Correlation between Corneal Biomechanics and Intraocular Pressure

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ABSTRACT

Background: measurement error in goldman applanation tonometry (GAT) may be due to the differences in central corneal thickness (CCT) or corneal stromal rigidity. Corneal hysteresis (CH) and corneal resistance factor (CRF) may prove a helpful guide to measure this relationship.

Purpose: To study the correlation between cornea biomechanical parameters as measured with the Ocular Response Analyzer (ORA) and intraocular pressure (IOP).

Patient and Method: The study is a comparative prospective cross-sectional clinical trial included 60 eyes of patients subdivided into three groups; 20 with primary open angle glaucoma (POAG), 20 with ocular hypertension (OHT) and 20 as normal population. They underwent measurement of IOP, CCT and corneal biomechanical parameters (CH, CRF) using GAT, ORA and ultrasound pachymetery.

Results: Thirty patients were enrolled in the study, 22 males (73%) and 8 females (27%). The mean age of patients involved is 44.2 ± 12.6 ranging between 25 and 60 years old. The IOP by GAT, IOPg and IOPcc were 21.6 ± 5.1 , 21.5 ± 5.1 , 22.1 ± 5.1 respectively. The CH and CRF were 14.2 ± 9.3 and 18 ± 11.2 . The CCT was 531.97 ± 20.4 . The correlation is insignificant between all parameters of IOP and CCT (P >0.05) while the correlation is significant between IOP and corneal biomechanics and between CCT and corneal biomechanics (P < 0.05).

Conclusion: CCT affect corneal biomechanical properties, the higher CCT the higher were CH and CRF and vice versa. Corneal biomechanics affect IOP more than CCT. The higher CH the lower was IOP while the higher CRF the higher was IOP. CH affect IOPcc more than GAT while CRF affect GAT more than IOPcc. CH decrease in glaucoma and in OHT more than normal while CRF increase in glaucoma and OHT more than normal. **Keywords:** Intraocular pressure – Ocular Response Analyzer – Goldmann Applanation Tonometry – Corneal

biomechanics.

INTRODUCTION

During the 16th century, when Bannister described a subset of blind patients with eyes that were firm to the touch, intraocular pressure has been regarded as a core vital sign of the eye, along with visual acuity, the pupillary exam, and the visual field. Measurement of IOP (tonometry) in a consistent and reliable manner is fundamental to the diagnosis and management of glaucoma¹.

Tonometry

Tonometry is the clinical measurement of IOP. It can be carried out using a range of different instruments but the single method with ultimate accuracy is cannulation of the anterior chamber and measurement of the intraocular pressure by direct manometry. As obvious as it sounds this method is excessively invasive, impractical and risky rendering it out of use except for academic and research purposes ².

All non-invasive tonometer follow a similar principle in that the higher the pressure in a sphere, the greater the force will be required to indent it. Tonometry measures IOP by quantifying the deformation of the globe and equating it to the force responsible for this shape change. This is carried out

either by contact, from the tonometer apparatus, or by non-contact, from a stream of air ³. All clinical measurements are an 'estimate' we can never approach the true underlying value of a clinical measurement without first understanding the pitfalls and limitations of a given measurement technique.

Goldman applanation tonometry

Practically, for years, Goldman applanation tonometry (GAT) has been considered to be the most accurate non invasive method of IOP measuring in spite of being affected by the corneal properties ⁴.

The GAT is based on the Imbert-fick law, which is demonstrated, by the following equation: (W = P X A) where p = pressure, A = area applanated and W = force needed for applanation. However, this equation in its current form assumes that the cornea is indefinitely thin, dry and perfectly elastic which is not the case. So, the equation was modified to match the corneal physical properties: (W + s = P X A + b) where s = surface tension caused by the tear film, b =

Received:20 / 3/2018 Accepted:30 / 3 /2018 bending resistance of the cornea. Luckily, it was found that at an applanation diameter of 3.06 mm, corresponding to an area of 7.35 mm^2 , s approximately equals b thus neutralizing each other allowing the use of the simpler first equation ⁵.

Central corneal thickness

In their original study, **Goldmann and Schmidt** ⁵ based their design on what they believed to be a relatively constant central corneal thickness (CCT) of 0.5 mm among otherwise normal individuals. They acknowledged that the accuracy of their device would be affected if CCT deviated from this value. We now know CCT varies greatly among the general population, to a degree that affects the accuracy of most tonometry techniques in daily practice.⁶

As a continuation of the work of Goldmann and Schmidt, **Ehlers** *et al.* ⁷ carried out a study in which they cannulated the anterior chamber of otherwise normal eyes undergoing cataract surgery to accurately measure their IOP and correlated corneal thickness with errors in GAT. They found that GAT most accurately reflected true intracameral IOP when the CCT was 520 μ m, any deviation from this number affects the accuracy of the device. Thick corneas will cause overestimation of IOP whereas thin corneas will cause its underestimation. This was confirmed by further studies using modern pressure transducers⁸.

