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 μm in the control group and 548.7 ± 33.0 μm 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.

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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

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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 (P_1) and force-out (P_2) applanations and provides a measure of viscous damping of the cornea. The CRF is derived from the formula ($P_1 - kP_2$), where k is a constant. The constant k was determined from an empirical analysis of the relationship between both P_1 and P_2 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 IOPg 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 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 that included measurement of noncontact IOP, CH, and CRF. The same examiner performed all assessments. Briefly, each patient was seated and asked to fixate on a target light and the measurement was taken. A noncontact probe scanned the central corneal area and released an air puff. Measured IOP, CH, and CRF values were displayed on the monitor of the computer. For each patient, 3 readings of good quality were obtained; good-quality images were defined as having a waveform with 2 distinct, nearly symmetrical peaks. Irreproducible out-of-scale measurements were excluded from the analysis. The mean values of each parameter were used for statistical evaluation.[13]

After the noncontact part of study assessments was finished, topical anesthesia of oxybuprocaine hydrochloride 0.4% drops (Localin) was administered. The CCT was measured by 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 α 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).

Table 1. Clinical characteristics.

Characteristic	Group	
	Diabetic	Control
Eyes (n)	40	40
Mean age (y) ± SD	60.9 ± 12.4	63.8 ± 9.0
Sex, n (%)		
Male	17 (42.5)	19 (47.5)
Female	23 (57.5)	21 (52.5)

Table 2. Study parameters and their statistical distribution.

Parameter	Mean ± SD		
	Diabetic Group	Control Group	*P* Value*
CH (mm Hg)	10.7 ± 1.6	9.3 ± 1.4	.0001
CRF (mm Hg)	10.9 ± 1.7	9.6 ± 1.6	<.0001
IOPcc (mm Hg)	16.6 ± 4.4	17.7 ± 4.9	.31
IOPg (mm Hg)	16.6 ± 4.3	16.1 ± 4.9	.66
IOP GAT (mm Hg)	15.0 ± 3.2	14.2 ± 3.4	.25
CCT (µm)	548.7 ± 33.0	530.3 ± 35.9	.019

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

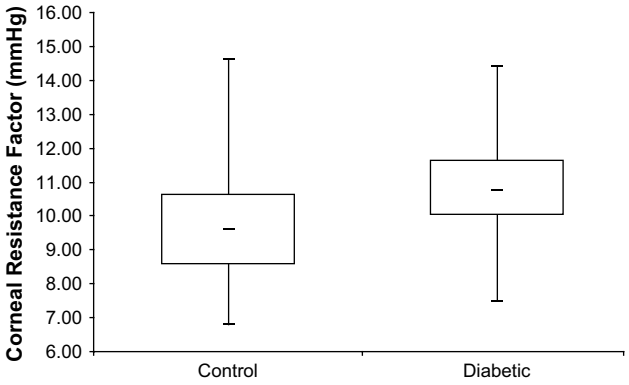

Figure 2. Box-and-whisker plots (smallest, median, and largest values with interquartile range) showing CRF in the control group and diabetic group.

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 study[18] 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 eyes[21–23] 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

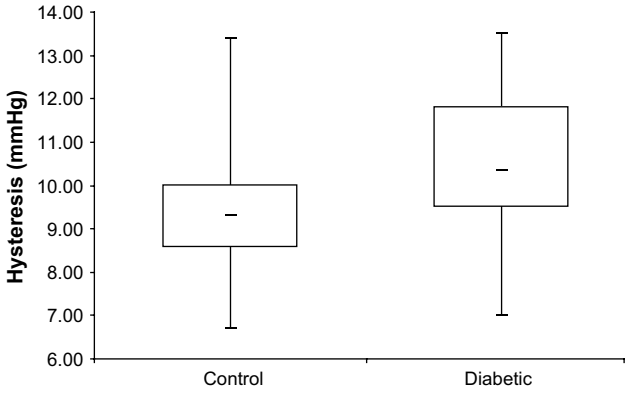

Figure 1. Box-and-whisker plots (smallest, median, and largest values with interquartile range) showing CH in the control group and diabetic group.

