Central corneal thickness measurements in patients with normal tension glaucoma, primary open angle glaucoma, pseudoexfoliation glaucoma, or ocular hypertension

A C Sobottka Ventura, M Böhnke, D S Mojon

Abstract

***Background/aims*—Recent studies have revealed patients with ocular hypertension to have thicker than normal central corneas and those with normal tension glaucoma to have thinner than normal ones, as determined by ultrasonic pachymetry. Since corneal thickness measurements and applanation tonometric estimates of intraocular pressure (IOP) correlate positively, monitoring of the former parameter have served as the basis for adjusting readings pertaining to the latter, with the consequence that many patients have had to be reclassified. With a view to validating these pachymetric studies, the central corneal thickness was determined in patients with normal tension glaucoma, primary open angle glaucoma, pseudoexfoliation glaucoma, or ocular hypertension, as well as that of normal subjects, using optical low coherence reflectometry, which is a new and more precise method than ultrasonic pachymetry.**

***Methods*—34 patients with normal tension glaucoma, 20 with primary open angle glaucoma, 13 with pseudoexfoliation glaucoma, and 12 with ocular hypertension, together with 21 control subjects, were included in this observational, concurrent case-control study. One eye per individual was randomly selected for investigation. IOP was measured by Goldmann applanation tonometry and central corneal thickness by optical low coherence reflectometry.**

***Results*—Central corneal thickness was significantly higher ($p \leq 0.001$) in patients with ocular hypertension than in normal individuals or in subjects with either normal tension glaucoma, primary open angle glaucoma, or pseudoexfoliation glaucoma, there being no significant differences between the latter four groups. Patients with ocular hypertension were also significantly younger ($p \leq 0.003$) than those within any of the three glaucomatous groups.**

***Conclusion*—This study confirms that a significant number of patients with ocular hypertension have normal IOPs after the appropriate adjustments have been made for deviations from normal in their central corneal thickness. The accurate measurement of this latter parameter is important not only for individual patient care, in permitting more precise estimations of IOP, but also for clinical studies, in assuring a more reliable classification of subjects.**

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Department of Ophthalmology, Inselspital, University of Bern, Switzerland
A C Sobottka Ventura
M Böhnke

Department of Strabismus and Neuroophthalmology, Kantonsspital St Gallen, Switzerland
D S Mojon

Correspondence to:
Angela C Sobottka Ventura, MD, Escola Paulista de Medicina, Universidade Federal de São Paulo, Department of Ophthalmology, R Botucato 822, São Paulo 04023-062, Brazil
draventura@oftalmo.epm.com.br

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In routine clinical practice, intraocular pressure (IOP) represents one of several important parameters (including an assessment of the condition of the optic nerve and nerve fibre layer, gonioscopic findings, and the compass of the visual field) used not only in the diagnosis of glaucoma but also for gauging the progression of this condition and its response to treatment. Clearly, though, its value as a diagnostic tool hinges upon the reliability of measurements taken. The technique most commonly employed for this purpose is applanation (Goldmann) tonometry, the accuracy of which is influenced by several factors, including scleral[1] and corneal[2–4] rigidity. Weakening of the cornea, evoked by stromal oedema,[4] excimer ablation,[2 3] or laser induced in situ keratomileusis (LASIK),[5–7] is known to elicit lower tonometric values. Corneal thickness, likewise, has been reported to influence IOP measurements.[8] Indeed, Goldmann and Schmidt discussed the association between these two parameters in their publication in 1957,[1] acknowledging a theoretical limit of 2.25 mm Hg for an infinitely thin cornea. Fourteen years later, Kruse Hansen and Ehlers demonstrated the existence of a positive linear correlation between central corneal thickness and IOP.[9] Subsequent studies have revealed tonometric readings taken from thicker corneas to be higher than the manometric pressure and vice versa.[10–13] An extreme case reported by Johnson *et al* confirmed the reality of this anomalous behaviour: a 17 year old female with an exceedingly thick cornea—measuring 900 μm in a central location—registered a tonometric value of 35 mm Hg and a manometric one of 11 mm Hg.[14] This association has also been demonstrated experimentally.[15]

More recent investigations have disclosed that people classified as having ocular hypertension have thicker corneas than controls,[16–20] whereas those with normal tension glaucoma have thinner ones.[19 20]

Since not only the tonometric measurement of IOP but also the ultrasonic monitoring of corneal thickness suffers a want of accuracy—with values deviating by up to 65 μm from the

true ones[21] and readings being, moreover, influenced to a marked degree by the positioning of the probe (thereby introducing a substantial observer bias factor)—the validity of these interrelations is open to question.

Optical low coherence reflectometry represents the most accurate and objective pachymetric technique currently available. The precision of central corneal thickness measurements lies in order of 1 μm, and the intraobserver, as well as interobserver, variability is very low.[22–25] This technique possesses an additional advantage in its non-contact feature mode of measurement.

In the present study, we used optical low coherence reflectometry to monitor the central corneal thickness of patients classified as having normal tension glaucoma, primary open angle glaucoma, pseudoexfoliation glaucoma, or ocular hypertension, as well as that of normal subjects. And this with a view to placing on a firmer footing the prevailing indications that people with high IOPs have thicker corneas.

