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Comparison between Corneal Biomechanics in Normal and Keratoconic Corneas Using Ocular Response Analyzer

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ABSTRACT

Background: keratoconus (KC) is an idiopathic degenerative eye disease characterized by localized thinning and conical protrusion of the cornea, which typically develops in the inferior-temporal and central zones. Consequently, visual acuity is reduced due to irregular astigmatism and high myopia resulting from asymmetric topographical changes in the corneal surface. KC is the most prevalent form of corneal ectasia and affects all ethnicities. However, higher incidence has been reported in Asians when compared to caucasians. **Aim of the work:** this study aimed to compare the biomechanical properties of the cornea between topographically normal individuals with topographically keratoconic patients.

Patients and methods: this prospective study was carried out from January 2017 to July 2017 on 40 eyes of patients attending outpatient clinic of Ain Shams University Hospitals and Ophthalmology Department of Research Institute of Ophthalmology in Giza.

All participant names were hidden and were replaced by code numbers to maintain privacy of the patients. Ocular response analyzer (ORA) values were obtained from 20 eyes of keratoconus patients and 20 eyes of non keratoconus subjects both topographically tested.

Results: corneal hysteresis (CH) was found to be higher in normal group than keratoconus group; the values were found to be 10.9 ± 1.5 in normal group and 7.88 ± 1.23 in keratoconus group. Corneal resistance factor (CRF) was found to be higher in normal group than keratoconus group, the values were found to be 12.7 ± 1.05 in normal group and 6.7 ± 1.7 in keratoconus group. Goldmann correlated intraocular pressure (ORA_IOPg) was found to be higher in normal group than keratoconus group, the values were found to be 13.13 ± 2.91 in normal group and 10.31 ± 2.99 in keratoconus group. Corneal compensated intraocular pressure (ORA_IOPcc) was found to be 14.17 ± 3.44 in normal group and 14.23 ± 2.01 in keratoconus group, there was no difference between normal group and keratoconus group.

Conclusion: corneal biomechanical properties, characterized by corneal hysteresis and the corneal resistance factor, provide new indicators for the diagnosis of keratoconus.

Recommendations: this study recommended to follow up IOP in keratoconus patients by ORA due to false low results which may be taken by using the Goldman applanation intraocular pressure. Large studies should be done to detect the prevelance of keratoconus in Egypt as this information was missing from peerviewed studies we researched.

Keywords: corneal biomechanics, keratoconic corneas, ocular response, topographically, corneal hysteresis.

INTRODUCTION

Keratoconus (KC) is an idiopathic degenerative eye disease characterized by localized thinning and conical protrusion of the cornea, which typically develops in the inferior-temporal and central zones [(1)]. Consequently, visual acuity is reduced due to irregular astigmatism and high myopia resulting from asymmetric topographical changes in the corneal surface. KC is the most prevalent form of corneal ectasia and affects all ethnicities [(2)]. However, higher incidence has been reported in Asians when compared to caucasians [(3)].While the etiology and pathology of the disease is still not fully understood, various biochemical, cellular and microstructural differences have been reported in the literature. For instance, biochemical changes included increased activity of proteolytic enzymes and a decrease in their inhibitors [(5)]**.** Increased proteoglycan (PG) content and altered distribution PG filaments had also been reported [(6)]. A progressive reduction in collagen-producing corneal keratocytes has been observed [(7)] **,** as well as a disruption to the highly organized orthogonal arrangement of collagens [(8)]. Further, a decrease in the mean fibril diameter and interfibrillar spacing of individual collagens and undulation of collagen lamellae have been reported [(6)].

A genetic predisposition to keratoconus is well documented with increased incidence in some familial groups and numerous reports of correspondence between monozygotic twins**.** Approximately, 6% - 23.5% of patients with keratoconushave a positive family history [(9)]**.**

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Similar to other ocular genetic disorders, a study indicated that relatives of keratoconus patients have an elevated risk compared to those with unaffected relatives [(10)]. The majority of familial keratoconus is inherited through an autosomal dominant pattern [(11)]. Other models of inheritance such as autosomal recessive pattern have been suggested, especially in populations of high consanguinity [(4)].

