

## Review

# In Vivo Measurements of Corneal Biomechanics and their Relevance in Keratoconus - A Review

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### Abstract

**Keratoconus is a progressive 1haracte disorder in which corneal deformation is associated with stromal thinning and biomechanical weakening. In recent years, there has been significant scientific interest in corneal biomechanical properties for a better understanding of physiology and physiopathology in order to provide a proper diagnosis and treatment of the disease. This review aims to explain different methods for the characterization of corneal biomechanics in keratoconus, both in the laboratory and clinical setting. Until now, many studies describing the measurement of corneal biomechanical properties using Ocular Response Analyzer (ORA) and Corneal Visualization Scheimpflug Technology (CorVis ST) devices have been performed and published. However, there has been an increasing development of new methods which allow a better understanding of the differences of corneal properties between some ocular pathologies and healthy corneas. Also, this review discusses the advantages and limitations using these instruments and techniques in the early detection of keratoconus. Further research is necessary in order to consolidate their diagnostic capabilities.**

**Keywords:** Biomechanical properties, Corneal resistance factor, CorVis ST, Hysteresis, Keratoconus, ORA

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## INTRODUCTION

Keratoconus is a progressive, usually bilateral corneal ectasia that generally appears in younger individuals (Rabinowitz, 1998; Krachmer et al., 1984; Corbu, 2014). Even if it is a disease that affects all ethnicities, higher incidence have been reported in Asians when compared to Caucasians (Ariela Gordon-Shaag et al., 2012; Jonas et al., 2009). It is 1haracterized by thinning and conical protusion of the cornea in the inferior zone. This leads to progressive myopia and irregular astigmatism causing a decreased visual acuity as the disease progresses (Corbu, 2014; Ariela Gordon-Shaag et al., 2012).

The etiology and pathophysiology of keratoconus is

multifactorial and not completely understood. Although it has been considered as a non-inflammatory disorder, recent evidence including high levels of proteolytic enzymes, the presence of cytokines, association with free radicals and oxidative stress support the inflammatory theory (Galvis et al., 2015; Catalina et al., 2016). It is usually an isolated disorder although it has been associated with some collagen diseases, revealing an abnormality in the structure of collagen which result in a weak and flexible cornea (Rabinowitz, 1998; Krachmer et al., 1984; Vellara and Patel, 2015). Other theories include hormonal changes, atopic conditions, and mechanical

factors such as eye rubbing (Munsamy et al., 2015). The clinical signs of keratoconus, corneal stress lines (Vogt's striae) and corneal hydrops (rupture of Descemet's membrane) suggest alterations in the biomechanical properties of the cornea (Vellara and Patel, 2015).

It is important to investigate corneal biomechanical properties in keratoconus because these changes occur before the topographically signs. Corneal alterations appear due to abnormalities in the layers containing collagen fibrils as a result of the disease process. In recent years an increasing interest has been shown in corneal biomechanics in order to detect early keratoconus thus remaining a clinical challenge (Vellara and Patel, 2015; Majid et al., 2013).

### Physical Properties of the Cornea

Corneal viscoelastic and biomechanical properties were described by Majid et al. (2013), Nyquist (1968) and Woo et al. (1972). An elastic response means that a material can have the ability to deform reversibly under an applied stress (Corbu, 2014; Majid et al., 2013; Nery et al., 2014). However, in contrast a viscous material does not regain the original shape as fast as an elastic material when the stress is removed (Corbu, 2014; Majid et al., 2013).

Viscoelastic tissues such as the cornea, present both characteristics so that another property is defined (Corbu, 2014; Vellara and Patel, 2015; Majid et al., 2013; Nery et al., 2014). This parameter is known as hysteresis and represents the response of a viscoelastic material to stress and measures the energy absorbed by the cornea during applanation (Corbu, 2014; Nery et al., 2014).

There are studies that emphasize that some of these properties presented above are altered in keratoconus (Vellara and Patel, 2015; Edmond, 1988).

### Histopathological changes in a keratoconic cornea and its biomechanical implications

All the five layers of the cornea, listed from the anterior to posterior: epithelium Bowman's membrane, stroma, Descemet's membrane and endothelium are known to be affected in keratoconus. A diverse range of histological changes that have been described in these layers provide the characterization of a biomechanical model in keratoconus patients (Sherwin and Brookes, 2004).