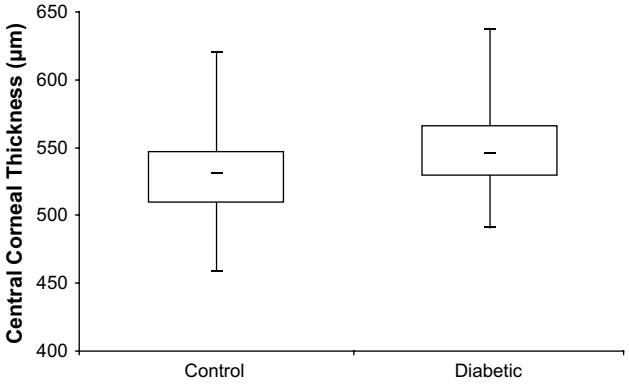

Figure 3. Box-and-whisker plots (smallest, median, and largest values with interquartile range) showing CCT in the control group and diabetic group.

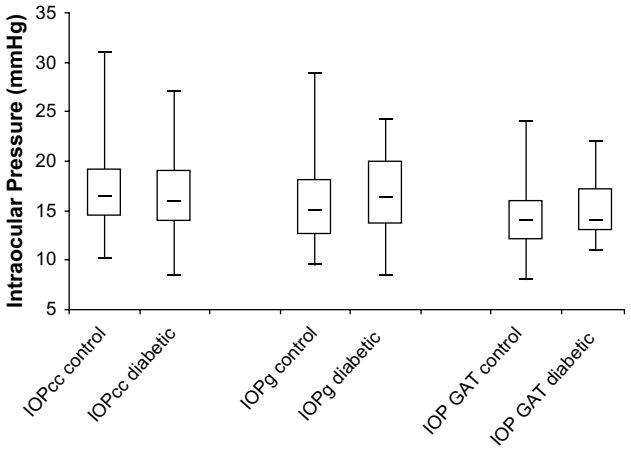

Figure 4. Box-and-whisker plots (smallest, median, and largest values with interquartile range) showing IOPcc, IOPg, and IOP GAT in the control group and diabetic group.

differences between the 2 groups may have been disproportionately influenced by the most severely affected patients in the study group. Some correlation between duration and severity of diabetes and corneal morphological abnormalities has been shown,[4,6] and further evaluation of such a correlation with corneal viscoelastic changes may be appropriate.

Recently, more advanced analysis of the raw ORA data in addition to the CH and CRF parameters in biomechanical evaluation has been suggested. This analysis is performed using graphically presented waves, including comparison of signal peak amplitudes and shape,[24] width of infrared peaks at their mid-height point, and the slope of the air pulse during the 2 applanation events (Glass DH, et al. IOVS 2008; 49:ARVO E-Abstract 646). Once the accuracy and reliability of these analytic tools are established, they can potentially be used for further evaluation of the influence of diabetes.

Corneal viscoelasticity may define corneal response to applanation forces during ocular tonometry. Broman et al.[25] showed that corneal thickness and CH can influence IOP measurements. Several population-based studies[26–29] found consistently higher IOP measurements in diabetic patients than in nondiabetic individuals. In our study, diabetic patients tended to have higher IOP GAT values than control subjects, although the difference was not statistically significant. This may reflect the small size of the study populations: Assuming a standard deviation of 3.0 mm Hg for IOP GAT; a sample size of about 800 subjects would be required to detect a difference of 0.6 mm Hg between the compared groups[29] given a significance level of 5% and a statistical power of 80%. In our study, the ORA noncontact IOP measurements were also not statistically significantly different between the 2 study groups.