The overall prevalence of keratoconus in the general population has been estimated to be between 5 and 23 per 10,000, respectively with both sexes equally affected [(13)]. However, it would not be surprising to expect an increase in the incidence and prevalence rates of this disease nowadays with the current wide spread use of newer diagnostic devices leading to early diagnosis [(12)].The Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, New York, USA) is a noncontact, non-invasive, device that uses a rapid metered collimated air pulse to applanate the cornea, situated between an infrared electro-optical transmitter and receiver system forming a 90 degree angle. It records inward and outward applanation events and it simultaneously assesses and compensates for the effect of the cornea's viscous and elastic qualities on IOP measurement. Corneal hysteresis may reflect mostly corneal viscosity; corneal resistance factor may predominantly quantify corneal rigidity. It is an indicator of the overall "resistance" of the cornea, including both the viscous and elastic properties [(14)]. This study aimed to compare the biomechanical properties of the cornea between topographically normal individuals with topographically keratoconic patients.

PATIENTS and METHODS

This prospective study was carried out from January 2017 to July 2017 on 40 eyes of patients attending outpatient clinic of Ain Shams University Hospitals and Ophthalmology Department of Research Institute of Ophthalmology in Giza.

All participant names were hidden and were replaced by code numbers to maintain privacy of the patients. Ocular response analyzer (ORA) values were obtained from 20 eyes of keratoconus patients and 20 eyes of non keratoconus subjects both topographically tested.

Patients were categorized into two groups:

Group 1: 20 eyes of 10 non keratoconic subjects.

Group 2: 20 eyes of 11 keratoconic patients.

Inclusion criteria:

Patients were included in our study according to:

1. Age between eighteen and forty years old
2. keratoconic cornea.
3. Normal fundus
4. Keratoconus topographic criteria includes:

i. Substantial inferonasal or inferotemporal steepening.

ii. Inferior steepening could extend centrally called crab-claw shape.

iii. Central corneal power greater than 47.2 diopters.

iv. Substantial displacement of the cornea from the center.

v. Inferior- superior (I- S) value greater than 1.4.

vi. Skewed radial axes

Exclusion criteria

1. Use of contact lenses.
2. Glaucoma
3. Dry eye
4. Pseudoexfoliation syndrome
5. Previous anterior segment surgery
6. Systemic diseases
7. History of any ocular surgery in the same eye
8. Corneal scarring or corneal dystrophies.

Data were collected from patients included age, past ocular and medical history, medications, allergies and family history of eye diseases,best corrected visual acuity, IOP measurement with applanation tonometry, dilated fundus examination with +20 D Volk lens.

Every patient was subjected to Ocular Response Analyzer **(**ORA; Reichert Ophthalmic Instruments, Depew, New York, USA) to measure corneal biomechanical parameters which included: corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann-correlated pressure (IOPg) and corneal- compensated intraocular pressure (IOPcc). The results obtained were tabulated and statistically analyzed using specific analytical program. This study was conducted in accordance with the ethical standards stated in the faculty of Medicine- Ain Shams University with informed consent obtained.

Patient's evaluation

I. History

1. Systemic:

a) Patients were asked about their previous general medical history

b) Female Patients were asked about their status regarding pregnancy, breast feeding, or the use of oral contraceptive drugs or the use of hormone replacement therapy.

2. Ocular

a) Patients were asked about their ocular history regarding medical and surgical ophthalmic history and the previous use of contact lenses,

trauma, and use of eye drops.
b) History of use of eyeglasses and changes in the previous prescriptions in the past year

II. Examination

1. **Vision:** patient's visual acuity was measured by **Snellen's chart** and their refraction both manifest and cycloplegic was also measured by Topcon Autorefractometer RM 8900.
2. **External examination:** to assess the eyelids infection.
3. Ocular motility and assessment of phorias and tropias.
4. **Slit-lamp examination for:**
a) Searching for signs of dry eye and tear film assessment (tear meniscus and breakup time), detailed examination of the cornea to rule out undiagnosed corneal dystrophies, allergic conjunctivitis, other pathologies of the conjunctiva and sclera.
b) Pupillary light reaction both direct and consensual reactions and diameters in light and dim situations.
c) Intraocular pressure was measured using Goldman applanation to exclude glaucoma.