It is known that the epithelium suffer the earliest morphological changes in keratoconus resulting in a significant thinning of the central part. In vivo confocal microscopy studies of the epithelium showed that even if in the periphery of the keratoconic corneas can be found normal cells, the superficial cells of the apex of the cone

are arranged in whorl like patterns (Scroggs and Proia, 1992; Somodi et al., 1997). However, the corneal epithelium accounting for 10% of the central corneal thickness has a minor contribution to the viscous behavior (Nery et al., 2014; Elsheikh et al., 2008).

The layers that have a major contribution to the overall strength of the cornea are those containing collagen fibrils: Bowman's layer and corneal stroma. Kenney and al. showed in their study that a keratoconic cornea can present gaps in Bowman's layer and fibrotic regions in the anterior stroma which can be visible through these breaks (Vellara and Patel, 2015; Sherwin and Brookes, 2004). The corneal stroma represents almost 90% of the corneal thickness and is composed of 300 to 500 collagen lamellae (Majid et al., 2013). Patients with keratoconus have a decreased number of lamellae and an altered orientation of the collagen fibrils from the lamellae. All of this provide loss of structural integrity and biomechanical instability of the tissue (Daxer and Fratzi, 1997).

The keratocytes and the proteoglycans from the extracellular matrix determine the viscous behaviour of the cornea (Vellara and Patel, 2015). In keratoconus the number of keratocytes is decreased due to apoptosis and the fact that proteoglycan distribution is altered. These changes give rise to a mechanical instability which can be explained by a decreased resistance to permanent deformation under a constant load (Vellara and Patel, 2015; Kaldawy et al., 2002).

Descemet's membrane and the corneal endothelium are the structures that present minor changes in keratoconus and have minimal contribution to mechanical properties of the cornea. However some abnormalities have been emphasized in cases of acute corneal hydrops (Danielsen, 2004; Lawrence et al., 2011). In some cases, there have been reported intracellular dark structures, pleomorphism and elongation of cells (Sherwin and Brookes, 2004).

A new theory for biomechanical model leading to progression in keratoconus was described by Roberts. She explained that the initiating event is the reduction in elasticity accompanied by thinning. The possible cause of this may be the genetic condition associated with an external trigger such as eye rubbing. The focal reduction in elasticity generates greater deformation and focal bulging with increased curvature and redistribution of stress from less affected areas to the cone region (Roberts, 2012).

### Insights on corneal biomechanics measurements

There has been an increasing interest in measuring the mechanical properties of the cornea for characterization of corneal biomechanics. There are two types of techniques described in the literature: ex vivo destructive

tests and in vivo nondestructive tests (Corneal Biomechanics, 2016).

### **Assessing corneal biomechanical principles using ex vivo testing**

These type of procedures involve testing the corneas or strips of cornea out of its physiological environment. Therefore these tests introduce the potential for error because of some factors such as corneal anatomy and hydration, tissue degradation and temperature. Recent studies emphasize that strips extensometry and pressure inflation of intact corneas are the main methods for ex vivo measuring of corneal biomechanical properties (Ahmed and Kevin, 2005). The test procedure for strip extensometry involves placing corneal strips with a constant width to the grips of a tensile testing instrument while monitoring its behaviour (Wollensak et al., 2003). The procedure for inflation tests involves studying the degree of extension of the cornea as a response to an increased IOP. Because it preserves corneal architecture, this is considered to represent better the in vivo corneal biomechanical properties than strip extensometry procedure (Vellara and Patel, 2015; Ahmed and Kevin, 2005). These techniques have been studied by several researchers thus leading to confirm some biomechanical principles.

In 2008, Hamilton et Pye demonstrated that the cornea show a non linear, inelastic, heterogeneous stress versus strain response which means that the stiffness rises as tissue stress increases (Kirsten et al., 2008).

Another biomechanical principle was described by Hjortdal JO in his study. He studied the regional mechanical performance of the cornea and limbus of 18 human eyes and found that the paracentral and peripheral regions are stiffer compared with the central region due to orientation of the collagen fibrils (Hjortdal, 1996).

Randleman et al proved that corneal elastic strength is dependent of stromal depth showing an increasing strength from the posterior 60% of the stroma to the 40% of the central corneal stroma (Randleman et al., 2008).

Elsheikh et al. investigated the stress-strain behaviour of corneal tissue and how the behaviour was affected by age. They observed the corneal stiffness is increasing with age due to additional age-related nonenzymatic cross-linking affecting the stromal collagen fibrils (Elsheikh et al., 2007).

