ORIGINAL RESEARCH

Evaluation of the relationship between corneal biomechanic and HbA1C levels in type 2 diabetes patients

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Purpose: To evaluate the corneal biomechanical properties due to the glycosylated hemoglobin (HbA1C) levels using the ocular response analyzer (ORA) in the patients with type 2 diabetes mellitus (DM).

Methods: ORA values were obtained from 156 eyes of subjects with type 2 DM and 74 eyes of healthy control subjects with similar age and sex. Subjects were divided into three groups: Group 1, healthy control subjects; Group 2, diabetes patients with HbA1C $<7\%$; and Group 3, diabetes patients with HbA1C $\geq 7\%$. Corneal biomechanical parameters: corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann-correlated pressure (IOPg), and corneal-compensated intraocular pressure (IOPcc) measurements were obtained using ORA. Ultrasound pachymetry was used for measurement of central corneal thickness (CCT).

Results: CH and CRF were significantly different in each of the three groups (P-values for CH respectively; Groups 1 and 2=0.008, Groups 1 and 3, and Groups 2 and 3, <0.001, and for CRF respectively; =0.002, <0.001, <0.001). CCT was significantly different between Groups 1 and 3 and Groups 2 and 3 ($P<0.001$) but was insignificant between Groups 1 and 2 ($P=0.965$). IOPcc was not different between Groups 1 and 2 ($P=0.524$), and Groups 2 and 3 ($P=0.115$), but was significantly different between Groups 1 and 3 ($P=0.003$). IOPg was statistically different between each of the three groups (respectively; Groups 1 and 2, $P=0.015$, Groups 1 and 3, and Groups 2 and 3, $P<0.001$).

Conclusion: Both diabetes groups were affected in terms of corneal biomechanical properties when compared to healthy subjects, there was also a positive correlation between HbA1C level and intraocular pressure.

Keywords: type 2 diabetes mellitus, HbA1C, ocular response analyzer, intraocular pressure, corneal biomechanical parameters

Introduction

Type 2 diabetes mellitus (DM) is a systemic disorder affecting the eyes in many different forms and it is characterised by hyperglycemia. The most prominant complications of the eye in diabetes patients are diabetic retinopathy, neovascular glaucoma, changes of refractions, and cataract progression.[1] Diabetes patients have a higher risk of epithelium healing problems, functional disorders of corneal endothelium, and permanent stromal edema after intraocular surgical procedures.[2,3] Many studies have shown that diabetes is commonly associated with thicker corneas, and thus, in many diabetes patients changes in the structure of the cornea are present.[4–9]

The ocular response analyzer (ORA; Reichert Technologies, Depew, NY, USA) is a device developed in recent years that reveals the biomechanical properties of the cornea.[10–13] It reflects certain biomechanical properties of the cornea such as

corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann-correlated intraocular pressure measurement (IOPg), and corneal-compensated intraocular pressure (IOPcc).[10–13] CH gives an idea about the viscosity of the cornea, thus it reflects the changes in the corneal stromal collagen organization. CH is not affected by the central corneal thickness (CCT). The ability to measure this effect is the key to understanding the biomechanical properties of the cornea and their influence on the intraocular pressure (IOP) measurement process.[10–13] CRF readings showing the elastic properties of the cornea are partially independent of IOP but have a strong relationship with CCT. CH and CRF are good indicators to identify the biomechanical properties of the cornea.[11–13]

In this study we aimed to investigate how changes occur in corneal biomechanical properties according to normal population and in patients with type 2 DM according to glycosylated hemoglobin (HbA1C) levels using the ORA.

Materials and methods

One hundred and fifty-six eyes of subjects diagnosed with type 2 DM, who were being followed by the endocrinology clinic, and 74 healthy control subjects participated in this study between January 2013 to July 2013. Both eyes of each patient were evaluated separately, and anterior segment examinations were included. Keratoconus, use of contact lenses, glaucoma, dry eye, pseudoexfoliation syndrome, previous anterior segment surgery, retinal photocoagulation applied in the last 3 months, or rubeosis iridis were accepted as exclusion criteria. Patients with systemic disease other than diabetes were excluded. Early stage proliferative diabetic retinopathy not needing treatment was not evaluated as exclusion criteria. Most of the diagnosis-period of diabetes was incorrect due to socio-cultural situation, so the duration of diabetes was excluded from the evaluation criteria. According to the principle of the Declaration of Helsinki, the study was explained to the subjects and they were asked to sign a written informed consent. The research was approved by the local ethics committee.

