Corneal biomechanical metrics in thin cornea of normal, keratoconus suspect and keratoconus in Egyptian population

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Research article

Keywords: Thin cornea, corneal biomechanics, keratoconus suspects, keratoconus

Posted Date: August 23rd, 2019

DOI: <https://doi.org/10.21203/rs.2.13518/v1>

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Abstract

Background To assess and compare corneal hysteresis (CH) and corneal resistance factor (CRF) in normal thin (NT) healthy corneas with central corneal thickness (CCT) 470-500 μm with matched thickness in keratoconus (KC) and keratoconus suspect (KCS) eyes. **Methods** A total of 66 eyes in three groups were included prospectively: NT, KCS and KC groups based on clinical examination and topography. Corneal hysteresis (CH) and corneal resistance factor (CRF) were measured by the ocular response analyzer. CH and CRF were compared between the three groups and statistically analyzed by variances test. **Results** The three groups consisted of 32 NT, 19 KCS, and 15 KC. The mean CH measured was 8.55 ± 1.77 , 9.03 ± 1.119 and 8.06 ± 0.85 mm Hg in NT, KCS and KC eyes, respectively. The mean CRF was 8.39 ± 1.47 , 8.27 ± 1.09 and 7.24 ± 1.27 mm Hg in NT, KCS and KC eyes, respectively. Within range of central corneal thickness (470 – 500 μm), only mean CRF was statistically significantly different between the NT and KC ($P < 0.05$); there was no statistically significant difference between NT and KCS, nor the mean CH between each groups ($P > 0.05$). **Conclusions** CRF only can be helpful in differentiating KC from NT eyes; however, it's not valuable for detecting KCS which is the main concern for refractive surgery. No benefit from CH in differentiating between the study groups. Further investigations & work focusing on more accurate tests for identifying KCS are still needed.

Background

Central corneal thickness (CCT) is a biometric factor,^[1] with a wide range of variability in healthy eyes, the cause of which is believed to result from different amounts of collagen fibrils and interfibrillar substance in the corneal stromal matrix.^[2] It is a measure of tissue mass and represent an indicator of corneal rigidity. Also, CCT changes among ethnic groups and show strong heritability among families.^[3]

The development of a test for reliable assessment of corneal rigidity and its response to excimer laser ablation was a vital point in the development of refractive surgery. This was a challenging issue until 2005, when the Ocular Response Analyzer (ORA) appeared in the market with its uses in ophthalmology medicine.^[4]

The ORA has an infrared electro-optical system that monitors corneal deformations. It delivers a precisely metered collimated air pulse to the eye. The cornea suffers an inward movement, passing a first applanation state before assuming a concave shape. The air pressure progressively declines after this first applanation and the cornea passes through a second applanation state while returning to its normal convex curvature. The test plots a waveform that contains two peaks, corresponding to the inward and outward applanation moments.

Using this bidirectional applanation measurement, the ORA is able to present the four original parameters. Corneal hysteresis (CH) is the difference between these two pressure values, which represents the corneal viscoelastic damping. The mean of these two pressures is the Goldmann-correlated IOP (IOPg). The Corneal-compensated IOP (IOPcc) is a pressure measurement that uses the CH

to determine an IOP value that is less affected by corneal properties, such as CCT. Corneal Resistance Factor (CRF) is calculated using a proprietary algorithm and represent overall cornea resistance. [5–7]

In the present study, we investigated the corneal biomechanical metrics in healthy eyes (NT) with CCT 470 to 500 μm and compared them with thickness matched keratoconus (KC), keratoconus suspect (KCS) cases.

Methods

This cross-sectional study was performed after receiving the approval of institutional ethical committee of faculty of medicine, Menoufia university, Egypt, all patients received a thorough explanation of the study design and aims; the study was conducted in compliance with informed consent regulations. Patients were selected from Ophthalmology outpatient clinics in at “Ophthalmology department of Menoufia University Hospitals & Memorial institute of ophthalmology in Giza- Cairo”. This prospective comparative study was carried out from December 2016 to November 2017.