5. Fundus examination

Detailed examination was done by Slit-lamp biomicroscopy and 90 D Volk lens to examine central retina to reveal signs of diabetic retinopathy, maculopathy or optic nerve disease. Also, indirect ophthalmoscopy was done to examine the retina periphery to exclude retinal detachment or peripheral retinal lesions.

III. Investigations

1. Corneal topography and corneal thickness were measured using a scheimpflug-based topography namely the Pentacam machine (WAVE LIGHT ALLEGRO OCULYZER serial NO.:1074-1-414).
2. Corneal hysteresis (CH), corneal resistance factor (CRF) were recorded for each eye by using ocular response analyzer (REICHERT ORA serial no:73116-1210).

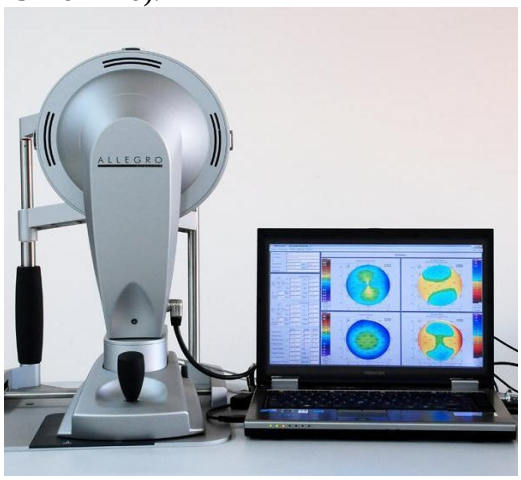

Figure 1: wave light allergo oculyzer pentacam

Figure 2: Reichert ocular response analyzer

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

RESULTS

The control group comprised 20 eyes of 10 emmetropic patients; 60% were men and 40%, women. The mean age was 29.90 ± 3.60 years (range 25 to 37 years). The mean spherical equivalent (SE) was -0.53 D ± 0.44 (SD). The mean (CRF) was12.7 ± 1.05 mm Hg while the mean (IOPg) and (IOPcc) were 13.13 ± 2.91 and 14.17 ± 3.44 mm Hg respectively.

On the other hand, the Keratoconus group comprised 20 eyes of 11 patients; 20% were men and 80%, women. The mean age was 23.70 ± 5.97 years (range 18 to 37 years). The mean spherical equivalent (SE) was -8.05 D ± 3.33 (SD). The mean (CRF) was 6.70 ± 1.76 mm Hg while the mean (IOPg) and (IOPcc) were 10.32 ± 3 and 14.23 ± 2.01 mm Hg respectively.

Table 1 shows summary of characteristics in both groups. **(Tables 1 &2).**

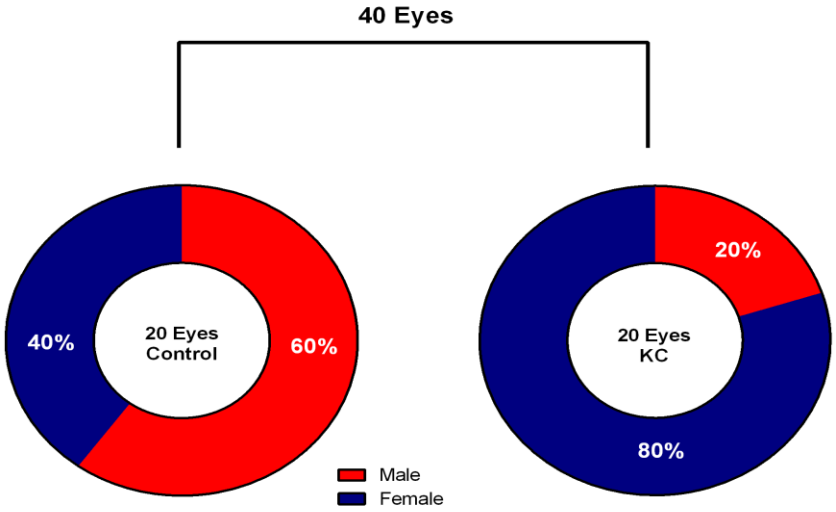

Figure 3: differences in gender between control group KC group and control group

A Chi-square test of independence was calculated the effect of gender on the results. A significant interaction was found (χ^2 (1) = 6.667, p = 0.010).