Corneal Biomechanics

It is corneal material properties, which refers to how a material deforms in response to an external stress.

Elastic materials are those for which deformation is directly proportional to stress, independent of time or rate at which the force is applied, and regains its original form when stress is removed ⁹.

Viscous materials are those for which the relationship between stress and deformation depends on time or rate. In other words viscosity can be defined as a material's resistance to flow, and when the stress is removed, the material does not return to its original shape ¹⁰.

Viscoelastic materials have elements of both viscosity and elasticity. Viscoelastic material will regain its original shape like an elastic material, but its deformations in response to stress are not • instantaneous and as a result energy is lost by these materials when stress is applied¹¹. Most biological • materials like the cornea have a liquid and a solid •

component, when exposed to stress they display both viscous and elastic behavior called viscoelasticity.

Hysteresis is a Greek word means coming behind or delay, Sir James Alfred Ewing of Scotland in 1890 was the first to describe the phenomenon of hysteresis as a property of certain physical systems characterized by the nature of its response times to an applied force. Corneal hysteresis is a new term describing some aspect of corneal viscoelastic biomechanical properties. It has been used more since the commercial introduction of the ORA, and in other words it is a specific measure of the ORA¹².

Ocular response analyzer

In 2004 ORA (Reichert Ophthalmic Instruments) has been introduced for the first time as a non-contact tonometer that not only measure IOP, but also corneal biomechanics.

The Ocular Response Analyzer utilizes a rapid air impulse to apply force to the cornea, and an advanced electro-optical system to monitor the deformation. In one simple, fast measurement, the instrument records two applanation events; one while the cornea is moving inward and the other as the cornea moves outward¹³. Due to the corneal viscoelastic properties the first applanation pressure (P₁) is higher than the second applanation pressure (P₂) and the difference between them is the corneal hysteresis (CH)¹⁴.

The special computer software of the ORA utilize the data obtained from the infra-red light detector and the air pulse transducer to plot the applanation signal curve and 4 parameters; corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann correlated IOP (IOPg), and Corneal Compensated IOP (IOPcc).

PATIENTS AND METHODS Patients

The work is a prospective comparative clinical study included 60 eyes of 30 patients subdivided into three groups: the first group included 20 normal eyes of 10 patients as a control group; the second group included 20 eyes of 10 patients with primary open angle glaucoma. The third group included 20 eyes of 10 patients with only ocular hypertension.

Inclusion criteria

Patients in the age group ranges between 20- 65 years old.

- Patients with primary open angle glaucoma.
- Ocular hypertensive patient

Exclusion criteria

- Corneal dystrophies.
- Corneal degenerations.
- Keratoconus.
- Post LASIK.
- Post cataract extraction
- Post glaucoma surgery

Methods

All Study patients were subjected to the following;

- 1. Full medical and ocular history taking.
- 2. Measurement of best-corrected visual acuity (BCVA) for distance.
- 3. Slit lamp examination:
- *Cornea:* evaluated for exclusion of corneal opacities or degenerations.
- *Lens:* evaluated for exclusion of pseudophakia and aphakia.
- *Anterior chamber:* evaluated for exclusion of flare, cells and hyphema.
- Iris: evaluated for exclusion of rubiosis.
- Fundoscopy using 90D non contact lens to evaluate CDR.
- Evaluation of the angle using three mirror Goldman contact lens.
- Measurement of IOP using Goldman applanation tonometry.
- 4. Measurement of central corneal thickness (CCT) using ultrasound pachymetry.
- 5. Measurement of CH, CRF, IOPg and IOpcc using ORA.
- 6. Assessment of visual field using Humphrey visual field.

Intraocular pressure parameter:

- 7. OCT optic disc.
- 8.

Statistical analysis

- Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 22.
- Data were summarized using mean, standard deviation, minimum and maximum in quantitative data.
- All tests were two tailed and considered statistically significant at p < 0.05 and highly statistically significant at p < 0.01.
- The relationship between 2 variables was assessed using Pearson Correlation. $r > \pm 0.65$ and p < 0.05 indicates a high-level correlation, $\pm 0.3 \le r \le \pm 0.65$ and p < 0.05 indicates a moderate-level correlation and $< \pm 0.3$ and p <0.05 indicates a low-level correlation.
- Comparisons between quantitative variables were done using the parametric student *t* test. Unpaired t test compare between variables in the different groups.
- Multiple linear regression analysis with stepwise variable selection was used to identify significant associations.