Patients were divided into three groups:

Group (NT): Normal thin corneas with CCT 470–500 μm with normal pentacam.

Group (KCS): Corneas with CCT 470–500 μm with suspicious pentacam.

Group (KC): Corneas with CCT 470–500 μm with keratoconus pattern in pentacam.

Inclusion criteria includes: Age from 18 to 35 years old, Central corneal thickness is between 470–500 μm , As regard keratoconus suspect group:- no clinical signs of keratoconus, CCT 470–500 μm , steep keratometric curvature greater than 47.0 diopters, minor topographic asymmetry defined as (inferior-superior difference $\geq 1.5\text{D}$, superior-inferior difference $\geq 2.5\text{D}$). As regard keratoconus group:-any grade of KC with CCT within the range selected in the study (470–500 μm).

Exclusion criteria includes: Previous ocular surgery, corneal scars or opacities, chronic use of topical medications, systemic collagen diseases e.g.: Marfan syndrome, Ehler Danlos syndrome, and previous history of corneal ulcers.

Each subject will have a comprehensive ophthalmologic examination, including a review of their medical history, corrected distance visual acuity, slit lamp biomicroscopy and fundus examination. Pentacam topography (*oculus pentacam, Optikgerate GmbH, Wetzlar, Germany*). and every patient was subjected to ORA (*Ocular Response Analyzer, Reichert, Walden Ave, NY USA*),, to measure Corneal biomechanical parameters: corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann correlated pressure (IOPg), and corneal-compensated intraocular pressure (IOPcc).

Two consecutive ORA measurements were made and the best waveform score from each patient was included in the analysis of the study.

The figures (1, 2 and 3) represent pentacam of study group 1 (Normal Thin cornea), group 2 (Keratoconus suspect) and group 3 (Keratoconus); respectively.

The ORA is a noncontact tonometer with automated eye centration alignment. Subjects were seated on a chair and instructed to place their foreheads on the headrest of the ORA device, and were instructed about a noncontact probe that would move toward the eye and emit a gentle puff of air. They were asked to fix on a blinking red light in the machine. Thereafter, the ORA was activated, and the air puff was emitted onto the center of the cornea. Only, the reliable ORA readings with good score were obtained & stored.

The manufacturer defined good-quality readings as both force-in and force-out applanation signal peaks on the ORA waveform being fairly symmetrical in height. The ORA displayed a graphic representation of the corneal response after each measurement (*Figure 4*).

The figures (5, 6, and 7) represent the ORA signals provided from our three study groups.

The red curve is the “dynamic map” of the cornea obtained during the rapid in/out deformation. That dynamic process generated two signal peaks that defined the two applanation states. The difference between these inward and outward motion applanation pressures ($P1$ and $P2$) was called corneal hysteresis (CH).

The ORA software utilized the CH to generate two additional parameters: the corneal-compensated IOP (IOPcc) and the corneal resistance factor (CRF). A Goldmann-correlated IOP (IOPg) was also provided by the machine.

Statistical Analysis

Data were statistically described in terms of mean standard deviation (SD), median and range, or frequencies and percentages when appropriate. Comparison of numerical variables between the study groups was done using independent samples t test. For comparing categorical data, Chi square (2) test was performed. Fisher's exact test was used instead when the expected frequency is less than 5. Comparison of the continuous variables was done by One-way ANOVA with Bonferroni correction for post-hoc analysis. The predictive ability of the ORA parameters was analyzed using Receiver operating Characteristics (ROC) Curve. P-values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; IBM Corp., NY, USA) version 21 for Microsoft Windows. ROC curves were developed using MedCalc biomedical statistics software version 15.8 (MedCalc Software bvba, Ostend, Belgium).

Results

A total of 66 eyes were enrolled in our study, of which 32 eyes showed normal thin corneas, 15 eyes with keratoconus suspect, and 19 eyes with frank keratoconus.

