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On the Relationship between Corneal Biomechanics, Macrostructure and Optical Properties

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Abstract: Optical properties of the cornea are responsible for correct vision, ultrastructure allows optical transparency and biomechanical properties governs the shape, elasticity or stiffness of the cornea affecting ocular integrity and intraocular pressure. Therefore, optical aberrations, corneal transparency, structure and biomechanics play a fundamental role in the optical quality of human vision, ocular health and refractive surgery outcomes. However, the convergence of those properties is not yet reported at macroscopic scale within the hierarchical structure of the cornea. This work explores the relationships between biomechanics, structure and optical properties (corneal aberrations and optical density) at macrostructural level of the cornea through dual Placido-Scheimpflug imaging and air-puff tonometry systems in a healthy young adult population. Results showed convergence between optical transparency, corneal macrostructure and biomechanics.

Keywords: Corneal Biomechanics; Corneal structure; Corneal Aberrations; Optical Density; Scheimpflug imaging; Ocular Response Analyzer.

1. Introduction

Corneal biomechanics is a branch of biomedical sciences which deals with the analysis of the stability of the tissue when an external load or pressure is applied [1, 2], or when the intraocular pressure fluctuates. Besides, biomechanical properties of the cornea are responsible of its shape and integrity, acting as unique convergence point between balanced ductility to preserve aspherical geometry (and correct ocular refraction), stiffness to compensate the intraocular pressure and ultra-structure that allows optical transparency. Biomechanical properties of the cornea can be affected by systemic diseases such as diabetes [3, 4] or sclerosis [5, 6]. In particular, corneal keratoconus may compromise the biomechanical stability modifying the micro-structure [7], weakening mechanical strength [8] and lead to corneal protrusion [9, 10], inducing optical aberrations [11, 12] that reduce the quality of vision or lead to transplants in advanced stages. The clinical relevance of the study of corneal biomechanics reached special interest with the development of refractive surgery techniques to modify the optical power of the cornea by laser ablation [13] or lenticular extraction [14]. These techniques consist of modifying the lamellar structure of cornea causing redistribution of mechanical stress. The biomechanical response is expected to provide the correct corneal curvature [15] and together with optical transparency, normal vision.

On the other hand, corneal transparency has been explained from the hierarchical structure of the cornea. At molecular scale, X-ray scattering revealed how the collagen ultrastructure

within the stroma is responsible for the tridimensional microstructure and consequently for the macroscopic geometry and biomechanics [16].

To date, the maximum level of structural hierarchy reported in living human eyes has been the microscopic scale using two-photon scanning microscopy [17]. However, only confocal microscopes are currently clinically available and although they allow visualization of the cellular matrix, they are invisible for the stromal architecture [18]. In this sense, Scheimpflug imaging provides excellent tomographic measurements of the macrostructure of the cornea as well as optical density (transparency) [19], widely reported in anterior segment analysis for the assessment of normal and keratoconus or ectatic corneas [20] or refractive surgery [21]. Corneal biomechanics is usually assessed employing air-puff tonometry [22], also the combination of Scheimpflug imaging and air-puff tonometry has been successfully integrated bringing excellent results in dynamic assessment of corneal biomechanics [23].

As stated, the molecular organization of the corneal stroma controls the optical transparency, macroscopic shape and structural stability (biomechanics) [16]. In this work we will investigate if the relationship between corneal transparency and optical properties, geometry and biomechanics is preserved at the macroscopic level of the hierarchical structure. Biomechanical properties, corneal geometry and optical properties and densitometry measurements were collected from 102 eyes of 51 young-adult healthy subjects using Scheimpflug imaging and air-puff tonometry.

This work focuses on the convergence of corneal biomechanics, optical and structural properties to bring a comprehensive macroscale characterization of the cornea that can also provide future predictive models of corneal biomechanics.

