the subjects included in this study were diagnosed with early-stage POAG and were under topical medical treatment. There was no statistically significant difference ($P > 0.05$) between progressors and non-progressors when topical medication was considered (ß-blockers: 16.5% vs 16.20%; PG analogues 16.86% vs 13.97%; CAI: 15.78% vs 11.17%; α-agonists: 11.98% vs 10.61%; ß-blocker and PG analogue; 14.35% vs 18.44%; ß-blocker and CAI: 13.99% vs 18.99% and ß-blocker and α-agonist 10.55%vs 10.61%).

The baseline correlation between IOP and corneal characteristics in the group of subjects that experienced progression during the follow-up and those who did not is disclosed in Table 2.

Figure 1 shows the cumulative probability of developing glaucoma progression in eyes when CH is over or below 11.21 mmHg, the median of all the patients included in this cohort. When categorizing the patients by the CH median, there were statistically significant differences between the curves (Mantel-Cox test; $p < 0.001$).

Table 3 presents HRs with a 95% confidence interval (CI) for univariate and multivariate models of risk factors associated with glaucoma progression. A likelihood ratio test demonstrated an interaction between CH and CCT in the risk of glaucoma progression ($p = 0.001$). Table 4 presents the hazard ratios with a 95% confidence interval for early glaucoma progression and the final Cox regression model accounting for the interaction between these two variables. The final equation representing the hazard ratio of glaucoma progression in early-stage POAG would be represented as:

$$HR = 1.01^{age} \times 1.41^{family\ history} \times 73.52^{CH} \times 1.05^{CCT} \times 0.99^{CH \times CCT}$$

Being, age as age in years, family history 1 as positive, 0 as negative, CH in mmHg and CCT in microns.

The effect of CH on the risk of early-stage glaucoma progression according to different CCT values and adjusting for glaucoma family history, IOP, gender and age is described in Table 5.

Discussion

In this study of patients with early-stage POAG, eyes with 1 mmHg lower baseline CH had twice the probability of developing glaucomatous visual field progression (HR:

Table 1 Baseline characteristics of patients with and without early glaucoma progression

Characteristic	Patients with POAG progression ($N = 179$)	Patients without POAG Progression ($N = 1394$)	Mean difference (95%CI)	P-value‡
Age mean years ± SD	65.31 ± 15.26	64.56 ± 15.45	−0.75 (−3.15–1.65)	0.540
CH mean mmHg ± SD	9.07 ± 1.69	11.35 ± 1.43	2.28 (2.05–2.51)	< 0.001
CCT mean µm ± SD	554.51 ± 23.20	570.75 ± 17.71	16.24 (13.37–19–10)	< 0.001
IOP mean mmHg ± SD	16.00 ± 2.04	15.99 ± 0.98	−0.01 (−0.31–0.30)	0.958
Follow-up time mean years ± SD	2.47 ± 1.58	3.36 ± 1.93	0.89 (0.56–1.23)	< 0.001

‡Determined using student *t* test; *CH*, corneal hysteresis; *CCT*, central corneal thickness; *IOP*, intraocular pressure; *SD*, standard deviation

Table 2 Correlation between intraocular pressure and corneal characteristics at baseline

	Patients with POAG progression ($N=179$)		Patients without POAG progression ($N=1394$)	
	Pearson correlation coefficient	*P*-value	Pearson correlation coefficient	*P*-value
IOP-CCT	−0.216	0.004	0.022	0.406
IOP-CH	0.057	0.449	0.016	0.545
CH-CCT	−0.207	< 0.001	−0.104	< 0.001

CH, corneal hysteresis; *CCT*, central corneal thickness; *IOP*, intraocular pressure

2.08; 95% CI: 1.92–2.27; $p < 0.001$). This relationship was present even in the multivariate model adjusting for other factors, such as age, gender, IOP, family history and CCT (HR: 2.12; 95% CI: 1.75–2.32, $p < 0.001$). However, in our historical cohort, the risk of progression associated with lower CH could not be separated from the one related to CCT; in a way that in this cohort of patients with early-stage POAG, higher CH and CCT were significantly associated with a lower risk of progression, and CCT modified the effect of CH in the risk of early glaucoma progression ($p = 0.001$). Our results indicate that a combination of high CCT and CH can be particularly beneficial in terms of glaucomatous progression. Consequently, even if CH was a risk factor for glaucoma progression, in our population, the risk associated with CH changed depending on CCT values, acting synergistically slowing the risk of glaucoma progression with higher values.

