ORIGINAL PAPER

THE RELEVANCE OF BIOMECHANICAL PROPERTIES IN PATIENTS WITH KERATOCONUS

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Abstract

The number of studies about biomechanics of the cornea is growing, due to the influence of these properties on the predictability of good results for refractive surgery procedures and the management of cross-linking. However, only recent studies have used techniques and devices that provide in vivo measurements. The purpose of our study is to evaluate the range of changes in time of the corneal biomechanical properties: corneal hysteresis (ch) and corneal resistance factor (crf) - measured using the ocular response analyzer (ora) (reichert corporation, depew, usa) in patients with keratoconus in different stages of disease progression. The present study is retrospective. 37 patients (59 eyes) with keratoconus were examined during 3 ophthalmological examinations (1 year interval) at a private clinic in bucharest, for a period of 3 years. The majority of patients with keratoconus in various stages of evolution (most of them stage i and ii) has been found to have a decreasing mean in time of the corneal biomechanical parameters (crf and ch). In conclusion, corneal biomechanical parameters correlate positively with the stage of the keratoconus.

Keywords*: cornea, biomechanics, hysteresis, keratoconus*

Introduction

Keratoconus is a noninflamatory eye condition, relatively frequent (prevalence in studies range from 1 to 500 to 1 to 2,000 [1]), of unknown etiology which causes changes in the central and paracentral cornea of young people aged between 12 and 35 years, time in which the disease may progress or may stop spontaneously. Visual acuity may be severely affected due to the irregular astigmatism. It is usually a bilateral condition, but around 17% of unilateral cases have been reported [2].

There is a grading system for keratoconus and according to the Amsler-Krumeich [3,4] classification there are 4 stages as follow :

1) Stage I: Eccentric steepening ; Myopia, induced astigmatism, or both <5.00 D; Mean central K readings < 48.00 D.

2) Stage II: Myopia, induced astigmatism, or both from 5.00 to 8.00 D; Mean central K readings < 53.00 D; Absence of scarring; Minimum corneal thickness > 400 μm.

3) Stage III: Myopia, induced astigmatism, or both from 8.00 to 10.00 D ; Mean central K readings > 53.00 D; Absence of scarring ; Minimum corneal thickness 300 to 400 μm

4) Stage IV: Refraction not measurable ; Mean central K readings >55.00 D ; Central corneal scarring ; Minimum corneal thickness 200 μm.

Eyes with keratoconus are considered to be more elastic and less rigid than normal ones and therefore can have different biomechanical properties [5].

The cornea is a composite material made of collagen fibers that stretch from limbus to limbus, consisting of lamellae arranged in parallel order and embedded in an extracellular matrix of glicosaminoglicans [6]. Layers glide easily over each other, indicating a very low resistance to friction [7], but the stroma itself is an elastic anisotropic structure (exhibits different physical properties when stress is applied in different directions), which distributes traction unevenly throughout its thickness, depending on corneal hydration [8]. If the cornea is dehydrated, the stress is distributed mainly posteriorly or symmetricaly on the entire structure. If the cornea is healthy or with edema, the anterior lamellae take the task [9].

Cornea reacts to stress as a viscoelastic material; for an initial stress, the resulting elongation is dependent on time. The viscoelastic property consists in immediate deformation followed by a second slower one. Elastic response of the eye seems to reflect the elastic properties of collagen fibers, and elastic equilibrium reflects the properties of corneal matrix [9].

With age the fibers become thicker through collagen continuing deposition and there is a cross-linking phenomenon between them [10].The result is an increased corneal stiffness with age [11].

Stromal hydration seems to have little effect on corneal response to tension and friction forces [12]. Freidenwald has described for the first time the viscoelastic properties of the cornea in 1937, followed by Nyquist and Woo in the next decades [13]. Cornea presents elastic and viscoelastic properties which give it the property of hysteresis [14].