2. Materials and Methods

2.1. Participants

This research was reviewed by an independent Ethical Committee of Research of the Health Sciences Institute of Aragon (Spain) approved with reference: C.P.-C.I.PI20/377. Measurements procedure and data collection were carried out according to the tenets of the Declaration of Helsinki. All participants were informed about the nature, risks and possible adverse consequences of the study and signed an informed consent document. The ethnicity of the participants involved in this study was European Caucasian, all of them students from the School of Optics and Optometry of the University of Zaragoza (Spain). 102 eyes from 51 healthy young subjects (mean age 24 ± 5) were analyzed using dual Placido-Scheimpflug imaging and air-puff tonometry systems. None of them presented ocular pathologies, corneal disorders or abnormal intraocular pressure.

2.2. Experimental measurements

Clinical measurements were carried out at the laboratory of Optometry of the Department of Applied Physics of the University of Zaragoza and conducted by an experienced clinical optometrist. Both eyes of all participants were analyzed in sequential procedure: First optical and geometrical properties (see Table 1) were acquired by dual Scheimpflug-Placido disk imaging system and next corneal biomechanics was assessed using an air-puff tonometer device.

2.2.1. Dual Placido-Scheimpflug imaging: Structural and optical parameters

Galilei Dual Scheimpflug Analyzer (Ziemer Ophthalmic Systems AG, Port, Switzerland) is a clinical optical system that combines Placido Disk imaging and a revolving Scheimpflug camera providing simultaneous acquisition of corneal topography based on the internal and external surfaces including eccentricity, astigmatism, pachymetry (measures of central middle and peripheral cornea), three dimensional analysis of the cornea, power measures, wavefront aberration and optical densitometry [24]. Fig.1 shows an example of wavefront aberration mapping and anterior segment Scheimpflug image from a participant of our study. Table 1 summarizes those Galilei outputs selected for data analysis.

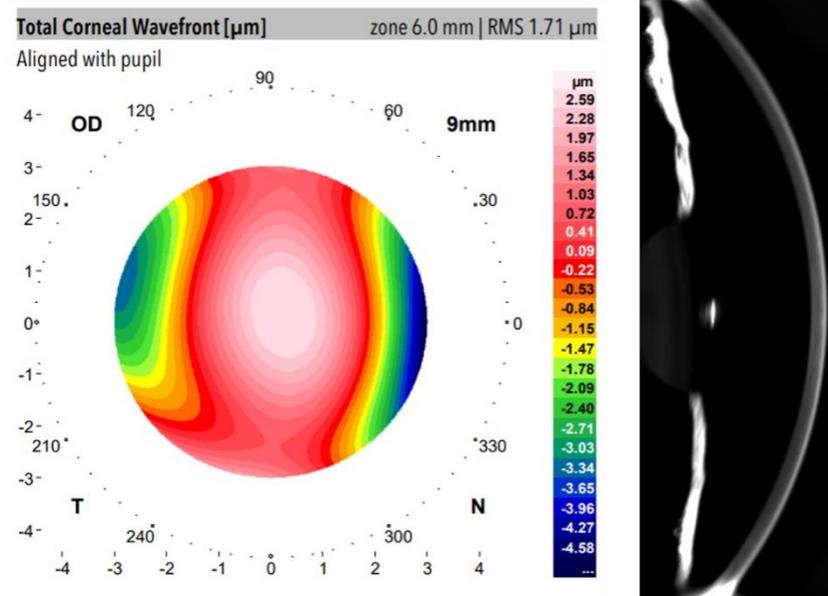


Figure 1. Total Corneal wave-front aberration map (left) and anterior segment Scheimpflug image (right) from a volunteer of the study.

Table 1. Structural and optical parameters from the Galilei system considered of interest in our study. Total and spherical aberration wavefront were numerically evaluated by its root mean square (RMS) value.