### **Insights into keratoconus from in vivo biomechanical perspective**

#### **Ocular Response Analyzer**

Even if there has been an increasing interest in the deve-

lopment of methods that measure the corneal biomechanical properties of the cornea in clinical practice which allow a better understanding of the differences in corneal properties between some ocular disease and healthy eyes, there are still a limited number of them. Two devices are described in the literature for measuring and characterizing corneal biomechanics in clinical practice: Ocular Response Analyzer (ORA) (Reichert, Buffalo, New York, USA) and CorVis ST (Oculus Optikgerate GmbH, Wetzlar, Germany) (Nery et al., 2014; David et al., 2015).

The Ocular Response Analyzer is a device introduced in clinical setting in 2005. This non-contact tonometer uses a rapid puff of air to indent the cornea and an infrared beam to record changes in corneal deformation during inward and outward deviation (Nery et al., 2014; Luce, 2005).

The device records two applanation measurements: the first one when the cornea suffers an inward movement achieving a first applanation (P1) and the second one after approximately 20 milliseconds when the cornea moves outward as the pressure decreases and the cornea return from concavity to its normal convex form. The air pressure is increased to a maximum level P max, then decreases gradually until the second applanation is detected at pressure P2 (Elsheikh et al., 2009; Fateme et al., 2016).

The parameters obtained from signal analysis of the ORA are described in Table 1 (Majid et al., 2013; Nery et al., 2014; Kotecha, 2007; Lam et al., 2007; Franco and Lira, 2009; Medeiros and Weinreb, 2006).

In the normal healthy eye, there is a significant variability in CH between 9.3+/-1.4 and 11.4+/-1.5 mmHg and in CRF between 9.2+/-1.4 and 11.9+/-1.5 mmHg (David et al., 2015). Several studies demonstrated that both CH and CRF values are significantly reduced in keratoconic eyes compared with healthy eyes. The decrease is stronger as the keratoconus severity increases and the difference of CH and CRF (CH-CRF) is positive and increases as the disease progresses. The studies also revealed that both CH and CRF had low sensitivity and specificity for discriminating between mild keratoconus and healthy corneas (Shah et al., 2007; Fontes et al., 2010; Naim et al., 2012; Shah and Laiquzzman, 2009; Mikielwicz et al., 2011; Viswanathan et al., 2015).

In a study on 179 eyes, Galletti and colleagues reported that CRF shown a better sensitivity and specificity in detecting patients with keratoconus, even if they had a normal topography in the fellow eyes and after the effect of CCT was disclosed (Majid et al., 2013; Galletti et al., 2012).

In 2013, Kara et colleagues compared CH and CRF in a group of topographically normal relatives of patients with keratoconus and age-matched controls. They found that both values were significantly lower in the relatives of patients with keratoconus than in the controls. Taking into