Table 1: demographic characteristics between control group KC group and control group

Group Mean Std. Deviation			
Age (year)	Normal(N=20)		3.60
	KC (N=20)	23.70	5.97
SE (D)	Normal(N=20)	-0.53	0.44
	KC (N=20)	-8.05	3.33
BCVA	Normal(N=20)	1.00	0.00
	KC (N=20)	0.35	0.19
IOP (Goldmann) (mm Hg)	Normal(N=20)	13.00	2.79
	KC (N=20)	11.10	2.17

SE= spherical equivalent; BCVA= best corrected visual acuity; IOP=intraocular pressure.

Table 2: biomechanical properties between control group KC group and control group

Group Mean Std. Deviation			
CH (mm Hg)	Normal (N=20)	10.09	1.51
	KC (N=20)	7.88	1.24
CRF (mm Hg)	Normal (N=20)	12.74	1.05
	KC (N=20)	6.70	1.76
IOPg (mm Hg)	Normal (N=20)	13.13	2.91
	KC (N=20)	10.32	3.00
IOPcc (mm Hg)	Normal (N=20)	14.17	3.44
	KC (N=20)	14.23	2.01

CH= corneal hysteresis; CRF= corneal resistance factor; IOPg = Goldmann-correlated pressure; IOPcc = corneal-compensated intraocular pressure

Comparison between means of the different parameters in both groups

An independent-samples t-test was performed in order to compare different parameters in both groups. There was a statistically significant difference in age (years) between normal eyes and eyes with KC conditions; t (3.98) =38, p=0.001. Similarly, there was a significant difference in best corrected visual acuity (BCVA) conditions; t (15.69) =38, p = 0.001 as well as corneal hysteresis conditions; t (5.05) =38, p = 0.001. In addition, a comparison of refraction (calculated as SE = spherical equivalent was calculated as the sum of the spherical power and half of the cylinder power) was held showing a significant difference between the two groups conditions; t (10.02) =38, p = 0.001. This significant difference also persisted in Goldmann-correlated pressure conditions; t (3.0) = 38, p =0.005. However, there was no significant difference in both corneal-compensated intraocular pressure and corneal resistance factor. **(Table 3)**

Table 3: summary of independent t-test results

Variable	Mean	SD	T	Df	p-value
Age in years					
Normal	29.9	3.6	3.98	38.0	0.001
KC	23.7	5.9			
Best corrected visual acuity (BCVA)					
Normal	1.0	0	15.69	38.0	0.001
KC	0.35	1.8			
Refraction					
Normal	-0.53	0.44	10.02	38.0	0.001
KC	-8.05	3.33			
Corneal hysteresis (CH) (mm Hg)					
Normal	10.09	1.5	5.05	38.0	0.001
KC	7.88	1.23			
Goldmann-correlated pressure (mm Hg)					
Normal	13.13	2.91	3.0	38.0	0.001
KC	10.31	2.99			
Corneal-compensated intraocular pressure (mm Hg)					
Normal	14.17	3.44	-.073	38.0	0.942
KC	14.23	2.01			
Corneal resistance factor (mm Hg)					
Normal	12.74	1.05	1.85	38.0	0.07
KC	6.7	1.76			

** Significant P value >0.05

Correlation between CRF, IOPcc, IOPg and the other parameters

As data were normally distributed, Pearson's correlation test was used to evaluate correlations between parameters (**Table 3**). CRF was positively correlated with Age, SE, BCVA, IOP (Goldmann), CH, IOPg and IOPcc. Similarly, IOPg was positively correlated was all other parameters with more significant results. However, IOPcc was negatively associated with SE and CH with positive correlation with the remaining parameters.