Structural Parameters	Optical parameters
Central Thickness	Total Aberration RMS
Middle Thickness	Spherical Aberration RMS
Peripheral Thickness	
Anterior Eccentricity	Optical Density
Posterior Eccentricity	
Total Corneal Astigmatism	

Galilei device does not provide a direct quantification of optical transparency of the corneal tissue, but optical density (OD) measurements expressed in standardized gray-scale units. Scheimpflug cameras cannot image through opaque tissues such as the sclera,

that is totally opaque due to irregular arrangement of collagen fibrils [16]. Nevertheless, towards the periphery of the iridocorneal angle in Scheimpflug images a reference gray-level from the sclera can be obtained from the Galilei outputs. In this work, the Optical Transparency Index (OTI) is defined as:

$$OTI = 100 \times \left[\frac{1}{OD_{Sclera}} (OD_{Sclera} - OD_{Cornea}) \right] (1)$$

OTI index ranges between 0 (total opacity) and 100 (absence of back-scattering light). The maximum value implies total corneal transmittance for the illumination wavelength underlying the understanding of corneal transparency. In that sense, OTI parameter is an equivalent quantification of corneal transparency calculated from densitometry measurements at Galilei dual system.

2.2.2. Corneal biomechanics assessment

Ocular Response Analyzer (ORA, Reichert Instruments, Depew, NY, USA) was employed to obtain measurements of corneal biomechanics. ORA is a non-invasive device based on air puff applanation tonometry that measures intraocular pressure and corneal biomechanics, in particular corneal hysteresis (CH) and corneal resistance factor (CRF) parameters. Briefly, the corneal hysteresis can be defined as the energy dissipation when an external stress is applied resulting in a time-dependent stain unlike purely elastic materials, that immediately recover the initial state once the stress stops. Thus, CH is a function of the corneal viscoelastic behavior and CRF is related to the elastic properties of the cornea[25].

CRF and CH are computed by quantifying the differential inward and outward corneal responses to an air pulse (see Fig.1) of approximately 24 milliseconds [26]. Once the first applanation is reached, the air pressure causes the cornea to move inward to a slight concavity that back to a second applanation before recovering the natural shape.

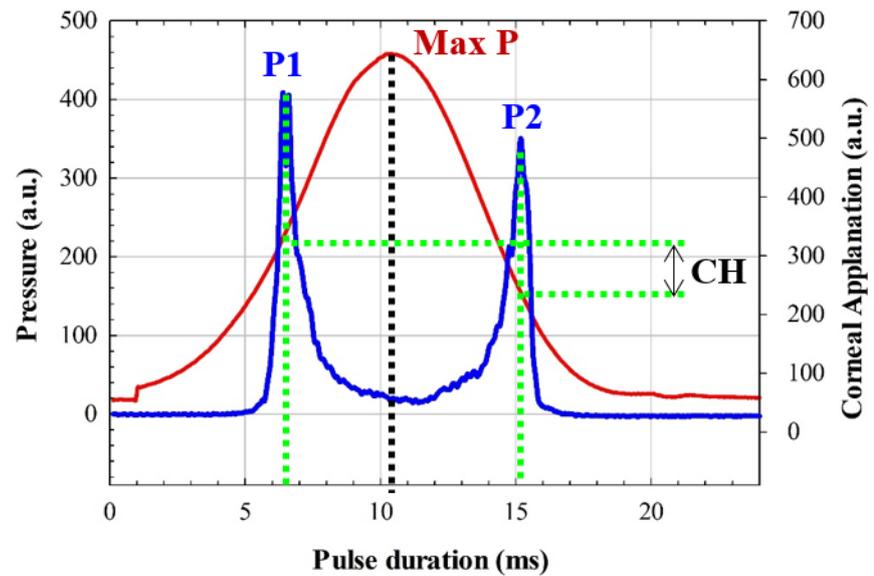


Figure 2. ORA measurement from a participant in our study. P1, P2, Max P and CH corresponds to first and second applanation, maximum pressure and corneal hysteresis, respectively.