It has been suggested that regardless of IOP, a thinner cornea is a risk factor for development of open-angle glaucoma[30] and for increased severity of glaucomatous damage at initial presentation.[31] Congdon et al.[32] 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)[33] 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.[34] 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.,[35] in their recent review, showed that increased compliance (ie, decreased stiffness) of the lamina cribrosa might be associated with increased glaucomatous damage. Lesk et al.[36] report an association between corneal thickness and lamina cribrosa stiffness, with less stiffness in eyes with thinner corneas, thus allowing greater lamina cribrosa displacement and increased axonal injury after IOP fluctuations. Increased corneal stiffness may be associated with increased stiffness of lamina cribrosa and thus provide protection against glaucomatous injury.

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.

REFERENCES

1. Sánchez-Thorin JC. The cornea in diabetes mellitus. Int Ophthalmol Clin 1998; 38(2):19–36
2. Azar DT, Spurr-Michaud SJ, Tisdale AS, Gipson IK. Decreased penetration of anchoring fibrils into the diabetic stroma; a morphometric analysis. Arch Ophthalmol 1989; 107:1520–1523
3. Azar DT, Spurr-Michaud SJ, Tisdale AS, Gipson IK. Altered epithelial-basement membrane interactions in diabetic corneas. Arch Ophthalmol 1992; 110:537–540
4. Siribunkum J, Kosrirukvongs P, Singalavanija A. Corneal abnormalities in diabetes. J Med Assoc Thai 2001; 84:1075–1083
5. Saghizadeh M, Brown DJ, Castellon R, Chwa M, Huang GH, Ljubimova JY, Rosenberg S, Spirin KS, Stolitenko RB, Adachi W, Kinoshita S, Murphy G, Windsor LJ, Kenney MC, Ljubimov AV. Overexpression of matrix metalloproteinase-10 and matrix metalloproteinase-3 in human diabetic corneas;

