Effect of diabetes mellitus on biomechanical parameters of the cornea

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PURPOSE: To compare parameters of biomechanical response of the human cornea measured as corneal hysteresis (CH) and corneal resistance factor (CRF) in patients with diabetes mellitus and healthy control subjects.

SETTING: Department of Ophthalmology, Assaf Harofeh Medical Center, Zerifin, Israel.

METHODS: In the right eye of each participant, the CH, CRF, Goldmann-correlated intraocular pressure (IOPg), and corneal-compensated intraocular pressure (IOPcc) were measured with the Ocular Response Analyzer. Central corneal thickness (CCT) was measured by ultrasonic pachymetry and intraocular pressure by Goldmann applanation tonometry (IOP GAT). Findings were compared between the 2 groups (control and diabetic).

RESULTS: Forty diabetic patients (17 women, 23 men) and 40 healthy subjects (19 women, 21 men) were prospectively recruited. The mean CH was 9.3 mm Hg ± 1.4 (SD) and 10.7 ± 1.6 mm Hg and the mean CRF was 9.6 ± 1.6 mm Hg and 10.9 ± 1.7 mm Hg in the control group and diabetic group, respectively (both \( P < .0001 \)). Diabetic corneas were significantly thicker \( (P = .019) \); the mean CCT was 530.3 ± 35.9 \( \mu \)m in the control group and 548.7 ± 33.0 \( \mu \)m in the diabetic group. The CH and CRF remained significantly different in multivariate analysis that included CCT. There was no statistically significant difference between the 2 groups in IOPcc, IOPg, or IOP GAT measurements.

CONCLUSIONS: Diabetes mellitus affected biomechanical parameters of the human corneas, including increased CH, CRF, and CCT. Whether this observation has implications in the clinical management and understanding of corneal ectasia and glaucoma requires further study.


The effect of diabetes mellitus on the human cornea may have clinical significance.\(^1\) Corneal changes induced by chronic abnormal glucose metabolism have been reported in the epithelial, stromal, and endothelial layers.\(^2,6\) Stromal changes include structural alterations produced by collagen crosslinking.\(^7\) In vitro studies show that collagen crosslinking causes increased stiffness of the cornea,\(^8,9\) which in turn may affect the measurement of intraocular pressure (IOP), causing overestimation of the true IOP.\(^10\) This may also explain the observation that diabetic corneas are less susceptible to development and progression of keratoconus.\(^11,12\)

Recently, the Ocular Response Analyzer (ORA, Reichert Inc.) became commercially available for in vivo measurements of the corneal biomechanical parameters of corneal hysteresis (CH) and corneal resistance factor (CRF) and for the noncontact assessment of IOP, described as Goldmann-correlated IOP (IOPg) and corneal-compensated IOP (IOPcc). The reproducibility\(^13\) and a detailed description\(^14\) of this instrument have been published. Briefly, the instrument measures corneal response to indentation by a rapid air.
pulse using an electrooptical system. The air puff indents the cornea, passing a defined point of applanation and into a slight concavity. After reaching the pressure peak, the pressure of the air pulse decreases and the cornea returns to its normal configuration, again passing the defined point of applanation. An electrooptical system monitors the entire process and calculates the above parameters. Corneal hysteresis represents the absolute difference between the 2 pressure values causing force-in (P₁) and force-out (P₂) applanations and provides a measure of viscous damping of the cornea. The CRF is derived from the formula \((P₁ - kP₂)\), where \(k\) is a constant. The constant \(k\) was determined from an empirical analysis of the relationship between both \(P₁\) and \(P₂\) and the central corneal thickness (CCT) to develop a parameter more strongly associated with CCT than CH (Luce D. IOVS 2006; 47:ARVO E-Abstract 2266). The IOPcc is the average of the 2 IOP measurements at the applanation points. The IOPcc is a pressure measurement that uses the information provided by CH to provide an IOP that is less affected by CCT or corneal curvature.14,15

The aim of this study was to compare the parameters of biomechanical response of corneas of diabetic patients and healthy controls and to test our study hypothesis that the diabetic cornea is stiffer than the healthy one.

PATIENTS AND METHODS

Diabetic patients and healthy subjects (control group) from the ophthalmology outpatient clinic of the Assaf Harofeh Medical Center were prospectively enrolled. For this study, a patient was defined as diabetic if he or she had a referring-physician diagnosis of diabetes and was taking antidiabetic medication. Patients and subjects with any type of known corneal disease, glaucoma, contact lenses, or chronic diabetic medication. Patients and subjects with any type of known corneal disease, glaucoma, contact lenses, or chronic use of topical ocular medications were excluded, as were those who had any type of eye surgery.

This study was approved by the Institutional Ethics Committee of Assaf Harofeh Medical Center, and written informed consent was obtained from each participant after the nature and intent of the study had been fully explained. The study protocol was consistent with the tenets of the Declaration of Helsinki. All participants had assessment with the ORA-attached handheld ultrasonic pachymeter. The probe was gently placed in a perpendicular orientation on the central corneal. The results of the CCT reading were displayed on the computer. Finally, applanation tonometry was performed once with the Goldmann applanation tonometer (IOP GAT). One examiner, who was masked to the previously recorded ORA data, performed all measurements.