Fig. 2 shows an ORA measure from a participant of our study. From pressures P1 and P2 (corresponding to the first and second applanation pressures, respectively), CH and CRF are calculated as [27]:

$$CH = P1 - P2 \quad (1)$$

$$CRF = (P1 - 0.70 * P2) - 3.08 \quad (2)$$

From an elastodynamic point of view, the first applanation is given when the air pulse compensates for the intraocular and atmospheric pressures. The stress-strain response of the cornea undergoes elastic deformation whereas the second applanation pressure is affected by energy dissipation, that is, P1 can be related to the pure elastic properties of the cornea whereas P2 is used for viscoelasticity estimation. For instance, a pure elastic cornea will provide null CH value and symmetrical pressure curve (see Fig. 2) during an ORA measurement, which implies applanation pressures equalization condition, $P1 = P2$. In that sense, a stiffness parameter has been reported as the ratio between resultant pressure at the first applanation and the deflection amplitude [28]. In this study equations (1) and (2) were employed to calculate P1 and P2 from ORA outputs (CRF and CH).

2.2.3. Data analysis

This study involved healthy young subjects who in absence of corneal straylight sources, will present oscillations in optical density around normal referenced values and hence good data visualization motivated group clustering for data mining. OTI values were cluster sampled in the range $OTI = [78.5, 81.5]$ with 0.5 cluster width.

Collected data were stored into an Excel spreadsheet and migrated to Origin Lab software (Origin Lab Corp.) for graphical representations.

Statistical analysis consisted of Spearman Rank Correlation Coefficient in order to establish or discard significant relationship between geometrical and optical parameters. Limits of agreement were used to quantify the agreement between those parameters.

Statistics was performed using the advanced statistical tool of Origin Lab software.

3. Results

This section shows results of our study that are structured in the analysis of the relationship between optical density of the cornea and three main factors: optical aberrations, biomechanics and macroscopic geometry of the cornea.

3.1. Optical Density and Corneal Aberrations

Fig. 1 showed an example of the total aberration wavefront map and Scheimpflug image from a participant measured with dual Galilei imaging system. Total and spherical aberration RMS and OTI average values (mean of 102 eyes measurements) are shown in Table 2. Since spherical aberration is the dominant high-order term at the cornea [29], it was evaluated apart from the total aberration RMS values. The statistical analysis revealed no correlation between optical aberrations (neither total nor spherical term) and OTI values of the cornea. Whereas aberrations govern the correct focus of light and retinal image quality [30], it seems not to affect the transparency of the cornea.

Table 2. Optical transparency index (OTI); Total aberration RMS (TA RMS); Spherical aberration RMS (SA RMS) and Spearman correlation analysis for the data collected from all participants of the study.

OTI	TA RMS* (μm)	SA RMS** (μm)	Spearman's*	Spearman's**
80.0 \pm 0.9	1.45 \pm 0.28	-0.15 \pm 0.05	Failed, $p=.38$.	Failed, $p=.26$.

3.2. Optical Density and Corneal Structure

The cornea and sclera are composed mainly of type-I fibrillar collagen whose structural organization at molecular scale is responsible for optical transparency. Due to the hierarchical structure of the cornea [31], the macroscopic structure is a consequence of the microscopic arrangement. This section investigates if the macroscopic structure of the cornea plays a role in the optical density or it disappears as corneal transparency factor within the hierarchical organization. Total corneal astigmatism, anterior and posterior eccentricity, central, middle and peripheral thickness were measured and compared with the OTI index for all subjects.