Corneal material properties:

A)Elasticity is the property of a material to regain its original shape in a direction of displacement completely reversible along the line of stress when the stress imposed is removed. Ex vivo studies have highlighted the nonlinear elastic behavior of the cornea which increases with the intensification of stress applied to it [15]. Moreover, the corneal elastic module is variable directional and regional, a higher module being on the meridians, at the center and paracentral areas and circumferentially at the limbus language, due to the specific arrangement of the collagen fibers described above [11].

B)Viscosity. Viscous materials flow when an outer stress is applied and unlike the materials with elastic properties they not regain their original shape when the stress is removed. Viscoelastic materials have elements of both viscosity and elasticity and as a consequence, the resulting energy is dissipated by these materials, when a stress is applied.

C)Hysteresis (CH) refers to the energy lost during the exercise cycle of deformation, being a direct measure of the biomechanical properties of the cornea and with direct dependence on intraocular pressure [14]. Like most biological materials, collagen is viscoelastic and therefore exhibits hysteresis. Corneal hysteresis is a property, resulting of the damping process that the cornea achieves due to its viscoeleastic properties. It is calculated as a difference between two measurements of applanation during the process of measurement [16]. Thus, the hysterezis represents the ocular resistance through the combined effect of some parameters such as the corneal thickness, ocular rigidity and viscoelastic properties.

D)Corneal Resistance Factor (CRF) provides an assessment of corneal resistance and is relatively unaffected by the changes of intraocular pressure.

These properties are not constant, being permanently modified with increasing age, corneal pathology and corneal hydration level, where the loss of the lamelae organization alters the biomechanics of the corneal stroma [17]. Corneal elasticity analysis may allow the screening of early changes in corneal biomechanics occurring in patients with keratoconus.

Currently the biomechanics of cornea is analyzed using the Ocular Response Analyzer - ORA (Reichert Corporation, Depew, USA), first described by Luce in 2005 [18]. It is the only instrument capable of measuring *in vivo* the corneal hysteresis (CH) and corneal resistance factor (CRF), indicators of the corneal biomechanical properties. This information is

different from thickness or topography, which are geometric attributes of the cornea.

Corneal hysteresis represents a tissue property that provides more comprehensive information about the ocular biomechanics [14] . It is an assessment of the capacity of the cornea to absorb and dissipate energy. Corneal hysteresis (CH) is the difference between internal and external values of pressure obtained during the process of bidirectional dynamic applanation made by ORA [16] as a result to corneal viscous damping. It is a characteristic of the capacity of energy absorption by the cornea, variable depending on the biomechanical properties of it.

The values of CH and CRF obtained during the ORA cycle use the following formulas:

$CH = P1 – P2$ $CRF = P1 – k\ P2$

Where: P1 = initial applanation pressure

P2 = final applanation pressure

k = constant (value approximately = 0.7) determined through an empirical analysis of the relationship between P1 and P2 with central corneal thickness, being associated more with this than with the corneal hysteresis.

According to the published literature, we have found the following results regarding the average CH and CRF values for eyes with no pathology (Table 1):

Authors	Average CH (mmHg)	Average CRF (mmHg)
Kirwan, O'Keefe (Ireland)	10.8 ± 1.5	
Shah et al. (UK)	10.7 ± 2.0	
Ortiz (Spain)	10.8 ± 1.5	10.8 ± 1.7
Hager et al. (Germany)	10.6 ± 2.3	
Carbonaro (UK)	10.24 ± 1.24	

Table 1 – Average CH and CRF for healthy eyes

CH and CRF are significantly altered after refractive surgery or after cross-linking procedures as a result of complex changes in the corneal biomechanics [19].

Materials and Method

The current study has a retrospective design and aims to evaluate the variation in time of corneal biomechanical parameters, assessed with the Ocular Response Analyzer (ORA). A number of 37 patients between 17 and 48 years were investigated at a private clinic in Bucharest between 2012 and 2015, with annual ophthalmic evaluation. Of these, 23 were male (62.16 %) aged between 17 and 48 years old and 14 (37.83 %) were female, aged between 22 and 43 years old. The average age of patients from the trial was 33.22 years old.