To the best of our knowledge, this is the first study to evaluate the role of corneal hysteresis as a risk factor for the development of perimetric progression in a homogeneous group of patients with early-stage POAG. Our findings support the existing evidence that the evaluation CH with CCT may add significant value to the assessment of the risk disease progression in glaucoma patients and that the same CH according to lower CCT values reflects an eye that is more susceptible to glaucomatous damage.

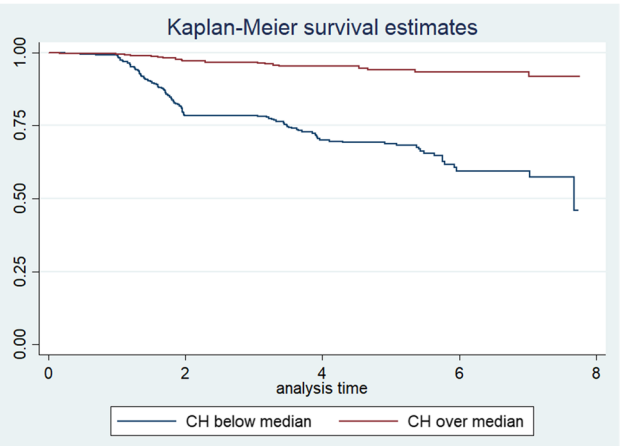

Fig. 1 Cumulative probabilities of glaucoma progression in early-stage POAG eyes with CH over that 11.21 and lower than 11.21

Other studies have demonstrated low CH values to be associated with glaucoma progression in glaucoma suspects and patients with established disease. However, when evaluating glaucoma progression, patients with different glaucoma types, such as pseudoexfoliation, have a faster progression rate and lower corneal hysteresis [20–23]. Moreover, there is no consensus on the association between corneal mechanical parameters, namely CH and CRF, and glaucoma severity [18, 24].

Corneal hysteresis (CH) is significantly lower in POAG patients than in ocular hypertension (OHT), glaucoma suspects and healthy controls, in whom it was maximum [8, 25]. In a retrospective study, De Moraes and associates [9] found a significant correlation between lower CH values and faster glaucomatous progression rates and inferred that although both corneal biomechanical (corneal hysteresis) and physical (CCT) properties are correlated with glaucoma progression, corneal hysteresis may have a stronger effect.

Medeiros et al. [10] conducted a prospective cohort study to determine if baseline corneal hysteresis was a predictive factor of visual field index (VFI) decline in glaucoma patients. They concluded that although CCT was associated with the rate of visual field loss, corneal hysteresis explained three times as much of the variation in slopes of VFI change than CCT; eyes with lower hysteresis had faster rates of visual field loss than those with higher hysteresis. Susanna and colleagues [11] demonstrated that lower CH measures could be related to an increased risk of developing glaucomatous visual field defects over time in patients with glaucoma suspicion, where 1 mmHg lower CH was associated with an increase of 21% in the risk of developing glaucoma during the follow-up.

The impact of corneal hysteresis in glaucoma progression has been reported as not significant in several publications after multivariate analyses [2, 26] so it is essential to consider whether residual confounding factors, including age, race sex, family history or IOP, can affect the results. In this study, all the patients were Caucasian (in order to avoid controversial reports on the effect of ethnicity [27, 28]), and the association remained, following a statistical adjustment for age, gender IOP and CCT in the multivariate analysis. It is also unlikely that tonometry error contributed to the association of CH and progression in our sample, as participants

Table 3 Hazard ratios with 95% confidence intervals for risk factors associated with early glaucoma progression