**Table 1.** Description of the Ocular Response Analyzer Parameters

Parameter	Description
CH(corneal hysteresis)	Is considered an indicator of viscous property of the cornea and is obtained by the difference between the two pressures: $CH=P1-P2$
CRF(corneal resistance factor)	Is an indicator of overall corneal resistance and is calculated using a proprietary algorithm
IOPg(Goldmann intraocular pressure)	The mean value of the two pressures measured by ORA.
IOPcc(Corneal Compensated IOP)	It uses the CH to determine an intraocular pressure value that is less affected by corneal properties, such as central corneal thickness
Aindex	Roughness of the upper 75% of the first applanation peak
Aplhf	Irregularity of the region between the peaks
aspect 1	Aspect ratio of the upper 75% of the first applanation peak(height/width)
aspect11	Aspect ratio of the upper 50% of the first applanation peak(height/width)
aspect 2	Aspect ratio of the upper 75% of the second applanation peak(height/width)
aspect22	Aspect ratio of the upper 50% of the second applanation peak(height/width)
Bindex	Roughness of the upper 75% of the second applanation peak; difference between the two applanation air pressure values(P1 and P2)
dive1	Distance from the first spike of Peak 1 to the top of the graph, measuring 75% of peak height
dive2	Distance from the first spike of Peak 2 to the top of the graph, measuring 75% of peak height
dslope1	Downward slope of the upper 75% of the first applanation peak
dslope11	Downward slope of the upper 50% of the first applanation peak
dslope2	Downward slope of the upper 75% of the second applanation peak
dslope22	Downward slope of the upper 50% of the second applanation peak
h1	Height of the upper 75% of the first applanation peak
h11	Height of the upper 50% of the first applanation peak
h2	Height of the upper 75% of the second applanation peak
h21	Height of the upper 50% of the second applanation peak
mslew1	The longest continuous line in peak 1 without a break, measuring 75% of peak height
mslew2	The longest continuous line in peak 2 without a break, measuring 75% of peak height
path1	Path length around the upper 75% of the first applanation peak
path11	Path length around the upper 50% of the first applanation peak
path2	Path length around the upper 75% of the second applanation peak
path22	Path length around the upper 50% of the second applanation peak
p1area	Area under the curve of the upper 75% of the first applanation peak
p1area1	Area under the curve of the upper 50% of the first applanation peak
p2area	Area under the curve of the upper 75% of the second applanation peak
p2area1	Area under the curve of the upper 50% of the second applanation peak
slew1	Aspect ratio of dive1(value of dive1 divided by width of dive1 region)
slew2	Aspect ratio of dive2(value of dive2 divided by width of dive2 region)
uslope1	Upward slope of the upper 75% of the first applanation peak
uslope11	Upward slope of the upper 50% of the first applanation peak
uslope2	Upward slope of the upper 75% of the second applanation peak
uslope21	Upward slope of the upper 50% of the second applanation peak
w1	Width of the upper 75% of the first applanation peak
w11	Width of the upper 50% of the first applanation peak
w2	Width of the upper 75% of the second applanation peak
w21	Width of the upper 50% of the second applanation peak

account the increased incidence of keratoconus in relatives, these results suggest that a decrease in CH and CRF may be an early indicator in detection of corneal changes in relatives of patients with keratoconus, preceding the topographic changes usually used in keratoconus screening (Majid et al., 2013; Kara et al., 2013).

Schwitzer et al. evaluated the ability of the Ocular

Response Analyzer to screen corneas with forme fruste keratoconus (FFK). This latent biomechanical instability is the main cause of corneal ectasia and can be activated by refractive surgery. They demonstrated that CH and CRF are decreased in FFK compared with the control eyes showing that ORA provides additional information, particularly when corneal topography does not suggest FFK. This findings agree with the other papers dealing

with this issues (Cedric et al., 2010).

The new version 2.0 ORA software provides 37 additional parameters that describe the waveform of the ORA response curve. 23 of these parameters are derived from the upper 75% of the applanation peak height and the others 14 describe characteristics of the upper 50% (Table A) (Mikielewicz et al., 2011; Bruna et al., 2013).

Mikielewicz et al. investigated the use of parameters obtained from the ORA on 119 subjects to distinguish between normal and keratoconic corneas, to determine the severity of keratoconus and to evaluate changes after the crosslinking (CXL) procedure. They reported that CRF and the second peak of the signal curve shown the best results in distinguishing between normal and keratoconic eyes. Besides these ones, other 10 parameters produced excellent results. This study also reported similar results with previous ones showing no significant changes in CH and CRF at 4 months after CXL treatment. Only two parameters (p2area and time 1) showed significant differences between preoperative and postoperative values (Mikielewicz et al., 2011).

In 2013, Ventura and colleagues evaluated 41 parameters derived from the applanation diagram obtained with the Ocular Response Analyzer from Reichert in a group of normal and keratoconic eyes. They found that four ORA parameters (p1area, p1area1, p2area, p2area1) produced the best performance in distinguishing between keratoconus and normal corneas. They also found that the four parameters (CH, IOPg, IOPcc, and CRF) are not ideal for differentiating these groups (Bruna et al., 2013).

Spoerl et al. evaluated the biomechanical changes after corneal collagen crosslinking in keratoconus using Ocular Response Analyzer. They detected that the p2 area value had a statistically significant change in 50 eyes before and 1 year after CXL, showing an increase of 35% after CXL, with values similar with those observed in healthy corneas. CH and CRF values were reduced in keratoconus, but no statistically significant differences were observed after CXL, which is consistent with the results of other studies (Steven et al., 2012; Mohammadreza et al., 2015). They also found a negative correlation between p2 area and the difference in CH-CRF. Taking into account that a low value of CH-CRF indicates a high shear stiffness, the increase of p2 area could be the result of an improvement of corneal shear stiffness (Eberhard et al., 2011).