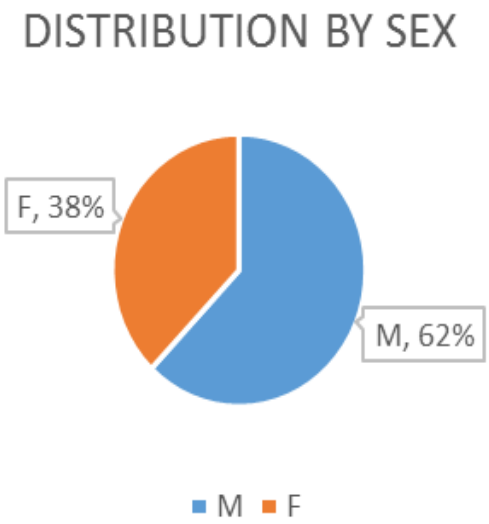

Figure 2- Distribution of age in relation to mean

During the 3 year period there were 3 complete ophthalmological examinations: the first examination was at diagnosis, the second at 1 year and the third at 2 years from diagnosis.

Examination protocol included:

- Visual acuity (VA) - LogMAR test = the best VA obtained with maximum optical correction;
- Electronic manifest refraction (spherical and cylindrical diopters);
- Slit lamp examination;
- Ultrasonic pachimetry (OcuScan RxP, Alcon, USA);
- Corneal Topography (Topcon CA 200F, Topcon Co, Japan);
- ORA measurement (CH and CRF).

The diagnosis of keratoconus was established on a thorough clinical examination, including slit lamp signs such as: stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, corneal scars, Vogt striae, rupture of Descemet / Bowman membrane and specific corneal topography.

Criteria of inclusion in the study:

- Age between 15-50 years old;
- Patients with unilateral/bilateral positive diagnosis for keratoconus ;
- A minimum of 3 examinations, each at 12 months in the clinic;
- Patients who have accepted the inclusion in the study.

Criteria for exclusion from the study: patients with previous eye surgery, glaucoma, eye infection, history of corneal trauma or other active ocular pathologies or general assets. We also excluded from the trial the patients with local eye treatments. Examinations/ measurements were performed by the same person with the same devices.

Patients wearing contact lens have been informed of the discontinuation of their use at least 2 weeks prior to the examination - for soft contact lenses and at least 4 weeks prior to the examination for those wearing hard contact lenses.

There were examined a total number of 74 eyes, of which only 59 (31 being right eye and 28 left eye) had specific changes of keratoconus.

The eyes found with keratoconus were divided in 4 stages, according to Amsler-Krumeich classification:

- Stage I included 21 eyes (35.60 %)
- Stage II included 23 eyes (38.99 %)
- Stage III included 11 eyes (18.64 %)
- Stage IV included 4 eyes (6.77 %)

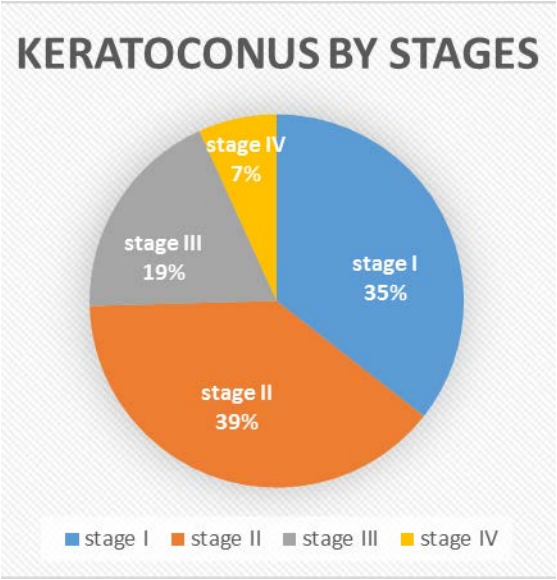

Figure 3 - Keratoconus distribution by stages

All the patients were informed of the inclusion in this study and signed an informed consent. It was analyzed, during 3 consecutive examinations of those 59 eyes, the variation in time of the biomechanical parameters such as CH and CRF regarding each eye and with the keratoconus staging.