RESULTS

Demographic data: The study included 60 eyes of 30 patients 44 eyes of male patient (73%) and 16 eyes of female patient (27%). The age range from 25 to 60 years old and the mean age was 44.23 ± 12.64 .

Group	DS	Ν	From	То	Mean	SD
	GAT	20	11.5	19	15.7	1.9561
NP	IOPg	20	11.6	19.5	15.92	2.01588
	IOPcc	20	11.9	20	16.57	2.05659
	GAT	20	12	29	24.325	4.09195
POAG	IOPg	20	12.5	29.8	23.84	4.62105
	IOPcc	20	14.9	29	24.565	4.37099
	GAT	20	21.5	30.5	24.73	2.5915
OHT	IOPg	20	21.5	30.9	24.68	2.66944
	IOPcc	20	22.3	32.9	25.08	2.98445

Table (1): show the mean, SD and range of IOP parameters in each group

Comparison of IOP between groups: there is significant increase in all IOP parameters in POAG group and OHT group more than NP group (P < 0.05) as shown in table (2) and figure (1).

-	-			
Groups		Unpaired t test		
Gloups		Т	P value	
	POAG	8.5	< 0.001	
GAT	OHT	12.4	< 0.001	
	NP	-	-	
	POAG	7.02	< 0.001	
IOPg	OHT	11.7	< 0.001	
	NP	-	-	
	POAG	7.4	< 0.001	
IOPcc	OHT	10.5	< 0.001	
	NP	-	-	

 Table (2): Comparison of IOP parameters between groups



Figure (1): Box and Whiskers plot shows IOP parameters in the groups.

Agreement between IOP measured by GAT and ORA: the levels of agreement between different methods of IOP measurement (GAT, IOPg and IOPcc) were calculated. GAT and IOPg showed the greatest amount of agreement with the mean difference between them -0.59 ± 1.52 SD mmHg. As for GAT and IOPcc they showed a much weaker agreement with the mean difference between them -3.36 ± 4.92 mmHg. Bland-Altman plots figures (2, 3) illustrate the results.



igure (2): Bland Altman Plot of the agreement of GAT and IOPcc. Bold line = mean difference between the 2 ethods, broken line = 95% limits

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Corneal biomechanics parameters: the mean, SD and range of corneal biomechanics parameters in each group as shown in table (3).

 Table (3): Corneal biomechanics parameters

groups		Ν	From	to	Mean	SD
NP	CH	20	8.60	11.80	10.1850	.91034
	CRF	20	8.50	12.10	10.3650	.91091
POAG	СН	20	6.90	11.30	9.0000	1.39019
	CRF	20	7.00	14.30	11.1450	2.00879
OHT	СН	20	5.80	14.20	9.1050	2.06333
	CRF	20	8.70	18.00	11.9800	2.20779

Comparison of corneal biomechanics parameters between groups: there is significant decrease of CH in POAG and OHT than NP and significant increase of CFR in OHT than NP, while the differences of CRF between POAG and NP groups are insignificant. As shown in table (4) and figure (4).



Figure (4): Box and Whiskers plot shows corneal biomechanics parameters

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Groups		Unpaired t test			
		Т	P value		
	POAG	-3.2	0.003		
СН	OHT	-2.1	0.039		
	NP	-	-		
	POAG	1.6	0.122		
CRF	OHT	3.02	0.004		
	NP	-	-		

Table (4): Comparison of CH and CRF between
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Central corneal thickness: Mean, SD and range of CCT in the groups as shown in table (5).

Table (5): CCT in the different groups

Group	Ν	From	То	Mean	SD
NP	20	495.00	560.00	530.7500	20.46274
POAG	20	500.00	558.00	524.5000	19.78968
OHT	20	504.00	580.00	540.6500	18.44843

Comparison of CCT between groups: There is insignificant differences of CCT between groups. P > 0.05 as shown in table (6) and figure (5).

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	Crowns	Unpaired t test			
Groups	Groups	Т	P value		
	POAG	-0.98	0.332		
	OHT	1.6	0.116		
	NP	-	-		

 Table (6): Comparison of CCT between groups



Figure (5): Box and Whiskers plot shows CCT in each group.

Correlation between corneal biomechanics parameters and IOP parameters: The correlation performed using the data from all the three groups. CH showed significant negative correlation with all IOP parameters. The correlation was highly significant with moderate level between CH and IOPcc and significant with low level between CH and GAT, IOPg as shown in table (7) and figures (6-8).