Table 4: correlations between CH, CRF, IOPcc, IOPg and the other parameters

Parameters		**Age**	**SE**	**BCVA**	**IOP (Goldmann)**	**CH**	**CRF**	**IOPg**	**IOPcc**
Corneal hysteresis (CH)	Pearson Correlation	0.390*	0.576**	0.633**	0.109	1	0.116	0.312	-0.383*
	P value	0.013	0.000	<0.001	0.503		0.47	0.050	0.015
	N	40	40	40	40	40	40	40	40
Corneal resistance factor (CRF)	Pearson Correlation	0.196	0.259	0.280	0.095	0.116	1	0.102	0.019
	P value	0.226	0.107	0.080	0.559	0.474		0.530	0.907
	N	40	40	40	40	40	40	40	40
Goldmann-correlated pressure (IOPg)	Pearson Correlation	0.586**	0.357*	0.472**	0.923**	0.312	0.102	1	0.754**
	P value	<0.00	0.024	0.002	<0.001	0.050	0.53		<0.001
	N	40	40	40	40	40	40	40	40
Corneal-compensated intraocular pressure (IOPcc)	Pearson Correlation	0.296	-0.054	0.023	0.829**	-0.015	0.019	0.754*	1
	P value	0.064	0.740	0.890	<0.001	0.015	0.90	<0.001	
	N	40	40	40	40	40	40	40	40

SE= spherical equivalent; BCVA= best corrected visual acuity; IOP= intraocular pressure; CH= corneal hysteresis; CRF= corneal resistance factor; IOPg= Goldmann-correlated pressure; IOPcc = corneal- compensated intraocular pressure; ** Correlation is significant at the 0.05 level

As regard to corneal hysteresis (CH)

Corneal hysteresis (CH) was found to be 10.9 ± 1.5 in normal group and 7.88 ± 1.23 in keratoconus group.

The difference between two groups was found statistically significant (p value = 0.001). (Table 3)

It has been found to correlate positively with age (r = 0.39, p value = 0.013), Spherical equivalent (SE) (r = 0.633, p value < 0.001), it correlates negatively with IOPcc (r = - 0.383, p value = 0.015) and it has no significant correlation with other factors. **(Table 4)**

As regard to corneal resistance factor (CRF)

Corneal resistance factor (CRF) was found to be 12.7 ± 1.05 mm Hg in normal group and 6.7 ± 1.7 mm Hg in keratoconus group. There was a statistical significant difference between two groups regarding CHF (p value = 0.007). **(Table 3).**

As regard Goldmann correlated intraocular pressure (ORA_ IOPg)

Goldmann correlated intraocular pressure (ORA_IOPg) was found to be 13.13 ± 2.91 mm Hg in normal group and 10.31 ± 2.99 mm Hg in keratoconus group.

The difference between two groups was found statistically significant (p value = 0.001). **(Table 3)**

It has been found to b e correlated positively with age (r =0.586, p value <0.001), Spherical equivalent (SE) (r = 0.357, p value = 0.024), BCVA (r = 0.472, p value = 0.002), IOP Goldmann (r = 0.923, p value < 0.001), IOPcc (r = 0.754, p value < 0.001) and it has no significant correlation with other factors. **(Table 4)**

As regard to Corneal compensated intraocular pressure (ORA_ IOPcc)

Corneal compensated intraocular pressure (ORA_IOPcc) was found to be 14.17 ± 3.44 mm Hg in normal group and 14.23 ± 2.01 mm Hg in keratoconus group.

The difference between two groups was found not statistically significant (p value = 0.942) as mentioned in table 3; It has been found to correlate positively with IOP Goldmann (r = 0.829, p value <0.001), ORA_ IOPg (r = 0.754, p value < 0.001) and it has no significant correlation with other factors. **(Table 4)**

Logistic regression of CRF, IOPcc and IOPg

A binary logistic regression analysis was conducted to predict keratoconus patients within the group using CRF, IOPg, IOPcc, CH and gender as predictors. **(Table 5)**

Nagelkerke's R^2 of 0.813 indicated a moderately strong relationship between prediction and grouping. Prediction success overall was 92.5% (90% for normal and 95% for KC.