The statistical analysis was Performed using Excel (Microsoft Corp.) and IBM SPSS Statistics for Windows version. 20.0.1 (SPSS Inc).

Results

A. In patients with keratoconus stage I:

The amplitude range of CH between the first and the last examination variated between – 2,9 mmHg and + 1.4 mmHg (Δ = 4.3 mmHg). 4 out of 21 eyes examined presented increased values of CH, while in 17 eyes the values were decreased compared to the initial consult.

CRF values between the first and the last examination varied between – 4,1 mmHg and + 1.3 mmHg (Δ = 5,4 mmHg). 6 out of the 21 eyes examined presented increased values of CRF, while in 15 eyes the values had decreased compared to the initial examination.

At the same eye, the decreasing values of CH corresponded with the decreasing values of CRF in 15 (out of 17) cases, while the increasing values corresponded in all 4 cases.

In 15 out of 17 eyes, both CH and CRF values had simultaneously decreased, while in 4 cases we observed their simultaneous increase.

B. In patients with keratoconus stage II:

The amplitude range of CH between the first and the last examination varied between – 2.2 mmHg and + 1.5 mmHg (Δ = 3.7 mmHg). 5 out of the 23 eyes examined presented increased values of CH, while in 18 eyes the values had decreased compared to the initial consult.

CRF values between the first and the last examination varied between – 1.8 mmHg and + 1.8 mmHg (Δ = 3.6 mmHg). 6 out of the 23 eyes examined presented increased values of CRF, while in 17 eyes the values had decreased compared to the initial examination.

At the same eye, the decreasing values of CH corresponded to the decreasing values of CRF in 17 (out of 18) cases, while the increasing values corresponded in all 5 cases.

In 17 out of 18 eyes, both CH and CRF values had simultaneously decreased, while in

all 5 cases we observed their simultaneous increase.

C. In patients with keratoconus stage III:

The amplitude range of CH between the first and the last examination varied between – 2.6 mmHg and + 0.8 mmHg (Δ = 3.4 mmHg). Only one out of the 11 eyes examined presented increased values, while in 10 eyes the values had decreased compared to the initial examination.

CRF values between the first and the last examination varied between – 1.7 mmHg and + 1.4 mmHg (Δ = 3.1 mmHg). 3 out of the 11 eyes examined presented increased values, while in 8 eyes the values had decreased compared to the initial examination.

At the same eye, the decreasing values of CH corresponded with the decreasing values of CRF in 8 (out of 10) cases, while the increasing values corresponded in a single case.

In 8 out of 10 eyes, both CH and CRF values had simultaneously decreased, while in only one case we observed a simultaneous increase.

D. In patients with keratoconus stage IV:

The amplitude range of CH between the first and the last examination varied between – 0.5 mmHg and + 0.1 mmHg (Δ = 0.6 mmHg). Only one out of the 4 eyes examined presented increased values, while in 3 eyes the values had decreased compared to the initial examination.

CRF values between the first and the last examination varied between – 0.8 mmHg and + 0.4 mmHg (Δ = 1.2 mmHg). Only one out of 4 eyes examined presented increased values, while in 3 eyes the values had decreased compared to the initial examination.

At the same eye, the decreasing values of CH corresponded with the decreasing values of CRF in 2 (out of 3) cases, while the increasing values failed to match in any case.

In 2 out of 3 eyes, both CH and CRF values had simultaneously decreased, while the increasing values failed to match in any case.

We can summarize the variations as following (Table 2):

Keratoconus stage	Values of CH variation	Values of CRF variation
Stage I (21 eyes)	– 2,9 and + 1.4 mmHg Δ = 4.3 mmHg	– 4,1 and + 1.3 mmHg Δ = 5,4 mmHg
Stage II (23 eyes)	– 2.2 and + 1.5 mmHg Δ = 3.7 mmHg	– 1.8 and + 1.8 mmHg Δ = 3.6 mmHg
Stage III (11 eyes)	– 2.6 and + 0.8 mmHg Δ = 3.4 mmHg	– 1.7 and + 1.4 mmHg Δ = 3.1 mmHg
Stage IV (4 eyes)	– 0.5 and + 0.1 mmHg Δ = 0.6 mmHg	– 0.8 and + 0.4 mmHg Δ = 1.2 mmHg

Table 2 – Variations of CH and CRF values

From a total of 59 eyes with keratoconus at 11 (18.65%) of them there have been increases in the values of CH, while 48 (81.35 %) showed decreased values. From the point of view of the values of CRF, 16 (27.12 %) had increased values, while 43 (72, 88%) had decreased values compared to the initial consult.