HbA1C is the metabolic product of a stable connection of glucose to the N-terminal valise of the beta-chain of hemoglobin. It defines the average blood glucose level of the preceding 3 months and shows the result of diabetes treatment. Normally the average HbA1C level varies between 4% and 6.4%. Higher values are a sign of insufficient blood glucose control and poor metabolic control.[14] An HbA1C target of <7.0% for the treatment of diabetes is generally accepted to lower the risk of long-term micro or macrovascular diabetes complications.[15] For this reason, patients with type 2 DM were divided into two groups according to their HbA1C blood levels.

To evaluate the metabolic status of the cases, the venous blood sample HbA1C levels and corneal biomechanics were measured at the same day as ORA measurements. The cases were divided into three groups: Group 1 (HbA1C <6.4%, control group), Group 2 (HbA1C <7%, type 2 DM patients with good metabolic control), and Group 3 (HbA1C ≥7%, type 2 DM patients with poor metabolic control).

The ORA utilizes a rapid air impulse to apply force to the cornea, and an advanced electro-optical system to monitor its deformation. A precisely-metered collimated air-pulse causes the cornea to move inwards, past applanation, and into a slight concavity. Milliseconds after applanation, the air pump shuts off and the pressure declines in a smooth fashion. As the pressure decreases, the cornea begins to return to its normal configuration. However, due to the dynamic nature of the air pulse, the viscous damping in the cornea causes delays in the inward and outward applanation events, resulting in two different pressure values (P1, P2). The difference between the values of these two pressures is known as CH.[10–13]

CCT was measured by ultrasonic pachymetry. Measurements were taken in the morning (between the hours of 9:50 am to 10:20 am). All procedures were performed by the same physician.

Statistical analysis

Statistical analyses were performed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). Sex distribution between the groups was investigated by a chi-square test. The distribution of age and HbA1C values were evaluated by one-way ANOVA. The group including all DM patients (Group 2 + Group 3) and control group (Group 1) were compared with independent-samples *t*-test. The differences in terms of other variables (CH, CRF, CCT, IOPg, IOPcc) between groups were evaluated by one-way multivariate anaylsis of variance (MANOVA). Tukey's multiple comparison test was performed to compare two groups at the same time. The level of significance was set to $P<0.05$.

Results

The three groups were not significantly different in terms of age and sex distribution (for age $P=0.983$, for sex $P=0.123$). The age distributions were detected as follows: 40–77 years (57.91±9.58) in the control group, 38–80 years (57.86±9.64) in diabetes patients with good metabolic

control, 42–82 years (57.65±8.74) in diabetes patients with poor metabolic control, respectively. There was a significant difference among the three groups in terms of HbA1C ($P<0.001$). HbA1C levels were 5.23%±0.55% in healthy control subjects, 6.26%±0.34% in diabetes patients with good metabolic control, and 9.88%±1.48% in diabetes patients with poor metabolic control (Table 1). There was no difference between any two groups in respect to age ($P=0.902$). There was a significant difference in HbA1C levels ($P<0.001$). There were significant differences between any two groups in respect to all parameters obtained by the ORA (CH, CRF, IOPg, IOPcc) and CCT. Looking at the readings details, all of the corneal parameters were higher in the type 2 DM patient groups (Table 2).

The description of the relationship between pairs was performed by using Tamhane's multiple comparison test. The results of Tukey's multiple comparison test were accepted for achieving equality of variance (Table 3). Variances were 0.450 (CCT), 0.382 (CRF), 0.285 (CH), 0.186 (IOPg), and 0.049 (IOPcc), respectively. There was a strong correlation between CCT and groups ($R^2=0.450$). A weak correlation was found between IOPcc and groups ($R^2=0.049$).

CH, CRF, CCT, IOPg, and IOPcc values were higher in Groups 2 and 3 than Group 1. All of the parameters were higher in Group 3 (the poor metabolic control group) (Table 3). With respect to the results obtained from the Tukey's test, there was a significant difference between CH ($P=0.022$), CRF ($P=0.002$) and IOPg ($P=0.029$) between Groups 1 and 2, but the CCT ($P=0825$) and IOPcc ($P=0.462$) did not differ significantly. There was a statistically significant difference between Groups 1 and 3 in all the corneal parameters ($P<0.001$ for CH, CRF, CCT, and IOPg, $P=0.03$ for IOPcc). There was a significant difference between Groups 2 and 3 for CH, CRF, CCT and IOPg ($P<0.001$) but IOPcc ($P=0.127$) did not differ significantly.