	Univariate model			Multivariate model*		
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	*P* value	*P* value (trend)
Sex (male)	1.24 (0.88–1.75)	0.204	n/a	1.32 (0.94–1.86)	0.108	n/a
Age (per 1 year older)	1.00 (0.99–1.02)	0.467	0.634	1.01 (0.99–1.02)	0.201	0.140
Family history (positive)	1.82 (1.22–2.71)	0.004	n/a	1.36 (0.89–2.10)	0.153	n/a
CH (per 1 mmHg lower)	2.08 (1.92–2.27)	< 0.001	< 0.001	2.13 (1.92–2.32)	< 0.001	< 0.001
CCT (per 1 µm thinner)	1.04 (1.03–1.05)	< 0.001	< 0.001	1.04 (1.03–1.05)	< 0.001	< 0.001
IOP (per 1 mmHg higher)	0.98 (0.84–1.37)	0.784	0.944	0.98 (0.93–1.03)	0.434	0.237
Medical treatment‡						
PG analogue	1.23 (0.66–2.32)	0.508	n/a	0.7 (0.36–1.33)	0.276	n/a
CAI	0.85 (0.44–1.63)	0.622	n/a	0.88 (0.45–1.46)	0.694	n/a
Alpha-agonist	1.2 (0.66–2.19)	0.555	n/a	0.77 (0.41–1.46)	0.43	n/a
Beta-blocker & PG analogue	1.01 (0.54–1.88)	0.974	n/a	1.02 (0.54–1.91)	0.961	n/a
Beta-blocker & CAI	0.83 (0.41–1.65)	0.588	n/a	0.67 (0.33–1.36)	0.264	n/a
Beta-blocker & alpha-agonist	0.18 (0.63–2.19)	0.609	n/a	0.88 (0.46–1.67)	0.695	n/a

CCT, central corneal thickness; *CH*, corneal hysteresis; *CI*, confidence interval; *HR*, hazard ratio; *PG*, prostaglandin; *CAI*, carbonic anhydrase inhibitor

*Multivariate model, adjusted for all predictive (risk) factors

‡Beta-blocker as the reference category for medical treatment

were not selected by IOP, and uncontrolled levels of IOP were an exclusion criterion of the study.

Our approach considered that POAG progression rates could be heterogeneous along the disease severity spectrum and could be different between different glaucoma types, hence the restriction to the early-stage [29] and primary open-angle glaucoma, and our results demonstrated that CH is a risk factor for glaucoma progression in the early stages of the disease.

Although it is not entirely clear what corneal hysteresis measures, it does appear that this variable describes the response of the cornea to rapid deformation, but it is still unknown why CH can be associated with the risk of glaucoma development and progression. Corneal hysteresis does not seem to modify IOP as much as central corneal thickness does so it seems unlikely that the predictive effect of CH would be related to artefacts or changes related to IOP measurements [4, 8]. Controversial theories about why a low CH might be related to the risk of visual field decay have been stated.

In a recently published study, Lee found an association between lower CH and lamina cribrosa curvature [19]; besides, they found that the LCCI was positively correlated with IOPCc and inversely correlated with CRF. The association of these findings could be explained as, although they have a different embryological origin, the collagen in the cornea and sclera may have similar material property. Nevertheless, limited evidence exists supporting the correlation between CH and structural changes of the wall and optic nerve head [7, 30].

Table 4 Hazard ratios with 95% confidence interval for early glaucoma progression

	HR (95%CI)	*P* value
Age	1.01 (0.99–1.02)	0.06
Glaucoma family history	1.44 (0.95–2.19)	0.089
CH†	74.57 (6.17–900.07)	< 0.001
CCT‡	1.04 (1.00–1.09)	0.04
CH-CCT[f]	0.99 (0.98–0.99)	< 0.001
Gender	1.45 (0.99–2.05)	0.55
IOP	0.98 (0.93–1.03)	0.454

HR, hazard ratio; *CI*: confidence interval; *CH*, corneal hysteresis; *CCT*, central corneal thickness

[f]CH-CCT, interaction of CH and CCT

†Hazard ratio of CH for early glaucoma progression when CCT value is 0

‡Hazard ratio of CCT for early glaucoma progression when CH value is 0

Table 5 Effect of central corneal thickness in corneal hysteresis HR of early-POAG progression when central corneal thickness is categorized in 50-µm intervals from 450 to 650 µm

CCT	HR (95%CI)	*P* value
450	1.23 (0.76–1.99)	0.392
500	0.78 (0.60–1.02)	0.075
550	0.49 (0.45–0.55)	< 0.001
600	0.32 (0.25–0.39)	< 0.001
650	0.20 (0.13–0.31)	< 0.001