Exp (B) value indicates that when CH is raised by one unit (one person) the odds ratio is 0.125 times as large while change in gender raise it nearly 136 times.

Table 5: results of Logistic regression

		B	S.E.	Wald	Df	P	Exp (B)
Step 3c	Gender	4.911	1.926	6.504	1	0.011	136
	CH	-2.082	0.820	6.444	1	0.011	0.125
	IOPg	-0.473	0.293	2.603	1	0.107	1
	Constant	21.202	8.625	6.043	1	0.014	1614291394

CH = corneal hysteresis;
IOPg = Goldmann-correlated pressure;
S.E. = standard error.

DISCUSSION

Keratoconus generally starts at puberty and progresses until the third or fourth decade of life after which it usually stabilizes [(15)].

Keratoconus is a slowly progressive, non inflammatory ectatic corneal disease characterized by changes in corneal collagen structure and organization. Though the etiology remains unknown, novel techniques are continuously emerging for the diagnosis and management of the disease [(16)]. Keratoconus is usually diagnosed and monitored by clinical signs and corneal topography [(17)].

Corneal biomechanical characteristics of CH and CRF, as measured by the bidirectional applanation of the cornea with an air pulse, only show moderate discriminatory ability. A similar decrease in CH and CRF in patients with keratoconus compared to controls and only a moderate correlation with keratoconus severity was also found in this study [(18)]. This suggests that the corneal biomechanical changes with keratoconus, as assessed by the parameters of CCT, CH and CRF are more complex than clinical

signs, and front corneal surface changes indicate that other corneal biomechanical characteristics should be considered.

Increased knowledge of corneal biomechanics, behaviour and the response to deformation is of great importance. Data generated from the ORA may expand our understanding and perhaps help with preoperative refractive surgery screening, glaucoma treatment, Fuchs dystrophy counseling, and other ocular conditions[19].

In our study, there was a significant difference in corneal hysteresis between the normal group and keratoconus group; corneal hysteresis values were found lower in keratoconus group than the normal group (10.9 ± 1.5 and 7.88 ± 1.23 respectively with (p value = 0.001) and this is in agreement with results of **Fontes *et al.*** [19], they found that CH was 8.23 ± 1.51 mmHg (range 4.60 to 11.80 mmHg) in keratoconus and 10.13 ± 1.75 mmHg (range 5.95 to 14.58 mmHg) in the control group [20], who stated that the corneal hysteresis and corneal resistance factor values were significantly lower in keratoconic eyes. Also found that Hysteresis was significantly higher in normal than in keratoconic eyes.

In our study, corneal resistant factor (CRF) values were found lower in keratoconus group than normal group (12.74 ± 1.05 and 6.70 ± 1.76 respectively with p value = 0.007) and this is in agreement with results of **Ortiz *et al.*** [20], who found that the corneal resistance factor values were significantly lower in keratoconic eyes.

Also [21] stated that mean values of CRF (P < 0.0001 and P < 0.0001 respectively) were significantly lower in keratoconic eyes than in the control group

In our study Goldmann correlated intraocular pressure (IOPg) values were found lower in keratoconus group than normal group (13.13 ± 2.91 and 10.32 ± 2.99 mm Hg respectively with p value = 0.001). There is no statistical difference regarding corneal compensated intraocular pressure (IOPcc) (14.17 ± 3.44 and 14.23 ± 2.01 mm Hg respectively with p value = 0.942). and this is in agreement with results of **Pniakowska and Jurowski** [21], who found that Goldmann correlated intraocular pressure (IOPg) values were found lower in keratoconus group than normal and found also that there is no statistical difference in mean IOPcc observed between Group 2 and control group (P > 0.05).