CRF showed significant positive correlation with all IOP parameters. The correlation was highly significant with moderate level between CRF and GAT, IOPg and significant with moderate level between CRF and IOPcc as shown in table (7) and figures (9-11).

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Figure. (6): Scatter plot of relationship between CH and GAT



Figure (7): Scatter plot of relationship between CH and IOPg



Figure (8): Scatter plot of relationship between CH and IOPcc



Figure (9): Scatter plot of relationship between CRF & GAT



Figure (10): Scatter plot of relationship between CRF & IOPg



Figure (11): Scatter plot of relationship between CRF & IOPcc

Table (7): Correlation between cornea biomechanics & IOP

	Pearson Correlation (r)	P value
CH & GAT	-0.264	0.04
CH & IOPcc	-0.525	< .001
CH & IOPg	-0.28	0.03
CRF & GAT	0.528	<.001
CR & IOPcc	0.324	0.01
CRF & IOPg	0.554	<.001

Correlation between CCT and IOP parameters: There was insignificant correlation between all parameters of IOP (GAT, IOPg and IOPcc) and CCT. Correlation between CCT and difference between GAT and IOPcc showed high significant with moderate level of correlation (table 8 and figure 12).

 Table (8): Correlation between CCT and IOP.
 IOP.

	Pearson coefficient (r)	P value
CCT&GAT	0.087	0.509
CCT&IOPg	0.062	0.639
CCT&IOPcc	-0.134	0.307
CCT& GAT-IOPcc	0.53	< 0.001



Figure (12): Scatter plot of relationship between CCT and difference between GAT and IOPcc.

Correlation between CCT and corneal biomechanics parameters: There was a highly significant with moderate level of correlation between CCT and corneal biomechanics parameter (CH and CRF) as shown in table (9) and figure. (13, 14).



Table (9): Correlation between CCT and corneal biomechanics

Figure (13): Scatter plot of relationship between CCT and CH

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Multiple effect of CCT, CH and CRF on IOP: In multiple regression analysis, only CRF and CH affected changes in GAT, IOPg and IOPcc and only CH affected the difference between GAT and IOPcc (table 10, 11).

Table (10): Multiple linear regression analysis with IOP obtained with ORA, and GAT as dependent variable

	GAT		IO	Pg	IOPcc	
	В	Р	β	Р	β	Р
CCT	.02	.47	.005	.809	001	.969
СН	-2.7	< .001	-2.77	< .001	-3.25	< .001
CRF	2.61	<.001	2.78	<.001	2.41	<.001

Table (11): Multiple linear regression analysis with difference between GAT and IOPcc as dependent variable

	GAT – IOPcc		
	β	P value	
CCT	.018	0.218	
CH	.551	0.004	
CRF	.195	0.185	

DISCUSSION

IOP is measured by applying a force to cause a relative flattening or deformation of the corneal surface. Goldmann and Schmidt⁵ were aware that the physical and physiological properties of the cornea may affect the measurement of IOP. They considered two factors as possible source of error in evaluating IOP. First, the resistance provided by the corneal tissue and second, the resistance of the surface tension of the preocular tear film. They concluded that for an applanation diameter of 3.06 mm, the corneal tissue and tear film resistance would neutralize each other for an average CCT of 0.5 mm. They were aware that this was an average measurement and expected some variation around this value for different corneal thickness¹⁵. Wolfs et al ¹⁶ proposed that either a measurement error in applanation tonometry may be due to the differences in CCT, a physiological effect on the IOP of corneal tissues, an increase of collagen fibers or corneal stromal rigidity or it might be due to all of the above-stated factors. Hysteresis and CRF may prove a helpful guide to measure this relationship.

In our study, we measured IOP by GAT and by ORA (IOPg and IOPcc) we found that there was a significant increase in all IOP parameters in POAG group and OHT group as compared to NP group, which was explained by absence of medical intervention. In our study, IOPcc showed a large disparity with GAT with a mean of -3.36 mmHg higher and less agreement compared to IOPg, which had a mean of only -0.59 mmHg higher than GAT and better agreement as shown by the 95% limits.

We measured corneal biomechanics (CH and CRF) by ORA and the results showed that there was

significant decrease of CH in POAG and OHT as compared to NP. In addition, there was a significant increase of CFR and OHT compared to NP. The correlation between CH and CRF showed highly significant moderate level positive correlation suggesting that they were not the measurement of the same parameters.

We measured CCT by ultrasound pachymetry and the results showed that there was insignificant differences between groups.