The latest version of ORA software (ORA 3.0) introduces another 2 parameters keratoconus match index (KMI) and keratoconus match probability (KMP).

KMI represents the similarity of the waveform of the examined eye against the same average waveform scores of the keratoconus eyes in the machine's database. In the literature normal KMI values is around 1 and keratoconus KMI values around 0.

The keratoconus match probabilities show how the given measurement matches to a normal reference

population and quantifies the probability that a cornea is normal, suspect or keratoconic. Potentially keratoconic corneas are classified into mild, moderate and severe (Georgios et al., 2013; Georgios et al., 2014).

Giogios et al. reported in their study on 114 keratoconic eyes compared with the corresponding ones from 109 normal eyes, a mean KMI value of 0,20 in keratoconic eyes versus 0,98 in control eyes. They evaluated the diagnostic capacity of these 2 indices and found that KMI may be a reliable index in keratoconus diagnosis and staging. On the other hand, KMP identified a significant percentage of control group eyes and keratoconus eyes as suspect (Georgios et al., 2013; Georgios et al., 2014).

As well as offering high accuracy and repeatability, the additional advantages of ORA include the fact that it provides the biomechanical metrics CH and CRF, both of them being influenced by the viscoelastic behaviour of corneal tissue. When compared with normal corneas, both CH and CRF decrease in keratoconic patients indicating mechanical softening of the stroma. The evidence suggests that when these parameters are used alone, they have low sensitivity and specificity. However when used in combination with other parameters they are useful in assessing pre-operative ectasia risk by improving the sensitivity and specificity of tomography and topography (Majid et al., 2013; Bruna et al., 2013; Fang et al., 2016; Jonathan et al., 2015). Better differentiation of the keratoconic cornea is possible with the new version 2.0 ORA software and the area under the second peak seems to be a promising parameter (Naim et al., 2012; Mikielewicz et al., 2011; Zhang et al., 2015).

Also, ORA has some limitations when comparing keratoconic eyes and normal eyes. It is clear that the large measurement overlap between both groups results in poor test performance for differentiating normal and keratoconic corneas. Keratoconus is associated with some irregularities which may be missed by ORA since analysis occurs in the central 3-4 mm of cornea (Majid et al., 2013; Bruna et al., 2013; Fang et al., 2016; Jonathan et al., 2015). Another limitation is the absence of relevant changes in ORA measurements after CXL treatment. This absence has several possible explanations. It is known that 80% of corneal volume depends on hydrated proteoglycans and only 20% on collagen fibril behaviour. ORA measures viscosity of the ground substance of the cornea, which consist of proteoglycans and glycozaminoglycans, and not the collagen matrix. So this can be an explanation for the limited possibility of ORA to evaluate the potential positive effect after CXL, which cross-links the collagen fibers and not the ground substance (Nery et al., 2014; Naim et al., 2012; Mikielewicz et al., 2011; Spoerl et al., 2009). Another explanation for the absence of significant changes in CRF and CH also might be explained by the change in stiffness which might be less than that which can be

**Table 2.** Parameters obtained from image analysis of the Corneal Visualization Scheimpflug Technology

Parameter	Description
IOP	A noncontact measurement based on the first applanation
pachy	Measurement of central corneal thickness with optical pachymetry
A1T(first applanation time)	Time from start until the first applanation
A1L(first applanation length)	Length of the flattened cornea in the first applanation
Vin(velocity inwards)	Corneal velocity during the first applanation moment
A2T(second applanation time)	Time from start until the second applanation
A2L(second applanation length)	Length of the flattened cornea in the second applanation
Vout (velocity outwards)	Corneal velocity during the second applanation moment
RoC (radius of curvature)	Radius of curvature at highest concavity
PD (peak distance)	Distance between the peaks at highest concavity
DA (deformation amplitude)	Maximum deformation amplitude , from start to the highest concavity, at the corneal apex

measured by the sensitivity of the ORA (Orhan et al., 2015; Maddalena et al., 2015; Salman, 2016; Katie et al., 2014).