In our study, CRF was positively correlated with SE, BCVA, IOP (Goldmann), CH, IOPg and IOPcc. This s partly in agreement with results of **Goldich *et al.*** [22] who stated that CRF was positively associated with CCT and DCT IOP and negatively associated with age and AL (scaled coefficients: CCT 0.89, p < 0.0001; DCT IOP 0.46, p < 0.01; age – 0.60, p < 0.0001; AL -0.37, p < 0.01; r2 = 0.43). There was no significant association between CC and CH or CRF.

In our study, Goldmann correlated intraocular pressure (IOPg) was positively correlated with Age, SE, BCVA, IOP (Goldmann), CH, IOPg and IOPcc. However, Corneal compensated intraocular pressure (IOPcc) was negatively associated with SE and CH with positive correlation with the remaining parameters and this is in agreement [21] who found positive correlation between CRF and IOPg. [23] found that CRF was weakly correlated with IOPg and IOPcc and strongly significantly correlated with IOPg, CH showed weak negative correlation with IOPcc, weak positive with IOPg, and no correlation with IOPg.

In our study, a binary logistic regression analysis was conducted to predict keratoconus patients within the group using CRF, IOPg, IOPcc, CH and gender as predictors. We found relation between CH and gender.

Changes in CRF and CH may be reflective of structural changes in the ground substance of the cornea. Thus, ORA provide invaluable information for delineating biomechanical conditions pertaining to the cornea, with special regard to ocular diseases, e.g. keratoconus and glaucoma. CH and CRF were found to decrease with the preogress in keratoconus (Mild, moderate, adavanced).

CONCLUSION

In conclusion, corneal biomechanical properties, characterized by corneal hysteresis and the corneal resistance factor, provide new indicators for the diagnosis of keratoconus. Further studies can be done to evaluate corneal biomechanics in keratoconic patients after cross linking, also to evaluate corneal biomechanics changes in contact lenses weares.

RECOMMENDATIONS

1. Corneal biomechanical properties study for any case suffering from irregular astigmatism and glaucoma.
2. keratoconic patients with glaucoma to measure intraocular pressure in their follow up visits by ORA due to false low reults by Goldman applanation tonometry due to affection of corneal biomechanics (low CH and CRF) .
3. Further studies can be done to evaluate corneal

biomechanics in keratoconic patients after cross linking , also to evaluate corneal biomechanics changes in contact lenses weares .

4. Further studies should be done to collerate CH and CRF with age, gender, myopes and hypermetropes with a large sample size.
5. Large studies should be done to detect the prevelance of keratoconus in Egypt as this information was missing from peerviewed studies we researched.
6. Limitation of our study: small sample size, the factor of age of age and gender was not fixed between keratoconus and control group.