CCT, central corneal thickness (in microns); *CH*, corneal hysteresis; *HR*, hazard ratio; *CI*, confidence interval

It has also been speculated that the corneal deformation induced by ORA displaces fluid in the anterior chamber so eyes with a higher corneal hysteresis as measured by ORA could diminish the spikes of IOP due to the biomechanical characteristics of the globe [31]. In eyes with low CH, the reduced capability of displacement and dampening effect could increase the strain in the LC and promote glaucomatous damage, as they are likely to have larger transient fluctuations and can have potential damaging results [6, 32, 33]. However, it is still unclear why CH might be related to the risk of glaucoma progression, and all these notions remain merely speculative.

The exact significance of corneal biomechanical properties, as measured with ORA, is unknown, and there are no exact formulas to calculate its relationship with GAT-IOP, CCT or glaucomatous progression [34]. The cornea exhibits viscoelastic properties owing to the large content of stromal water and the flexibility of interfibrillar spacing and exhibits planar variations in biomechanical responses due to varying orientations [35]. CH is a variable that describes the damping response of the cornea to rapid deformation, and it would be expected that more corneal stiffness would be present in patients with higher CCT measurements [36]. Even more, it seems to represent the aggregated effects of corneal thickness, rigidity, hydration and other non-defined factors [37]. There is no doubt that IOP is the main risk factor for glaucoma progression, but corneal properties, such as CCT and CH, can influence and be influenced by IOP measurements and have to be acknowledged in the decision tree of glaucoma diagnosis and management.

The present study must be considered in the set of its limitations. Its results can only be extrapolated to Caucasian patients showing POAG in its early stage (according to the Bascon-Palmer Glaucoma Score System for Octopus perimetry) so further studies would be necessary to understand the impact of CH in different ethnic groups. Besides, we included only baseline values for the covariates included in the multivariate model. As the CH can vary with glaucoma treatment [38] and surgery [39], it is possible that longitudinal information from these variables would show different results.

Being a historical cohort study, it is more difficult to assess the temporal relationship between the variables to disease outcome; however, given the sample size of this study, it has enough power to assess the value of CH as a predictive factor for glaucoma progression in early-stage primary open glaucoma.

Besides, this study has the advantage of including a large sample, enough to ascertain the development of the outcome with 90% power. The design of the study has also eliminated the possible confounding factors associated with different glaucoma types and ethnicity.

In conclusion, our study suggests that lower CH measurements could be considered a risk factor for early-POAG progression. It enhances the conception that corneal biomechanical properties are of great importance in the field of glaucoma, and both corneal hysteresis and central corneal thickness can account for a high risk of progression of the disease and should be evaluated together when evaluating the risk of progression. Also, it shows that it is essential to incorporate CH to evaluate the influence of corneal risk factors in clinical practice in a way to improve risk assessment in glaucoma. As mentioned before, further studies should be performed to assess the reproducibility of our findings amongst other ethnic groups and glaucoma types and stages.

Data availability Although we have not included it in our submission, the data is available for reviewers to check.

Code availability Not applicable.

Declarations

Ethics approval A cohort study was approved by the Institutional Review Board at the Hospital Clínico San Carlos, and informed consent to access and publication of their clinical records and data selected from it were obtained from all patients. The research was carried out in accordance with the principles of the Helsinki Declaration for medical research involving human subjects.

Conflict of interest Jimenez, M.: travel reimbursements and speaker fees by Allergan plc, Novartis. Sáenz-Francés, F.: travel reimbursements by Thea, Bausch and Lomb Inc, Allergan plc, consulting fees by Santen. Martínez-de-la-Casa, J.M.: travel reimbursements and speaker fees: Glaukos Corp, Allergan plc, Bausch and Lomb Inc, Zeiss AG, Esteve, Thea, consulting fees by Santen. García Feijóo, J.: travel reimbursements and speaker fees by Zeiss A.G., Heidelberg AG, Novartis AG, Glaukos Inc, Santen. Jáñez-Escalada, L. and Sánchez-Jean, R. declare no conflict of interest.

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