### Corneal Visualization Scheimpflug Technology

Another device used for describing in vivo corneal biomechanical properties is Corneal Visualization Scheimpflug Technology (Corvis ST) which combine corneal imaging with non contact tonometry. It was introduced in clinical setting in 2011 and it is a non-contact tonometer that emits a precisely metered air-puff thus leading to the movement of the cornea. The movements are recorded with a high-speed Scheimpflug camera and the deformation profile is analyzed in real time and provides multiple parameters. First of all the cornea begin to move inward reaching the first applanation then continues the movement until reaches the highest concavity and returns from concavity to another point of applanation (the second applanation) and then to its natural, convex state (David et al., 2015; Johannes et al., 2014; Qin et al., 2015).

These movements generates the parameters that are described in table 2 (Vellara and Patel, 2015; Nery et al., 2014).

Tian and colleagues compared the corneal biomechanical properties of keratoconic patients and age-matched controls using Corvis ST. They found that the deformation amplitude parameter had the best predictive value with a sensitivity of 81,7% and a specificity of 83,3% and without taking into account the central corneal thickness, which may explain the high values of sensitivity and specificity obtained [65]. These findings were similar with other studies results showing that corneal deformation induced by keratoconus are deeper and affects more the whole cornea making it easier to deform (Michele et al., 2014).

Ali, Patel and McGhee studied the obtained parameters with CorvisST in normal and keratoconic eyes with similar mean CCT and IOP. They reported that

keratoconic corneas are associated with greater deformation amplitude than in normal corneas without obtaining an ideal value for sensitivity and specificity. Therefore, the deformation amplitude cannot be used solely to differentiate between keratoconic and healthy corneas (Vellara and Patel, 2015; Alin et al., 2014).

Johannes Steinberg et al. investigated the effect of corneal crosslinking in progressive keratoconus using corneal visualization Scheimpflug Technology. They identified statistically significant difference between four obtained parameters before and 3 months after CXL: IOP, corneal central pachymetry, A1time and A2 time. The time until the cornea reaches the status of the first applanation increased (A1time; median +0,12ms,  $p < 0,05$ ) and the time of the second applanation A2 time decreased ( median -37ms,  $p < 0,05$ ), thus indicating an increase of the corneal stiffness after the treatment (Johannes et al., 2014).

Vinciguera et colleagues proposed a new biomechanical index, corneal biomechanical index (CBI), in order to test the capability of the Corvis ST to separate normal from keratoconic corneas. The CBI includes deformation amplitude ratio at 1 and 2 mm, applanation 1 velocity, standard deviation of DA at highest concavity, ARTh( Ambrosio's Relational Thickness to the horizontal profile), Novel Stiffness Parameter (SP-A1). Ambrosio's Relational Thickness, which enables the characterization of the thickness data on the horizontal Scheimpflug image, is combined with corneal deformation parameters in order to improve ectasia detection (Ambrosio et al., 2016; Allan et al., 2016). They demonstrated that CBI was able to identify 98.2% of the keratoconic corneas with 100% specificity (Allan et al., 2016).

Koprowski and Ambrosio Jr reported a new algorithm for image analysis and processing allowing for the separation of individual features from a corneal deformation image. The features used are directly related to corneal vibrations and provide a specificity of 98% and and a sensitivity of 85%. The obtained results confirm the possibility to distinguish between keratoconic and non keratoconic corneas using corneal vibrations during

intraocular pressure measurement with the Corvis ST tonometer (Koprowski and Ambrosio, 2015; Kaprowski, 2015).

Both ORA and Corvis ST measure corneal deformation. However, one of the advantages of Corvis ST is that it displays corneal deformation in real time in comparison with ORA which cannot display the dynamics of the deformation process in real time, the parameters being derived from a proprietary algorithm applied to the measured waveform (Lei et al., 2014). The other advantages are that Corvis ST provides a two-dimensional image of a cross-section of the deforming cornea during applanation and measures the apical displacement of the cornea. However, unlike the ORA, the Corvis ST has the ultra-fast Scheimpflug camera that takes 140 frames during the 33 ms of the measurement, which allows a more detailed evaluation of corneal deformation (Ambrosio et al., 2013). It also measures the IOP and CCT in comparison with ORA which doesn't measure both parameters, the second being considered an useful index for diagnostic and monitoring disease (Sushma et al., 2015; Hon and Lam, 2013)

### **New perspectives on keratoconus biomechanics as revealed by other devices**

Another instrument used for the measurement of the human corneal dynamics during an air puff is the swept source optical coherence tomography (ssOCT), which provides quantitative and qualitative corneal maps. As shown in previous studies, the amplitude of corneal displacement is more pronounced when the measurement is taken on the thinner central region of the cornea. The biomechanical properties of different corneal regions play an important role, as the cornea has been reported to have different elastic regional properties (Hjortdal, 1996; David-Alonso et al., 2011; Mukesh et al., 2015).