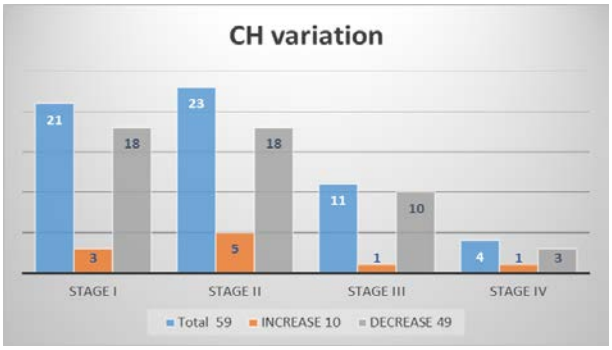

Figure 4 - Variation of Corneal Hysteresis

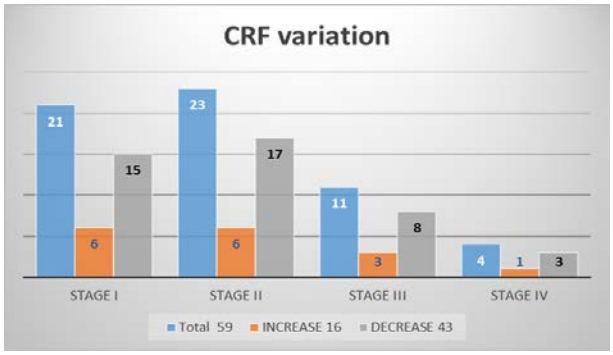

Figure 5 - Variation of Corneal Resistance Factor

Discussions

The mean age at the inclusion in the study is over the mean described in the literature for the debut of keratoconus (15.4 years according

to a study by Olivares [20]), probably due to reduced access and addressability to specialized ophthalmic services in our country.

The distribution by sex in our study showed an incidence of keratoconus almost double in males than females (23 men vs 14 women). In literature the data concerning the distribution by gender is conflicting. Thus, Amsler in 1961 showed a higher incidence in women compared to males, while in 2009 Ertan shows a higher prevalence in males [21].

About three quarters (74.59%) of the eyes have presented keratoconus stage I and II and only a quarter (25.41%) stage III and IV.

Corneal biomechanical parameters (CH and CRF) offer a more complete characterization of the cornea compared to the geometrical parameters - central corneal thickness (CCT) and topography, making these values useful in preoperative evaluation of candidates for refractive surgery and cross-linking.

At the majority of eyes with keratoconus the biomechanical parameters had decreased in time, fact explained perhaps by corneal changes produced by the advancement of keratoconus and corneal thinning, being not age related changes. Thus we had 81.35 % of eyes were the CH values had decreased, while 72.88 % of eyes had the values of CRF decreased.

In most cases we observed a direct correlation between the decrease of CH and the CRF at the same eye.

Conclusions

Keratoconus progression changes the biomechanical parameters of the cornea and the variation in time correlates positively with the evolution of this condition.

Hysteresis evaluates the biomechanical status of the cornea, but a clear separation of normal and keratoconic corneas is not possible because of interindividual variations.

Ocular Response Analyzer (ORA) is an important evaluation device of the cornea that makes an addition to the diagnosis, guides the treatment and may be useful to assess progression in different ocular pathologies. CH and CRF parameters are useful in evaluating the corneal ectasia risk after refractive procedures, while the other 2 parameters measured by ORA (IOP G – Goldmann correlated IOP and IOP CC – corneal compensated IOP) offer important information for glaucoma / glaucoma suspect patients, but further studies are needed to be done.

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