The age of our study groups ranged from 18 to 35 years, with an average of 29.59 ± 3.02 years for Group (NT) and 26.86 ± 5.42 for Group (KCS) and 30.26 ± 3.85 for Group (KC). (*Table 1*)

Our study included forty eyes of male patients and twenty six eyes of female patients. The gender distribution is summarized in *Table 2*.

The central corneal thickness ranged from 470 to 500 μm , with an average of $492.90 \pm 8.07 \mu\text{m}$ for group (NT) and $488.53 \pm 9.47 \mu\text{m}$ for group (KCS) and $486.10 \pm 9.41 \mu\text{m}$ for group (KC). The difference between the three groups was statistically insignificant ($p\text{-value} = 0.057$). (*Table 3*)

The mean CH of the study groups was $8.55 \pm 1.77 \text{ mmHg}$, $9.03 \pm 1.119 \text{ mm Hg}$, 8.06 ± 0.85 for groups (NT), (KCS), and (KC) respectively. (*Table 4*) which is statistically insignificant. The mean CRF of the study groups was $8.39 \pm 1.47 \text{ mmHg}$, $8.27 \pm 1.09 \text{ mm Hg}$, 7.24 ± 1.27 for groups (NT), (KCS), and (KC) respectively which significant only between (NT) & (KC). (*Table 5*)

Discussion

Forme fruste keratoconus (FFKC) and keratoconus suspect (KCS) diagnosis remain a dilemma, despite the advances in using topographic and tomographic tools; there is no specific accepted consensus for categorizing an eye as KCS [8]. Many cases of post refractive corneal ectasia still reported, that is why searching for a supplementary investigation to detect FFKC and KCS is needed. For decision making to perform corneal ablation procedure in these cases, the surgeon should depend on analysis of multiple investigations & parameters. [9–13]

Ocular response analyzer (ORA) represents a relatively new perspective for in vivo measurement of corneal biomechanics; since its development by Luce [5] many studies have evaluated the ORA parameters (CH and CRF) for detecting keratoconus (KC) and keratoconus suspect (KCS) and normal thin (NT) eyes. [14–18] Other reports have determined that CH and CRF are significantly lower in KC eyes than in NT eyes and reported CH and CRF as poor properties for discriminating mild KC from NT eyes. [6, 19–20] In spite of the various studies performed to evaluate the ORA accuracy for detecting KC and KCS from NT eyes, the diagnostic performance of the CH and CRF remains of limited value and the role of CCT as a confounding factor is not yet clearly defined. [6, 14–18]

The current study tried to reveal the diagnostic value of ORA as an auxiliary test to differentiate thin corneas with different topographic diagnoses (KC, KCS and NT). Our results showed that only the mean CRF was significantly lower in KC eyes compared to NT ones, but no significant difference was seen in CCT, CH and CRF parameters of KCS eyes compared with NT eyes.

Various studies have assessed the CH and CRF between NT and KC eyes. Fontes et al⁶ found significantly lower CH and CRF in KC in comparison to NT eyes. However we found that only the CRF was significantly lower in KC than NT eyes, with no significance to CH.

Our study shows comparable results to Galletti JG et al ^[20] which prove that corneal resistance factor was better than CH for detecting keratoconic corneas once the effect of CCT on ORA measurements was considered, even for topographically unaffected fellow eyes of patients with keratoconus. The CCT-corrected CRF cutoff values and transformed indices may be of clinical use. In other words; CH is probably decreased in eyes with keratoconus but not to the point that it can be clinically useful in ORA-based subclinical keratoconus detection.

The present study also demonstrated that the mean CH, CRF and CCT in KCS did not differ from NT eyes. Using the principle Orbscan criterion to identify KCS that was a difference of 1.5 diopters or greater between superior and inferior corneal curvature, did not find any significant difference between groups. Saad et al used a computer-based calculation from Nidek OPD scan videokeratographer, found a significant difference between NT and KCS first, which failed to remain significant after controlling for CCT.^[21]

A possible hypothesis for this finding might be the mysterious role of corneal thickness on corneal biomechanics. CH and CRF are known to be highly correlated to corneal thickness. ^[6, 22–23] As corneal thickness decreases significantly in keratoconic eyes ^[24] and usually is within NT limits in KCS and NT eyes, any changes in CH and CRF could be related to the changes in CCT. After controlling for the CCT in our study, only CRF differences between NT and KC remained significant. The CCT between NT and KCS were not significantly different, therefore, could not play a confounding role.