Statistical Analysis

Data are presented as frequency or mean ± standard deviation. Independent-samples t tests were used to assess differences between the compared groups in CH, CRF, CCT, IOPcc, IOPg, and IOP GAT. Linear regression was used to evaluate the differences in CH and CRF after accounting for age, sex, IOP GAT, and CCT. A 2-tailed P value of 0.05 was selected for the threshold of statistical significance. Because 6 measurements were compared between cases and controls, to avoid multiple-comparison problems, a Bonferroni correction was performed and an \(\alpha\) level of 0.0085 was applied for each test. Analyses were performed using SPSS for Windows (version 14, SPSS, Inc.).

RESULTS

Forty diabetic patients and 40 healthy subjects were included in the study (Table 1). There were no statistically significant differences between the 2 groups in age or sex distribution \((P > .23)\). Only the right eye was examined.

Table 2 shows CH, CRF, IOPcc, IOPg, GAT IOP, and CCT measurements in the diabetic group and control group. Corneal hysteresis, CRF, and CCT were statistically significantly greater in the diabetic group. Figures 1 to 3 show the distribution of these parameters in the 2 groups. A multivariate analysis that included sex, age, GAT IOP, and CCT, which was performed to examine whether the differences in corneal biomechanical parameters reflected the effect of confounding factors, showed that CH remained statistically significantly different between the 2 groups \((P < .001)\). The IOPg, IOPcc, and IOP GAT values were not statistically significantly different between the diabetic group and control group (Table 2 and Figure 4).

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<th>Table 1. Clinical characteristics.</th>
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<td>Characteristic</td>
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<td>Sex, n (%)</td>
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DISCUSSION

The results in our study show that the CCT, CH, and CRF in diabetic eyes were significantly higher than in nondiabetic eyes. Corneal structural integrity and stiffness may be described using anatomical and biomechanical parameters. Anatomical properties customarily include CCT and biomechanical parameters may be presented through the CH and CRF parameters measured by the ORA. The relationship between these factors and their relative contribution to corneal elasticity and stiffness are not clearly understood.16,17

Diabetes mellitus has a significant effect on morphologic, metabolic, physiologic, and clinical aspects of the human cornea.1 A previous study18 using ultrasound pachymetry found that the CCT was increased in diabetic eyes. Hyperglycemia was shown to influence corneal biomechanical properties by inducing stromal collagen crosslinking through glycosylation and lysyl oxidase enzymatic activity.19 Both increased thickness of nonedematous cornea and crosslinking of collagen fibers may eventually result in increased corneal stiffness.9 Keratoconus is characterized by thinning and increased distensibility of the corneal stroma that consists predominantly of collagen fibers.20 Any further change in the arrangement of these fibers may influence stromal, and thus corneal, stiffness. It was recently shown that keratoconus progression may be slower in diabetic eyes, probably due to biomechanical corneal changes.11,12 Previous studies of keratoconic eyes21–23 found that low CH, CRF, and CCT values were well correlated with the ectatic corneas. The increased CH, CRF, and CCT values in the diabetic patients in our study may implicate increased corneal stiffness and explain this diabetic protective phenomenon.

One possible weakness of our study was the lack of specific consideration of the severity and duration of diabetes, as can be assessed by the presence of diabetic neuropathy, retinopathy, nephropathy, and measurements of glycolated hemoglobin. Considering the marked heterogeneity of diabetes, the measured

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<td><strong>Parameter</strong></td>
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<td>CH (mm Hg)</td>
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<td>CRF (mm Hg)</td>
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<td>IOPcc (mm Hg)</td>
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<td>IOPg (mm Hg)</td>
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<td>IOP GAT (mm Hg)</td>
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<td>CCT (µm)</td>
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CCT = central corneal thickness; CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = corneal-compensated intraocular pressure; IOPg = Goldmann-correlated intraocular pressure; IOP GAT = Goldmann applanation tonometer intraocular pressure *t test
It has been suggested that regardless of IOP, a thinner cornea is a risk factor for development of open-angle glaucoma and for increased severity of glaucomatous damage at initial presentation. Congdon et al. showed that low CH by itself was associated with increased glaucomatous injury. Plausibly, both higher CCT and higher CH may be associated with some protection against glaucoma. The results of the Ocular Hypertension Treatment Study (OHTS) suggest there may be some protective effect of diabetes on the progression to open-angle glaucoma. Although this finding has been much debated, the results in our study may support it. Increased corneal stiffness, in addition to and independent of increased thickness, may cause overestimation of IOP when measured by GAT. This overestimation may explain the apparent protective role of diabetes on progression to open-angle glaucoma reported in the OHTS. An additional theoretical hypothesis involves biomechanical changes that occur in the lamina cribrosa in diabetic patients. The same processes that lead to increased corneal stiffness in diabetes may happen in other eye structures containing collagen fibers. Burgoyne et al. in their recent review, showed that increased compliance (ie, decreased stiffness) of the lamina cribrosa might be associated with increased glaucomatous damage.

In summary, our study showed that persons with diabetes mellitus had increased CCT, CH, and CRF, possibly reflecting greater stiffness of diabetic corneas. Whether this observation has implications in the clinical management and understanding of corneal ectasia and glaucoma requires further investigation.

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