a possible mechanism of basement membrane and integrin alterations. Am J Pathol 2001; 158:723–734; Available at: http://ajp.amjpathol.org/cgi/content/full/158/2/723. Accessed December 17, 2008
6. Lee JS, Oum BS, Choi HY, Lee JE, Cho BM. Differences in corneal thickness and corneal endothelium related to duration in diabetes. Eye 2006; 20:315–318
7. Monnier VM, Sell DR, Abdul-Karim FW, Emancipator SN. Collagen browning and cross-linking are increased in chronic experimental hyperglycemia; relevance to diabetes and aging. Diabetes 1988; 37:867–872
8. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. J Cataract Refract Surg 2003; 29:1780–1785
9. Dupps WJ Jr, Netto MV, Herekar S, Krueger RR. Surface wave elastometry of the cornea in porcine and human donor eyes. J Refract Surg 2007; 23:66–75
10. Krueger RR, Ramos-Esteban JC. How might corneal elasticity help us understand diabetes and intraocular pressure? J Refract Surg 2007; 23:85–88
11. Seiler T, Huhle S, Spoerl E, Kunath H. Manifest diabetes and keratoconus: a retrospective case-control study. Graefes Arch Clin Exp Ophthalmol 2000; 238:822–825
12. Kuo IC, Broman A, Pirouzmanesh A, Melia M. Is there an association between diabetes and keratoconus? Ophthalmology 2006; 113:184–190
13. Moreno-Montañés J, Maldonado MJ, García N, Mendiluce L, García-Gómez PJ, Seguí-Gómez M. Reproducibility and clinical relevance of the Ocular Response Analyzer in nonoperated eyes: corneal biomechanical and tonometric implications. Invest Ophthalmol Vis Sci 2008; 49:968–974
14. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg 2005; 31:156–162
15. Medeiros FA, Weinreb RN. Evaluation of the influence of corneal biomechanical properties on intraocular pressure measurements using the Ocular Response Analyzer. J Glaucoma 2006; 15:364–370
16. Kotecha A. What biomechanical properties of the cornea are relevant for the clinician? Surv Ophthalmol 2007; 52(suppl 2):S109–S114
17. Dupps WJ Jr. Hysteresis: new mechanospeak for the ophthalmologist [editorial]. J Cataract Refract Surg 2007; 33:1499–1501
18. Su DHW, Wong TY, Wong W-L, Saw S-M, Tan DTH, Shen SY, Loon S-C, Foster PJ, Aung T. Diabetes, hyperglycemia, and central corneal thickness; the Singapore Malay Eye Study. Ophthalmology 2008; 115:964–968
19. Sady C, Khosrof S, Nagaraj R. Advanced Maillard reaction and crosslinking of corneal collagen in diabetes. Biochem Biophys Res Commun 1995; 214:793–797
20. Edmund C. Assessment of an elastic model in the pathogenesis of keratoconus. Acta Ophthalmol (Copenh) 1987; 65:545–550
21. Ortiz D, Piñero D, Shabayek MH, Arnalich-Montiel F, Alió JL. Corneal biomechanical properties in normal, post-laser in situ keratomileusis, and keratoconic eyes. J Cataract Refract Surg 2007; 33:1371–1375
22. Shah S, Laiquzzaman M, Bhojwani R, Mantry S, Cunliffe I. Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes. Invest Ophthalmol Vis Sci 2007; 48:3026–3031. Available at: http://www.iovs.org/cgi/reprint/48/7/3026. Accessed December 17, 2008
23. Touboul D, Roberts C, Kérautret J, Garra C, Maurice-Tison S, Saubusse E, Colin J. Correlations between corneal hysteresis, intraocular pressure, and corneal central pachymetry. J Cataract Refract Surg 2008; 34:616–622
24. Kerautret J, Colin J, Touboul D, Roberts C. Biomechanical characteristics of the ectatic cornea. J Cataract Refract Surg 2008; 34:510–513
25. Broman AT, Congdon NG, Bandeen-Roche K, Quigley HA. Influence of corneal structure, corneal responsiveness, and other ocular parameters on tonometric measurement of intraocular pressure. J Glaucoma 2007; 16:581–588
26. Klein BEK, Klein R, Jensen SC. Open-angle glaucoma and older-onset diabetes; the Beaver Dam Eye Study. Ophthalmology 1994; 101:1173–1177
27. Tielsch JM, Katz J, Quigley HA, Javitt JC, Sommer A. Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. Ophthalmology 1995; 102:48–53
28. Dielemans I, de Jong PTVM, Stolk R, Vingerling JR, Grobbee DE, Hofman A. Primary open-angle glaucoma, intraocular pressure, and diabetes mellitus in the general elderly population; the Rotterdam Study. Ophthalmology 1996; 103:1271–1275
29. Mitchell P, Smith W, Chey T, Healey PR. Open-angle glaucoma and diabetes: the Blue Mountains eye study. Australia. Ophthalmology 1997; 104:712–718
30. Dueker DK, Singh K, Lin SC, Fechtner RD, Minckler DS, Samples JR, Schuman JS. Corneal thickness measurement in the management of primary open-angle glaucoma; a report by the American Academy of Ophthalmology (Ophthalmic Technology Assessment). Ophthalmology 2007; 114:1779–1787
31. Herndon LW, Weizer JS, Stinnett SS. Central corneal thickness as a risk factor for advanced glaucoma damage. Arch Ophthalmol 2004; 122:17–21
32. Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol 2006; 141:868–875
33. Brandt JD, Beiser JA, Kass MA, Gordon MO. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS); the Ocular Hypertension Study (OHTS) Group. Ophthalmology 2001; 108:1779–1788
34. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. J Cataract Refract Surg 2005; 31:146–155
35. Burgoyne CF, Downs JC, Bellezza AJ, Suh J- KF, Hart RT. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. Prog Retin Eye Res 2005; 24:39–73
36. Lesk MR, Hafez AS, Descovich D. Relationship between central corneal thickness and changes of optic nerve head topography and blood flow after intraocular pressure reduction in open-angle glaucoma and ocular hypertension. Arch Ophthalmol 2006; 124:1568–1572

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