Table 1 The clinical properties of the type 2 diabetes mellitus and the control groups

Features	Group 1 (n=74)	Group 2 (n=74)	Group 3 (n=82)	P-value
Age (year ± SD)	57.91±9.58	57.86±9.64	57.6±8.74	0.983*
Sex				0.123**
Male	24	34	26	
Female	50	40	56	
HbA1C (% ± SD)	5.23±0.55	6.26±0.34	9.88±1.48	<0.001

Notes: *One way ANOVA. **Chi-square test. Group 1 (HbA1C <6.4%, control group), Group 2 (HbA1C <7%, type 2 DM patients with good metabolic control), and Group 3 (HbA1C ≥7%, type 2 DM patients with poor metabolic control).
Abbreviations: SD, standard deviation; HbA1C, glycosylated hemoglobin; ANOVA, analysis of variance; DM, diabetes mellitus.

Table 2 Comparison of corneal biomechanic parameters in the control group and type 2 DM groups (Group 2 and Group 3)

Parameter	Control (Group 1)	Type 2 DM (Group 2 + Group 3)	P-value
CH (mmHg)	8.98±1.45	10.37±1.91	<0.001*
CRF (mmHg)	8.99±1.52	11.06±2.30	<0.001*
CCT (μM)	541.40±22.94	555.90±30.85	<0.001*
IOPg (mmHg)	14.80±2.97	17.63±3.93	<0.001*
IOPcc (mmHg)	16.56±2.47	17.70±3.27	=0.026*
HbA1C (%)	5.23±0.55	8.16±2.11	<0.001*
Age (year)	57.91±9.58	57.75±9.15	=0.902*

Notes: Values are expressed as the mean ± standard deviation, unless expressed otherwise. *Independent sample t-test. Group 1 (HbA1C <6.4%, control group), Group 2 (HbA1C <7%, type 2 diabetic patients with good metabolic control), and Group 3 (HbA1C ≥7%, type 2 diabetic patients with poor metabolic control).
Abbreviations: DM, diabetes mellitus; CH, corneal hysteresis; CRF, corneal resistance factor; CCT, central corneal thickness; IOPg, Goldmann-correlated pressure; IOPcc, corneal-compensated intraocular pressure; HbA1C, glycosylated hemoglobin.

Discussion

When examining the results of diabetes patients with good metabolic control and healthy control subjects, CH and CRF were in favor of the diabetes patient group which showed a significant increase but no significant difference in the value of CCT. The average of the two applanation measurements (IOPg value) in favor of both DM patient groups increased. According to these results, we can assume that the deterioration of the corneal biomechanical parameters begins before the CCT is affected in DM patients. Thus, no significant difference was observed between the two groups in terms of IOPs that were considered to be (free) purified from corneal effects (IOPcc). So, there has not been an increase of IOP in real terms in the DM patient group with good metabolic control. In other words; there are significant changes in corneal viscosity and corneal resistance factor while there is no change of CCT in the well-regulated DM patient group.

When the DM groups were compared with each other, in Group 3 (HbA1C ≥7%) there was a significant increase in values of CH, CRF, CCT, and IOPg in comparison to Group 2 (HbA1C <7%). In spite of the fact that IOPcc was detected in lower quantity in Group 2, it was not statistically significant. With respect to this statistical data, the well-regulated DM patient group, not only in terms of corneal biomechanical properties but also CCT, showed that significant changes occur in the poorly regulated diabetes group.

When the control group and the third group (HbA1C ≥7%) were compared, significant increases occurred with regard to all parameters in favor of Group 3. In particular, significant increases in the value of IOPcc. Recent studies have shown that the IOPcc is not affected by corneal properties and thus it provides true measurement of IOP. And yet, these studies

Table 3 The mean and R^2 values of corneal biomechanic parameters

Parameter	Group 1	Group 2	Group 3	R^2	Groups 1 and 2*	Groups 1 and 3*	Groups 2 and 3*
CH (mmHg)	8.98±0.20	9.75±0.20	10.94±0.19	0.285	$P=0.022$	$P<0.001$	$P<0.001$
CRF (mmHg)	8.99±0.22	10.12±0.23	11.91±0.21	0.382	$P=0.002$	$P<0.001$	$P<0.001$
CCT (µM)	541.41±3.12	542.97±3.16	566.35±2.96	0.450	$P=0.825$	$P<0.001$	$P<0.001$
IOPg (mmHg)	14.80±0.41	16.31±0.42	18.81±0.39	0.186	$P=0.029$	$P<0.001$	$P<0.001$
IOPcc (mmHg)	16.57±0.35	17.13±0.36	18.20±0.33	0.049	$P=0.462$	$P=0.03$	$P=0.127$

Notes: *The interaction of differences of the corneal biomechanical parameters (one-way MANOVA, Tukey's). Group 1 (HbA1C <6.4%, control group), Group 2 (HbA1C <7%, type 2 DM patients with good metabolic control), and Group 3 (HbA1C ≥7%, type 2 DM patients with poor metabolic control).
Abbreviations: DM, diabetes mellitus; CH, corneal hysteresis; CRF, corneal resistance factor; CCT, central corneal thickness; IOPg, Goldmann-correlated pressure; IOPcc, corneal-compensated intraocular pressure; HbA1C, glycosylated hemoglobin; MANOVA, multivariate anaylsis of variance.

argue that IOPcc is a powerful alternative to Goldmann applanation tonometry measurement.[10–13] If the accuracy of this assumption is accepted, this study can draw the following conclusion: In the poorly regulated diabetes patients, IOP is elevated independently from CCT.