Table 3 shows the mean values of thickness, corneal astigmatism and eccentricity computed from the 102 measured eyes. The statistical analysis revealed that the corneal thickness does not affect the transparency, however both total corneal astigmatism and posterior eccentricity (i.e. the inner surface of the cornea) showed strong correlation with OTI parameter. These results imply that in absence of pathological or physiological (aging) scattering contributions at the cornea, its optical transparency depends on the

shape but not how wide it is. Fig. 3 shows the graphical representation of the cluster sampled OTI values as a function of total corneal astigmatism (Fig. 3a) and posterior eccentricity (Fig.3b). As shown, OTI is positively correlated with astigmatism and negatively with posterior eccentricity whereas anterior eccentricity does not affect corneal transparency.

Table 3. Mean values of geometrical parameters and correlation results with OTI index.

Structural Parameter	Location	Mean Value	Spearman's
Corneal Thickness	Central	554±30 μm	Failed, $p=.58$.
	Middle	601±30 μm	Failed, $p=.42$.
	Peripheral	674±69 μm	Failed, $p=.29$.
Corneal Astigmatism	Global	0.87±0.34 Dp.	$R^2=0.87$, $p<.0001$
Anterior Eccentricity	Global	0.24±0.16	Failed, $p=.39$
Posterior Eccentricity	Global	0.42±0.12	$R^2=0.94$, $p<.0001$

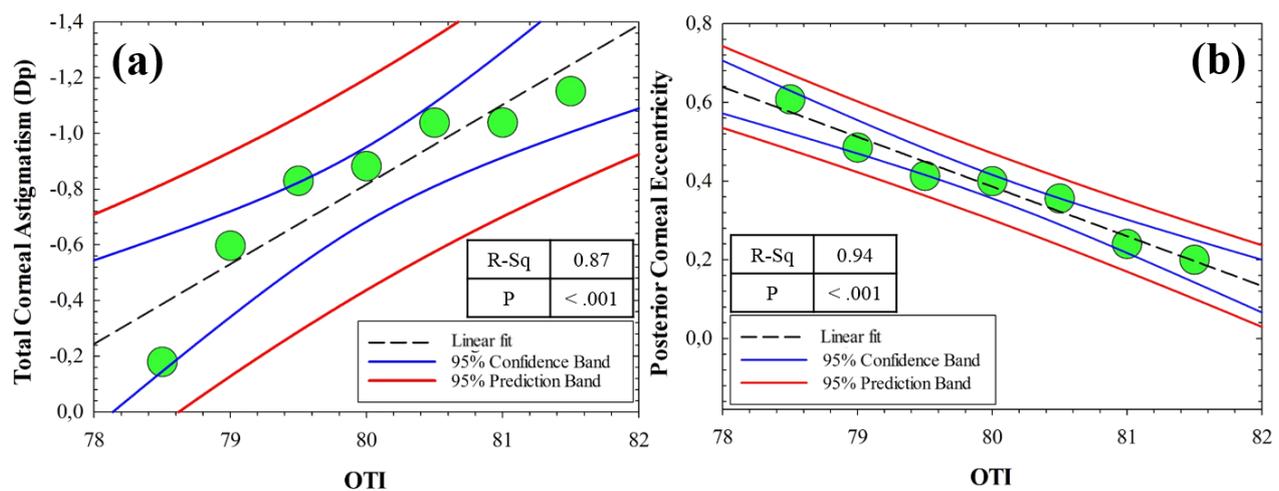


Figure 3. Mean clustered OTI values as function of corneal astigmatism (a) and corneal eccentricity (b) for all subjects. R-Sq.: Squared correlation coefficient; P: p-value.

3.1. Optical Density and Corneal Biomechanics

Finally, this subsection investigates the impact of biomechanics on corneal transparency. Fig. 4 shows a biomechanical image that represents the dynamic stress-strain response of the cornea during an air-puff applanation measurement at ORA device. The maximum deformation occurs at approximately 10 milliseconds. It can be observed that the pressure distribution is not symmetric but lopsided, this weakness is due to the viscoelastic nature of the cornea while symmetric distributions correspond to pure elastic corneas.