High speed SS OCT has some advantages over the Scheimpflug system and it is a promising technology for quantitative corneal evaluation. It provides a better tomogram quality and shorter measurement time. The most important advantage is that topographic analysis can be done along with the high-quality cross-sectional imaging. SS OCT can be used not only for elevation-based topography but also for the evaluation of the corneal structure, including the epithelium. Thus, as a decrease in epithelial thickness masks the presence of an underlying cone on front surface topography, SS OCT may be helpful in detecting keratoconus at a very early stage (Karol et al., 2011; Reinstein et al., 2009; Steinberg et al., 2015).

Other techniques that have demonstrated potential for clinical implementation include Brillouin light scattering microscopy, corneal optical coherence elastography,

supersonic shear imaging (Michael et al., 2015).

Brillouin Optical Microscopy is another noninvasively, noncontact technique used for three-dimensional mapping of corneal modulus and measurement of corneal stiffening by corneal collagen crosslinking (Scarcelli et al., 2012). It is based on Brillouin scattering that arises from the interaction between light incident on a medium of interest and spontaneous acoustic photons within the medium. The elastic properties are determined by measuring the frequency shift induced by the acousto-optic interaction (Giuliano et al., 2013).

The use of Brillouin microscopy has been reported in the literature in *ex vivo* experiments (Cherfan et al., 2013), showing notable differences between healthy and keratoconic corneas. The mechanical loss is primary concentrated within the area of the keratoconic cone. Outside the cone, the Brillouin shift is comparable with that of healthy cornea (Giuliano et al., 2014). Like-wise, some measurements with human eyes have been shown in several articles. The possibility of applying the technique to a living patient offers a good opportunity for early detection of ocular problems, such as presbyopia and corneal ectasia. As well as localizing weak areas of the cornea, Brillouin microscopy can measure local elastic properties in biologic tissue. A limitation of the instrument for use in the clinic is the relatively long acquisition time (Giuliano and Seok, 2012).

Another method to measure the corneal biomechanical properties uses Optical Coherence Tomography Elastography (Ford et al., 2011). This method generates *in vivo* 2D maps of corneal deformation by using a cross-correlation algorithm and thus measuring local and depth variations throughout all the stroma. The advantage of this technique is that it enjoys the maximum spatial resolution within the stroma among all techniques (Abhijit et al., 2013). Other advantages are that this noninvasive method may be useful for *in vivo* detection of keratoconus and also evaluation of therapeutic interventions such as crosslinking (Singh et al., 2016; Jiasong et al., 2014).

Shear wave propagation imaging is another promising imaging technique which can measure corneal biomechanical properties *in vivo*, by using the linear elastic theory, in which the Young's modulus can be estimated from the shear wave speed (Liu et al., 2007; Dupps et al., 2007). The method generates shear waves in the anterior stroma using focused ultrasound and the speed of propagation of the shear waves in the stroma is measured. As optical coherence elastography, this method has been used to measure the biomechanics of the cornea after collagen crosslinking (Nguyen et al., 2012).

### **CONCLUSIONS**

An understanding of biomechanical corneal behaviour is

fundamental to the diagnosis and treatment of corneal ectasia and it also allows a better screening of this disease.

Recent advances in technology have enabled the development of other techniques with potential for clinical implementation. The current study was conducted to review the development, validity and potential of such clinical devices that are capable of characterising true corneal material properties.

The published literature provides a better understanding of the interactions between corneal biomechanics, structural and functional changes of the tissue. It is considered that the primary alteration in keratoconus is due to the altered structure of proteoglycans and glycosaminoglycans, which lead to reduced stromal interlamellar cohesion and a decreased bending stiffness (Akhtar et al., 2008; Elsheikh et al., 2009).

After reviewing the recently published results, we can state that even if many techniques have been researched, there are only two devices capable of measuring corneal biomechanics in the clinical setting: ORA and Corvis ST. However both of them have limitations and many of these two device's parameters are still poorly understood. Further research analysis and future studies are necessary to consolidate the utility of the corneal biomechanics as a clinical tool.

We conclude that the early detection of keratoconus remains a challenge in the clinical practice. However the new technologies are promising and may enhance their diagnostic capabilities.

## Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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