Abitbol et al. ¹⁷ measured CH and CCT in normal and glaucomatous eyes; they found that CH like CCT significantly decrease in glaucomatous eyes than normal eves. Congdon et al.¹⁸ measured CH. CCT and assessment of VF and CDR in glaucomatous patient; they postulated that lower CH might be associated with a progressive field worsening and thinner CCT that was associated with the state of glaucoma damage as indicated by CDR. Shah et alError! Bookmark not defined. 20 measured CH, CRF and CCT in NTG, POAG and OHT; they found that CH decreased in POANG and OHT as compared to NTG. CRF increased in POAG and OHT as compared to NTG. Moreover, CCT decreased in POAG and increased in OHT. Our results agreed with previous studies in all results except in that differences of CCT between groups that were insignificant which may be due to low number of patient in each group and considerable overlap in the CCT values.

We analyzed the possible relationship between variables using the data from all the three groups. Concerning the relations between CCT and corneal biomechanics, a simple regression line revealed a relationship between CCT and CH and CCT and CRF showing a positive effect, that is, the higher the CCT the higher was the corneal biomechanics and vice versa. Although the relationship was statistically significant, the correlation coefficient was not that strong implying that CH, CRF and CCT were related but they were not the measurements of the same biomechanical parameter. It may be a measurement of dynamic resistance component and CRF measurement of viscoelastic properties of the cornea.

Concerning the relation between corneal biomechanics and IOP parameters, a simple regression line revealed a relationship between CH & GAT, CH & IOPg and CH & IOPcc showing a negative effect that is the lower the CH the higher was the IOP and vice versa. Although these relations are significant, the correlation coefficient is strong between CH and IOPcc than others. While the regression line revealed a relationship between CRF & GAT, CRF & IOPg and CRF & IOPcc showing a positive effect that is the higher the CRF the higher was the IOP and vice versa. Although these relations are significant, the correlation coefficient was weak between CRF and IOPcc than others.

Concerning the relation between CCT and IOP parameters in our study, we found that the correlations were insignificant between CCT and all IOP parameters (GAT, IOPg and IOPcc). While the difference between GAT and IOPcc has significant positive correlation with CCT. This means that patients with thicker corneas tended to have higher GAT IOP measurements compared with IOPCC, whereas in patients with thin corneas, GAT IOP measurements tended to be lower than IOPCC.

According to Medeiros et al.¹⁹, GAT was significantly correlated with CCT while IOPcc measurements were not significantly associated with CCT. The difference between GAT and IOPcc measurements was significantly influenced by corneal thickness. CRF had significant correlations with CCT and with GAT. According to Abitbol et al.¹⁷, moderate correlations were found between CCT and CH in both the control and glaucoma groups. According to Shah et al. 20, CH and CRF had a positive but moderate correlation to CCT. Our results, agree with previous studies in all results except in that there was no correlation between CCT and GAT; may be due to the thinnest cornea in our study (was 495). The thickest was 580, and about 80% of them are in the average thickness of cornea (500-540), which did not affect the GAT. Ehlers et al. performed manometry and applanation tonometry on 29 eyes about to undergo cataract or glaucoma surgery and calculated that the GAT would only give accurate measurements when CCT was 520µm.

Our results of multiple regression analysis, showed that only CRF and CH affect changes in GAT and IOPcc, and only CH affects the difference between GAT and IOPcc. According to **Shin** *et al.*²¹, results of multiple regression analysis suggested that the corneal biomechanical factors (corneal hysteresis and corneal resistance factor) are more important than CCT in influencing IOP measured by GAT, ORA and ICare in patients with NTG. According to **Mallon** *et al.*²², when all corneal factors (corneal hysteresis, corneal resistance factor, and CCT) were modeled, CCT was found to be unimportant for IOP measurements made by GAT, ORA, Pascal dynamic contour tonometry, and the Tonopen.

CONCLUSION

In conclusion, ORA evaluation of the corneal behavior when submitted to the stress produced by an

air-jet pulse seems to provide useful indices of corneal biomechanical properties, CH and CRF. Hysteresis, CRF, and CCT appear to be related but are not measurements of the same physical / biomechanical parameter. These measures might help to clarify the role of ocular rigidity (elasticity) in IOP measurement. CCT affect corneal biomechanical properties, the higher the CCT the higher was the CH and CRF and vice versa. Corneal biomechanics affect IOP more than CCT. The higher CH the lower was IOP, while the higher CRF the higher was the IOP. CH affect IOPcc more than GAT while CRF affect GAT more than IOPcc. CH decreased in glaucoma and in OHT than normal, while CRF increased in OHT than normal.

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