However, our results are not in agreement with a number of previous studies. Schweitzer et al ^[16] used the NT fellow eye of a manifest keratoconic with KISA index of <60% for defining KCS. They found a significant difference between NT and KCS eyes which remained significant after controlling for CCT in the thinner groups. Johnson et al ^[14] used the keratoconus severity score (KSS) score developed by the collaborative longitudinal evaluation of KC study group to define and grade the severity of KCS also found a significant difference between KCS and NT eyes after adjustment for CCT, age and sex. The KCS grading of severity performed in this study has made the comparison of their result with other studies directly impossible. This discrepancy between the studies may be caused by the various definitions of KCS used in different studies; therefore the use of a unified grading scale for defining KCS in future studies is highly useful for comparing the results.

As the receiver operating characteristic (ROC) curve analysis between KC and NT eyes showed, selecting the cutoff points for CH (8.4) and CRF (7.6) provided that 84.2% sensitivity and 46.8% specificity for CH, and 78.95% sensitivity and 68.09% specificity for CRF. Because there was no significant difference between KCS and NT eyes in CH and CRF, the ROC curve analysis was only done for NT and KC group and the KCS were not included in the present study. The ROC curve analysis performed in the Fontes et al study ^[7] showed a poor overall predictive value of CH (74.83%) and CRF (76.97%) with the cutoff points of 9.64 mmHg and 9.60 mmHg respectively.

The ORA parameters can be helpful in differentiating KC eyes from NT ones, but CH and CRF cannot discriminate KCS from NT eyes; therefore ORA alone would not be a helpful diagnostic tool for detecting KCS eyes. However, as mentioned before, the clinical challenge is to have a test that could detect KCS with high accuracy from NT eyes.

Conclusion

CRF only can be helpful in differentiating KC from NT eyes; however, it's not valuable for detecting KCS which is the main concern for refractive surgery. No benefit from CH in differentiating between the study groups. Further investigations & work focusing on more accurate tests for identifying KCS are still needed.

List Of Abbreviations

NT: Normal thin cornea

KC: Keratoconus

KCS: Keratoconus suspect

CCT: Central corneal thickness

ORA: Ocular Response Analyzer

CH: Corneal hysteresis

CRF: Corneal resistance factor

IOPg: Goldmann- correlated intraocular pressure

IOPcc: Cornea-compensated IOP

ROC: receiver operating characteristic

Declarations:

- Ethics approval and consent to participate:

This study was approved by Ethical Committee of the Menoufia University Hospital, all patients received a thorough explanation of the study design and aims followed by a signed informed consent; the study was conducted in compliance with the tenets of the Declaration of Helsinki.

- Consent for publication:

Not applicable

- Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

- Competing interests:

The authors declare that they have no competing interests

- Funding:

No funding was received

- Authors' contributions:

AGZ designed the study and analyzed the results. MSA performed the ORA examination, HMM and MAEH was a major contributor in writing the manuscript. MFE performed pentacam. NMB contributed to statistical analysis. All authors read and approved the final manuscript.

- Acknowledgements:

Not applicable

References

1. Doughty M. J. and Zaman M. L. (2000): Human corneal thickness and its impact on intraocular pressure measures: A review and meta-analysis approach. *Surv. Ophthalmol.*, 44 (5): 367–408.
2. Boote C, Hayes S, Abahussin M. and Meek K. M. (2006): Mapping collagen organization in the human cornea: Left and right eyes are structurally distinct. *Invest. Ophthalmol. Vis. Sci.*, 47 (3): 901–8.
3. Torres R. J., Jones E., Edmunds B., Becker T., Cioffi G. A. et al. (2008): Central corneal thickness in Northwestern American Indians/Alaskan Natives and comparison with White and African-American persons. *Am. J. Ophthalmol.*, 146 (5): 747–51.
4. Roberts C. (2000): The cornea is not a piece of plastic. *J. Refract Surg.*, 16 (4): 407–13.
5. Luce D. A. (2005): Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J. Cataract Refract Surg.*, 31 (1): 156–162.
6. Fontes B. M., Ambrósio R Jr., Alonso R. S., Jardim D., Velarde GC. et al. (2008): Corneal biomechanical metrics in eyes with refraction of –19.00 to +9.00 D in healthy Brazilian patients. *J. Refract Surg.*, 24 (9): 941–5.
7. Fontes B. M., Ambrósio R Jr., Velarde GC., Nose W. (2010): Ocular response analyzer measurements in keratoconus with normal central corneal thickness compared with matched normal control eyes. *J. Refract Surg.* May, 19: 1–7.

8. Schlegel Z, Hoang-Xuan T, Gatinel D.(2008): Comparison of and correlation between anterior and posterior corneal elevation maps in normal eyes and keratoconus-suspect eyes. *J Cataract Refract Surg.*; 34:789–95.
9. Mohammad Pour M. (2007): Corneal ectasia after LASIK in one eye and uneventful PRK in the fellow eye. *J Cataract Refract Surg.*;33:1677.
10. Mohammad Pour M. (2008): Risk for ectasia with LASIK. *J Cataract Refract Surg.*;34:181–2.
11. Touboul D, Roberts C, Kérautret J, Garra C, Maurice-Tison S, Saubusse E, et al.(2008): Correlations between corneal hysteresis, intraocular pressure, and corneal central pachymetry. *J Cataract Refract Surg.*; 34:616–22.
12. Klein SR, Epstein RJ, Randleman JB, Stulting RD.(2006): Corneal ectasia after laser in situ keratomileusis in patients without apparent preoperative risk factors. *Cornea.*;25:388–403
13. Kymionis GD, Bouzoukis D, Diakonis V, Tsiklis N, Gkenos E, Pallikaris AI, et al.(2007): Long-term results of thin corneas after refractive laser surgery. *Am J Ophthalmol.*;144:181–85
14. Johnson RD, Nguyen MT, Lee N, Hamilton DR. (2011): Corneal biomechanical properties in normal, forme fruste keratoconus, and manifest keratoconus after statistical correction for potentially confounding factors. *Cornea.* 30:516–23.
15. Kirwan C, O'Malley D, O'Keefe M.(2008): Corneal hysteresis and corneal resistance factor in keratoectasia: Findings using the Reichert ocular response analyzer. *Ophthalmologica.*; 222:334–7.
16. Schweitzer C, Roberts CJ, Mahmoud AM, Colin J, Maurice-Tison S, Kerautret J.(2010):Screening of forme frusta keratoconus with the ocular response analyzer. *Invest Ophthalmol Vis Sci.*; 51(5):2403–10.
17. Shah S, Laiquzzaman M, Bhojwani R, Mantry S, Cunliffe I..(2007): Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes. *Invest Ophthalmol Vis Sci.*; 48:3026–3031.
18. Shah S, Laiquzzaman M, Yeung I, Pan X, Roberts C.(2009): The use of the ocular response analyser to determine corneal hysteresis in eyes before and after excimer laser refractive surgery. *Cont Lens Anterior Eye.* 32:123–8.
19. Galletti JG, Pförtner T, Bonthoux FF.(2012): Improved keratoconus detection by ocular response analyzer testing after consideration of corneal thickness as a confounding factor. *J Refract Surg.*; 28:202–8.
20. Saad A, Lteif Y, Azan E, Gatinel D. (2010): Biomechanical properties of keratoconus suspect eyes. *Invest Ophthalmol Vis Sci.*; 51(6):2912–6.
21. Fontes BM, Ambrósio R, Jr, Velarde GC, Nosé W.(2011): Corneal biomechanical evaluation in healthy thin corneas compared with matched keratoconus cases. *Arq Bras Oftalmol.*; 74:13–6.
22. Kamiya K, Hagishima M, Fujimura F, Shimizu K.(2008): Factors affecting corneal hysteresis in normal eyes. *Graefes Arch Clin Exp Ophthalmol.*; 246:1491–4.