Patients and methods

PATIENTS

A total of 79 white patients (34 patients with normal tension glaucoma, 20 with primary open angle glaucoma, 13 with pseudoexfoliation glaucoma, and 12 with ocular hypertension), together with 21 control subjects, were included in this study, which followed the tenets of the Declaration of Helsinki. Individuals were examined between January and October 1999 at the department of ophthalmology, University of Bern, Switzerland, each having given their consent to undergo optical low coherence reflectometry.

Patients with normal tension glaucoma had untreated IOPs of less than 22 mm Hg on at least two diurnal curves, an open, normal angle, a glaucomatous optic disc, and glaucomatous visual field defects. Individuals with primary open angle glaucoma had untreated IOPs of 22 mm Hg or higher, an open, normal angle, a glaucomatous optic disc, and glaucomatous visual field defects. Subjects with pseudoexfoliation glaucoma had untreated IOPs of 22 mm Hg or higher, an open angle, typical pseudoexfoliation material within the angle and upon the lens, a glaucomatous optic disc, and glaucomatous visual field defects. Patients with ocular hypertension had untreated IOPs of 22 mm Hg or higher, an open, normal angle, normal optic discs, normal visual fields, and no family history of glaucoma.

METHODS

In all patients, the registered condition was bilateral, one eye per individual being randomly selected for investigation.

IOP was monitored according to a standard protocol using a calibrated Goldmann applanation tonometer.

Visual fields were mapped with an automated perimeter Octopus 101, using the G2 glaucoma program in conjunction with a normal strategy.

Central corneal thickness was measured with an optical low coherence reflectometer, operating at a scanning speed of 0.5 m/s and a repetition rate of 15 Hz, and used in conjunction with a superluminescent diode (λ = 850 nm). The mean and standard deviation of three determinations, each consisting of 20 scans, was calculated for each eye. All measurements were made by the same examiner.

Details pertaining to the experimental design of the instrument used have been documented elsewhere[21–25]; only a few relevant features are presented here. The design of the optical reflectometer is based on a Michelson interferometer. A superluminescent diode serves as the broad band light source, this having an output power of 8 mV at 850 nm and a spectral width of 18 nm. It is coupled to a fibre optic Michelson interferometer, the light being split between the two arms of this instrument in a 50/50 coupler. One arm runs to the cornea and the second to a rotating cube. An aiming diode laser is integrated into the interferometer with a 95/5 coupler. Longitudinal scanning is achieved by means of the rotating cube. The detection system consists of a silicon photodiode, an amplifier and an oscilloscope for signal display. Large signals are detected at interfaces where there is a pronounced change in refractive index—that is, at the air/tear and endothelial/aqueous humour junctions. The longitudinal scanning system of the instrument, which permits a scanning speed of more than 20 m/s and a repetition rate of about 400 Hz, is based on a rotating glass cube. The whole instrument is attached to a clinical slit lamp (Haag Streit International, Switzerland). The superluminescent diode and the fixation laser signal are positioned before the front lens of the slit lamp, thereby allowing the reflectometer's server to direct the instrument with biomicroscopic stereopsis. The pilot lasers are attached horizontally and converge on the slit lamp's focal point, thereby facilitating the alignment of the instrument with the x-y-z control of the slit lamp, and that of the latter with a chin and head rest. With the aid of two converging pilot lasers, the centre of the longitudinal scan, which is adjusted to coincide with the focal point of the slit lamp, is aligned with the cornea at the appropriate distance. The optical centre of the cornea is located by the subject's fixation of a low power laser beam, aligned coaxially with that of the 850 nm superluminescent diode. The diameter of the measuring beam emitted from the superluminescent diode and impinging on the surface of the central cornea is about 20 μm. The instrument was calibrated with a BK7 glass window (Melles Griot, USA) with a thickness of 1 mm and a refractive index of 1.5100 at 850 nm. For a given position of the glass, measurements were found to be reproducible to 1 μm. The thickness of the cornea was calculated from the optical distance using an average corneal refractive index value of 1.376.

A specific strategy for data collection and evaluation was adopted. From a series of 20 longitudinal scans, the upper and lower five values were deleted. From the remaining 10,

Table 1 Central corneal thickness, IOP readings, number of different glaucoma medications administered, the number of surgical interventions performed for the glaucomatous condition, and age of individuals for each of the investigated groups: normal subjects (controls) and patients with normal tension glaucoma (NTG), primary open angle glaucoma (POAG), pseudoexfoliation glaucoma (PEXG), or ocular hypertension (OHT). All values represent means (SD)