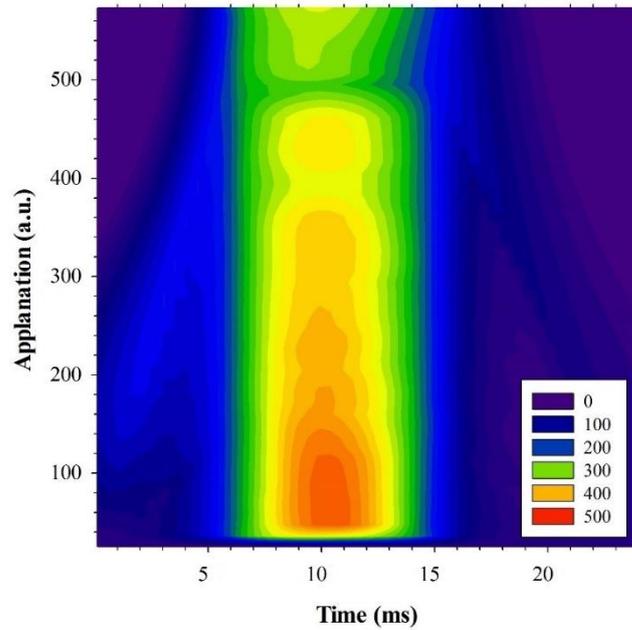


Figure 4. Dynamical representation of corneal appplanation as a function of time from a volunteer of the study. Air pulse pressure is scaled in arbitrary units shown in the bottom right corner legend.

As described in Methods, ORA device provides CH and CRF biomechanical parameters, from them we derived the appplanation pressures P1 and P2 which are related to pure elastic (P1) and viscoelastic (P2) properties of the cornea. Fig.5 shows the graphical representation of the clustered sampling OTI values as a function of P1 (Fig. 5a) and P2 (Fig. 5b). The statistical analysis revealed significant (negative) correlations of OTI with P1 and P2 what proves that biomechanics is one of the factors responsible of corneal transparency.

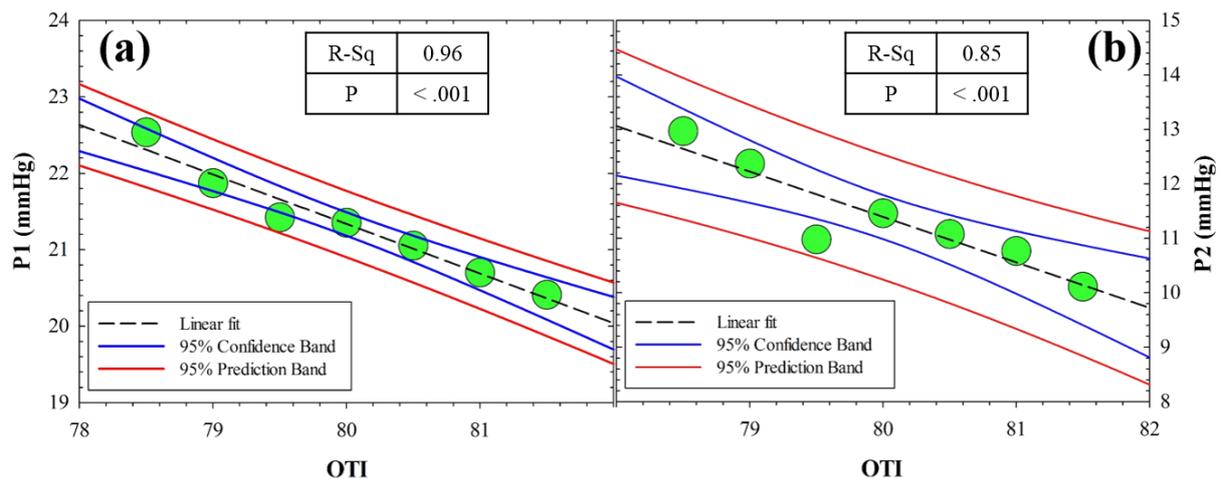


Figure 5. Mean clustered OTI values as function of first (a) and second appplanation pressures (b) for all subjects. R-Sq.: Squared correlation coefficient; P: p-value.