REFERENCES

1. **Auffarth GU, Wang L and Völcker HE (2000):** Keratoconus evaluation using the Orbscan topography system. J. Cataract Refract. Surg., 26:222–228.
2. **Weed KH, MacEwen CJ, Giles T, Low J and McGhee CN(2008):** The Dundee University Scottish keratoconus study: demographics, corneal signs, associated diseases and eye rubbing. Eye , 22(4):534–541. doi: 10.1038/
3. **Georgiou T, Funnell CL, Cassels-Brown A and O'Conor R(2004):** Influence of ethnic origin on the incidence of keratoconus and associated atopic disease in Asians and white patients. Eye, 18(4):379–383. doi: 10.1038/sj.eye.6700652.
4. **Abu-Amero KK, Kalantan H and Al-Muammar AM (2011):** Analysis of the VSX1 gene in keratoconus patients from Saudi Arabia. Mol. Vis.,17:667–672.
5. **Kenney MC, Chwa M, Atilano SR, Tran A, Carballo M and Saghizadeh M (2005):** Increased levels of catalase and cathepsin V/L2 but decreased TIMP-1 in keratoconus corneas: evidence that oxidative stress plays a role in this disorder. Invest. Ophthalmol. Vis. Sci., 46(3):823–832. doi: 10.1167/iovs.04-0549.
6. **Akhtar S, Bron AJ, Salvi SM, Hawksworth NR, Tuft SJ and Meek KM (2008):** Ultrastructural analysis of collagen fibrils and proteoglycans in keratoconus.Acta Ophthalmol., 86(7):764–772.doi:10.1111/j.1755-3768.2007.01142.x.
7. **Ku JY, Niederer RL, Patel DV, Sherwin T and McGhee CN(2008):** Laser scanning *in vivo* confocal analysis of keratocyte density in keratoconus. Ophthalmology, 115(5):845–850. doi: 10.1016/j.ophtha.04.067.
8. **Meek K, Tuft S, Huang Y, Gill PS, Hayes S and Newton RH (2005):** Changes in collagen orientation and distribution in keratoconus corneas. Invest. Ophthalmol. Vis. Sci., 46(6):1948–1956. doi: 10.1167/iovs.04-1253.
9. **Karimian F, Aramesh S, Rabei HM, Javadi MA and Rafati N(2008):** Topographic evaluation of relatives of patients with keratoconus. Cornea, 27:874–878.
10. **Rabinowitz YS(2003):** The genetics of keratoconus. Ophthalmol. Clin. North Am., 16:607–620.
11. **Stabuc-Silih M, Strazisar M, Ravnik-Glavac M, Hawlina M and Glavac D (2010):** Genetics and clinical characteristics of keratoconus. Acta Dermato-venerol. Alp. Panonica Adriat., 19:3–10.
12. **Matalia H(2013):** Imaging modalities of keratoconus. Indian J. Ophthalmol., 61(8): 394–400.
13. **Espandar L(2010):** Keratoconus: overview and update on treatment. Middle East Afr. J. Opphthalmol., 17:15-20.
14. **Luce D(2012):** Ocular response analyzer, understand the cornea, understand the pressure, corneal biomechanics and accurate IOP in one simple instrument / ORA master presentation Reichert ophthalmic instruments depew. Available at: http://kcglobal.org/archives/ ORAM aster presentation. ppt
15. **Li X, Rabinowitz YS, Rasheed K and Yang H(2004):** Longitudinal study of the normal eyes in unilateral keratoconus patients. Ophthalmology, 111:440–446.
16. **Shetty R., Kaweri, L., Pahuja, N., Nagaraja, H., Wadia, K., Jayadev, C and Arora V(2015):** Current review and a simplified "five-point management algorithm" for keratoconus. Indian Journal of Ophthalmology, 63(1): 46–53.
17. **de Sanctis UD, Loiacono C and Richiardi L(2008):** Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/ subclinical keratoconus. Ophthalmology, 115:1534–1539.
18. **Shah S and Laiquzzaman M(2009):** Comparison of corneal biomechanics in pre and post-refractive surgery and keratoconic eyes by ocular response analyzer. Contact Lens Anterior Eye, 32:129–132.
19. **Fontes BM1, Ambrósio R Jr, Velarde GC and Nosé W(2011):** Ocular response analyzer measurements in keratoconus with normal central corneal thickness compared with matched normal control eyes.J. Refract. Surg., 27(3):209-215.
20. **Ortiz D, Piñero D, Shabayek MH, Arnalich-Montiel F and Alió JL(2007):** Corneal biomechanical properties in normal, post-laser in situ keratomileusis, and keratoconic eyes. J. Cataract Refract. Surg., 33(8):1371-1375.
21. **Pniakowska Z1 and Jurowski P(2016):** Detection of the early keratoconus based on corneal biomechanical properties in the refractive surgery candidates. Indian J. Ophthalmol., 64(2):109-113. doi: 10.4103/0301-4738.179725.
22. **Kotecha A1, Russell RA, Sinapis A, Pourjavan S, Sinapis Dand Garway F(2014):** Heath DF. Biomechanical parameters of the cornea measured with the Ocular Response Analyzer in normal eyes. BMC.Ophthalmol.,14:11-16. doi: 10.1186/1471-2415-14-11.
23. **Goldich Y1, Barkana Y, Avni I and Zadok D(2010):** Goldmann applanation tonometry versus ocular response analyzer for intraocular pressure measurements in keratoconic eyes. Cornea, 29(9):1011-1015.