23. Rabinowitz YS, Rasheed K. (1999): KISA% INDEX: a quantitative videokeratography algorithm embodying minimal keratometric criteria for diagnosing keratoconus. J cataract refract surg.; 25(10):1327–1335.

Tables

Table 1: The age of the study groups in years.

	Group 1 (Normal Thin)	Group 2 (keratoconus suspect)	Group 3(Keratoconus)
Mean± SD (in years)	29.5938± 3.02526	26.8667± 5.42305	30.2632± 3.85634
Range (in years)	26-35	18-35	23-35
p- value	0.053		

Table 2: Showing gender distribution in both groups.

	Group 1 (Normal Thin)	Group 2 (keratoconus suspect)	Group 3(Keratoconus)	Total
Males	20	8	12	40
females	12	7	7	26
Total	32	15	19	66
The Pearson Chi-Square	0.806			

Table 3: Showing CCT in three groups.

	Group 1 (Normal Thin)	Group 2 (keratoconus suspect)	Group 3(Keratoconus)
Mean± SD (in μm)	492.90625± 8.0776848	488.53333± 9.470756	486.1052± 9.415676
Range (in μm)	477-500	471-500	472-500
p- value	0.057		

Table 4: The corneal hysteresis (CH) of the study group in mm Hg.

	Group 1 (Normal Thin)	Group 2 (keratoconus suspect)	Group 3 (Keratoconus)
Mean ± SD (in mmHg)	8.5593 ± 1.7757	9.0333 ± 1.11909	8.0578 ± 0.85395
Range (in mmHg)	5.7-14.10	7.50-10.80	6.50-10.80
p- value	Between group 1 and 2	0.878	
	Between group 2 and 3	0.157	
	Between group 1 and 3	0.689	

Table 5: The corneal resistance factor of the study groups in mm Hg

Group 1 (Normal Thin) Group 2 (keratoconus suspect) Group 3(Keratoconus) Mean ± SD (in mmHg)
8.3906 ± 1.4732 8.2733 ± 1.09444 7.24210 ± 1.2720 Range (in mmHg) 5.7-12.50 6.90-10.10 5-9.70 P
value Between group 1 and 2 1 Between group 2 and 3 0.088 Between group 1 and 3 0.013

Figures

Figure 1

Figure 1: Represents pentacam of the left eye of patient number 22 of the group 1 (Normal).

Figure 2

Figure 2: Represents pentacam of the right eye of patient number 9 of the group 2 (Keratoconus suspect).

Figure 3

Figure 3: Represents pentacam of the left eye of patient number 14 of the group 3 (Keratoconus).

— Applanation signal — Pressure (air pulse)

Figure 4

Figure 4: ORA signals

Waveform and measurement values

Waveform Parameters
Deviation From Mean

Keratoconus Match Probabilities

Keratoconus Match Index

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IOPg, IOPcc, CH and CRF values are expressed in mmHg.

Figure 5

Figure 5: Represents ORA signal of the left eye of patient number 22 of the group 1 (Normal).

Waveform and measurement values

Waveform Parameters Deviation From Mean

Keratoconus Match Probabilities

Keratoconus Match Index

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IOPg, IOPcc, CH and CRF values are expressed in mmHg.

Figure 6

Figure 6: Represents ORA signal of the right eye of patient number 9 of the group 2 (Keratoconus suspect).

Waveform and measurement values

Waveform Parameters
Deviation From Mean

Keratoconus Match Probabilities

Keratoconus Match Index

Memorial Institute
BARMED

IOPg, IOPcc, CH and CRF values are expressed in mmHg.

Figure 7

Figure 7:.. Represents ORA signal of the left eye of patient number 14 of the group 3 (Keratoconus).