	Controls (n = 21)	*NTG (n = 34)*	*POAG (n = 20)*	*PEXG (n = 13)*	*OHT (n = 12)*
Central corneal thickness (μm)	524 (25)	518 (0.5)	515 (35)	507 (25)	563 (29)
IOP (mm Hg)	13.9 (2.3)	15.2 (1.9)	18.7 (6.3)	21.6 (6.7)	22.8 (2.0)
No of different glaucoma medications administered	0	0.8 (0.6)	1.5 (1.0)	1.4 (1.3)	0.6 (0.7)
No of surgical interventions	0	0.2 (0.5)	0.4 (0.5)	0.8 (0.8)	0.2 (0.4)
Age (years)	58.3 (24.9)	64.2 (13)	71.7 (13.5)	76 (5.2)	51.7 (11.9)

the mean was calculated as the current thickness value, and the range and standard deviation determined. The results were recorded online in a database, which stores the identity of the subject, the date and time of the measurement, and the individual scan values, including technical information on their generation from each series. The computed mean from three scan series was recorded manually together with the range and standard deviation. A set of 10 ultrasound pachymetric measurements was also obtained to confirm the magnitude of the optical low coherence reflectometric ones.

The statistical analysis was performed using ANOVA, the Student-Newman-Keuls test being then implemented for multiple comparisons.

Results

The central corneal thickness of patients with ocular hypertension (mean 563 (SD 29) μm; range 515–611 μm) was significantly higher ($p \leq 0.001$) than in normal (control) individuals (mean 524 (25) μm; range 483–570 μm) or in subjects with normal tension glaucoma (mean 518 (0.5) μm, range 469–564 μm), open angle glaucoma (mean 515 (35) μm; range 454–581 μm), or pseudoexfoliation glaucoma (mean 507 (25) μm; range 470–567 μm), there being no significant differences between the latter four groups (Table 1). Patients with ocular hypertension were also significantly younger than those within any of the three glaucomatous groups ($p \leq 0.003$).

Discussion

The influence of scleral rigidity and central corneal thickness on IOP readings was first discussed by Goldmann and Schmidt in 1957.[1] But a further 18 years elapsed before these intimations were put on a firm footing by Ehlers *et al*, who postulated that the applanation tonometry yielded accurate measurements only at a central corneal thickness of 520 μm.[10] They calculated the average error evoked by a thicker or thinner cornea to be 0.7 mm Hg per 10 μm deviation from the "normal" value of 520 μm. This estimate was later corroborated in a case report of a patient with a 900 μm thick cornea, in which instance a tonometric error of 0.63 mm Hg per 10 μm corneal thickness deviation was calculated.[14] On the basis of these calculations, Copt *et al*[19] and Shah *et al*[20] reclassified 36% and 44%, respectively, of their normal tension glaucomatous patients as having open angle glaucoma, and 56% and 35%, respectively, of individuals with ocular hypertension as being normal.

On the other hand, more recent cannulation studies have revealed average corrections per 10 μm deviation in corneal thickness to be considerably lower—namely, 0.18 to 0.23 mm Hg[12 13] and 0.19 mm Hg.[15]

Optical low coherence reflectometry represents the most precise pachymetric method now available. Using these technique, we confirmed that patients with ocular hypertension had thicker than normal central corneas. This circumstance is responsible for the artificially high estimates of IOP within this group of individuals. Using Ehlers *et al*'s formula of 0.7 mm Hg per 10 μm deviation from the normal corneal thickness value, six of our 12 patients with ocular hypertension had to be reclassified as normal. The highest overestimation of IOP in this group was 8.5 mm Hg. And even when using the more conservative formula based upon cannulation studies (0.2 mm Hg per 10 μm deviation) five of the 12 individuals had to be reclassified as normal.

In our study, patients with normal tension glaucoma did not have thinner central corneas than either normal subjects or individuals with primary open angle glaucoma or pseudoexfoliation glaucoma, although we cannot rule out the possibility that if our sample size had been larger a difference would have become manifest. Using Ehlers *et al*'s formula, the greatest underestimation of IOP in the normal tension glaucomatous group was only 3.57 mm Hg; and, accordingly, none of these patients had to be reclassified as having primary open angle glaucoma.

When one takes into account all relevant factors—the inaccuracy of both applanation tonometry[2 4 10 11 15] and ultrasonic pachymetry,[21] the existence of various formulas for adjusting estimates of IOP according to central corneal thickness, and high interindividual variability in corneal thickness—it becomes abundantly clear that the reclassification of patients is not a straightforward business—that it cannot be conducted in a decisive and unequivocal manner.[26 27] Given this situation, there would appear to be little justification for monitoring central corneal thickness on a routine basis for diagnostic purposes.[26 28]

However, in chronic conditions, a deviation of only 10% from the normal central corneal thickness has a measurable impact on tonometry, as was confirmed in a recently published meta-analysis.[26] Hence, the measurement of central corneal thickness may be useful in selected cases. This issue is likely to become of increasing importance in the near future, as widespread performance of refractive

surgery—with ensuing changes not only in corneal thickness but also in the structure of the cornea—affect the reliability and reproducibility of applanation tonometry in a manner as yet not fully appreciated.[2 3 5–7 29]

Current efforts to develop a new tonometric head—combining optical low coherence reflectometric pachymetry with Goldmann applanation tonometry—are thus well worthwhile, the accurate measurement of central corneal thickness being important not only for individual patient care, in permitting more precise estimations of IOP, but also for clinical studies, in assuring a more reliable classification of subjects.

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