4. Discussion and Conclusions

Whereas the role of corneal ultrastructure in the three-dimensional architecture at microscale, corneal transparency and mechanical stability is well-understood [16], the convergence of those properties at macroscale within the hierarchical corneal structure has not been investigated.

Considering that most of the medical devices for corneal analysis offer macro-structural resolution and information, in this study we explore the relationship between biomechanics, shape and optical properties of the cornea in healthy young subjects. We analyzed wave-front aberration, optical density, geometrical parameters (thickness, eccentricity and total corneal astigmatism) and corneal biomechanics using dual Placido-Scheimpflug analyzer and air-puff applanation tonometry systems, respectively.

Corneal aberrations and, in particular spherical term, seem to play a compensation mechanism to keep stable the retinal image quality in the presence of intraocular scattering [30], also in traumatic injuries corneal opacity appears together with high-order aberrations [32]. In particular, the decrease in optical density and corneal spherical aberration is correlated in contact lens wearers due to corneal swelling [33]. Our findings showed that in young and healthy subjects, corneal aberrations and OTI calculations are not related.

Regarding structural aspects, corneal thickness and optical density change in dry eye syndrome, diabetes and glaucoma [34] and are correlated in edema processes such as corneal swelling associated with contact lens wear [33]. However, our findings showed that corneal thickness does not affect the optical transparency in healthy young subjects.

In addition, corneal surface irregularities are associated not only to optical aberrations but also to light scattering [35]. In that sense, our study also included as macro-structure parameters total corneal astigmatism and anterior and posterior eccentricities. As shown in Results, the higher the OTI value the higher the corneal astigmatism and the lower the posterior eccentricity of the cornea. It is worth to mention that only posterior corneal eccentricity depends on corneal astigmatism [36] and even not shown in results, total corneal astigmatism and posterior corneal eccentricity were negatively correlated ($R^2=0.88$, $p=0.028$) what implies that optical transparency and corneal macrostructure are related by means of the relative shape of the cornea independently of the thickness.

Finally, molecular structure of Type-I corneal collagen is responsible for the optical transparency and three-dimensional arrangement of the stroma [16]. Three dimensional-arrangement of the cornea determines its shape (geometry) and biomechanics [37]. Changes in corneal structure associated to aging or disease factors alter corneal biomechanics [38]. Thus, in our work we also explored if biomechanics and corneal transparency are actually related at the macroscopic level of study. Results showed (see Fig. 6) that both elastic- (P1) and viscoelastic-related parameters (P2) are strongly correlated with OTI, the viscoelastic parameter is more weakly correlated that implies the dominance of the elastic property in corneal transparency.

To conclude, within the hierarchical structure of the cornea, the nano-scale lead to optical transparency whereas the microscopic architecture models corneal biomechanics that impacts the macroscale [16]. Previously to our work, Garzón et al [39] reported a study on corneal densitometry and its correlation with aging, corneal thickness and curvature and refractive error using Scheimpflug imaging, they found no correlation between optical transparency and refractive parameters. In our study we expanded the analysis of those factor that could have an impact on corneal transparency.

In conclusion, the macroscopic structure of the cornea plays a relevant role in optical transparency, in particular the shape of the cornea measured by total astigmatism and

posterior eccentricity. Optical transparency is sensitive to corneal biomechanics, in particular the elastic property seems to be the dominant contribution. Future research will include aging and pathological conditions to help us to develop predictive models in terms of the convergence of optical properties, structure and biomechanics of the cornea.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Research of the Health Sciences Institute of Aragon (Spain) with reference: C.P.-C.I.PI20/377.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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