There is a progressive decrease of CCT in patients with keratoconus and a progressive increase of CCT in Fuchs corneal dystrophies due to deterioration of endothelial pump function. But the CH value was lower in Group 2 and Group 3. These results have shown that the CH value is a corneal marker independent from CCT.[11,13] CRF provides information about the elasticity of the cornea and is strongly linked with CCT.[11,13]

Corneal resistance factor and CH values are affected by aging. This study is mainly composed of middle to advanced age patients. Over time, the structure of corneal collagen cross-link are increasing in number and so the cornea becomes a more rigid and strong structure. However, this hardening reduces the viscoelastic response of the cornea. In a study by Kida et al[16] they examined the effects of aging and diurnal changes in the biomechanical properties of the cornea. According to this study, CH and CRF values decrease with age and indicate diurnal variations.[16] In our study, the average age of all three groups was created uniformly, thus the effect of age on the parameters was excluded. ORA measurements were performed in all patients between the hours of 9:50 am and 10:20 am to exclude diurnal differences.

Several studies conducted with specular microscopy show that the corneal endothelium of DM patients when compared with healthy individuals consists of some morphological changes.[17,18] McNamara et al have reported that hyperglycemia disrupts corneal structure, impairing corneal hydration and therefore affecting corneal thickness in diabetes patients.[19] In the study by Schultz et al barrier and pump function of the corneal endothelium were studied with fluorometric methods and some inability was identified. As a result, changes in corneal thickness in patients with DM has been

claimed.[17] According to the results of the experimental study of Herse, the measured decrease in diabetic rabbit endothelial homogenate Na+/K+ ATPase activity strongly suggests that endothelial fluid pump dysfunction is a major component in the abnormal corneal hydration system found in the uncontrolled diabetic rabbit.[20] Most of the studies emphasized that the thickness of the cornea increases with diabetes owing to the disrupting of endothelial pump function.[5–7] S Biswas et al investigated the factors associated with high IOP in patients with type 2 DM. According to the results of this study high HbA1C levels, systemic hypertension, smoking, and female sex are risk factors for high IOP in patients with type 2 DM.[21] In another study conducted by Zhou et al 6,101 people over the age of 30 years without glaucoma were examined. Younger age, female sex, presence of DM, higher blood pressure, higher body mass index, thicker central cornea, and higher myopia were associated with higher IOP.[22]

In another study conducted by Scheler et al, as in our study, patients with diabetes were divided into two groups according to level of HbA1C% and these groups were compared to each other and a control group.[23] It was observed that there was no significant difference between the healthy control subjects and the diabetes patients with good metabolic control with respect to values of CH and CRF. However, in the diabetes patients with good metabolic control, there was a significant increase in the values of CH and CRF relative to the other two groups. Increase in the values of IOP and CCT in the diabetes patient groups in comparison to the control group was also detected in this study. In contrast, in a study by Sahin et al CH was significantly lower and CRF showed no significant differences in diabetes patients.[24] However, in this study, mean CCT, IOPg, and IOPcc were significantly higher in diabetes patients.

Conclusion

In this study, the biomechanical properties of the cornea in DM patients were found to be deteriorated; increases in

IOP were closely related to HbA1C levels, not to deterioration of the corneal biomechanical properties; and HbA1C levels were positively correlated with IOP. In other words poor metabolic control, which means an increase in HbA1C levels, is related to higher IOP. It is possible that the disease diabetes, by activating an unknown mechanism, disrupts the viscoelastic properties of the cornea in the early period and in advanced stages leads to an increase in IOP. Mechanisms, such as degradation mechanisms that facilitate the flow of intraocular fluid or hyperosmolar state due to increased glucose in the anterior chamber may be responsible for higher intraocular pressure in patients with poorly regulated diabetes. We hope this study throws light on in vitro and in vivo studies to disclose these possible mechanisms.

Author contributions

Involved in design and conduct of the study (SY, UC, HK, OA); preparation and review of the study (VA, BC, AE, MT); data collection (SY, OA). All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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