Distribution of Central Corneal Thickness and Its Association With Intraocular Pressure: The Rotterdam Study

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- **PURPOSE:** To perform a cross-sectional study on the distribution of central corneal thickness and its association with intraocular pressure in an elderly population.
- **METHODS:** We measured central corneal thickness and intraocular pressure in 395 subjects (352 control subjects, 13 patients with ocular hypertension, and 30 patients with primary open-angle glaucoma) aged 55 years or more.
- **RESULTS:** Mean central corneal thickness in the 352 control subjects was 537.4 μm (95% confidence interval [CI], 533.8 to 540.9 μm ; range, 427 to 620 μm), with a maximal difference between eyes of 42 μm . There were no differences between sexes and no significant association with age. Linear regression analysis showed an increase

of 0.19 mm Hg in intraocular pressure with each 10- μm increase in central corneal thickness (95% CI, 0.09 to 0.28 mm Hg). This association was similar in both eyes and in both sexes. The 13 patients with ocular hypertension had corneas a mean of 16.0 μm thicker (95% CI, -2.6 to +34.6 μm) compared with control subjects ($P = .093$); the 30 patients with primary open-angle glaucoma had corneas a mean of 21.5 μm thinner (95% CI, 8.8 to 34.1 μm) compared with control subjects ($P = .001$).

- **CONCLUSION:** Mean central corneal thickness was similar to that found in clinical studies, was slightly higher in patients with ocular hypertension, and was significantly lower in patients with primary open-angle glaucoma. Intraocular pressure was positively related with central corneal thickness. Central corneal thickness may influence the division between normal and increased intraocular pressure at a simple cutoff point of 21 mm Hg.

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INTRAOCULAR PRESSURE IS USED FOR DIAGNOSIS AND management of many eye diseases, including several types of glaucoma. Goldmann applanation tonometry is the gold standard of measurement but provides only an estimate of intraocular pressure. The accuracy of this estimate depends on many factors.¹ To a large extent, errors can be avoided by a correct measurement technique²; however, errors caused by other factors, notably central corneal thickness,

which influences the rigidity of the cornea, cannot be avoided. On the other hand, on statistical grounds a cutoff value of 21 mm Hg is widely used to differentiate between normal and abnormal intraocular pressure. When they calibrated the Goldmann tonometer, Goldmann and Schmidt³ assumed central corneal thickness to be 0.5 mm and stressed that variation in thickness could theoretically affect the measurement. Information on differences in corneal thickness from *in vivo* measurements has subsequently become available.⁴⁻⁷

Central corneal thickness can be measured by an optical method and with ultrasound, the latter being more reliable.⁸ Ultrasonic pachymetry has been proven to be very accurate and reproducible, with a lower interobserver and intraobserver variability than optical pachymetry.⁸⁻¹⁰ Most studies on central corneal thickness have been performed in clinic-based populations. We set out to study in a cross-sectional way in an elderly population-based cohort the distribution of central corneal thickness and the association between central corneal thickness and intraocular pressure.

SUBJECTS AND METHODS

THIS STUDY WAS PERFORMED AS PART OF THE ROTTERDAM Study, a population-based cohort study of 7,983 residents, aged 55 years and more, of a suburb of Rotterdam, The Netherlands. The Rotterdam Study aims at investigating determinants of chronic disabling ophthalmologic, cardiovascular, neurogeriatric, and locomotor diseases.¹¹ The study was approved by the Medical Ethics Committee of Erasmus University, and written informed consent was obtained from all participants. The baseline measurements were performed between 1990 and 1993. This baseline phase consisted of an extensive home interview, registration of used medication, and a medical examination, including a complete ophthalmologic examination, as described in detail previously.¹² Overall response was 77.7%.

The first follow-up part of the Rotterdam Study, including a medical and ophthalmologic examination, was performed in 1993 and 1994. For 2 months of this follow-up study, central corneal thickness was

measured with ultrasound pachymetry in randomly chosen (by postal code) participants ($n = 408$) visiting the examination center for routine follow-up. Of these, only persons with normal corneas on slit-lamp examination and having had no eye surgery within the previous year were included for the present study ($n = 365$ [89.5%]). Of the 365 participants, 352 were control subjects with no ocular abnormalities, and 13 were diagnosed as having ocular hypertension; eight of these 13 were treated to lower their intraocular pressure. In addition to the randomly chosen participating subjects, as many patients with primary open-angle glaucoma from the first phase of the Rotterdam Study as possible were reinited to take part in the present study. In all, 30 patients with primary open-angle glaucoma participated, all under treatment for their glaucoma at the time of this study. In a pilot study, we found no influence by use of ultrasound on intraocular pressure; thus, before intraocular pressure measurements were made, five consecutive measurements of the central corneal thickness were taken in both eyes of all participants, and the mean of the middle three (in terms of numeric value) measurement values was used in the analyses. For the patients with primary open-angle glaucoma, the examiner was masked with regard to the category in which the participants belonged.

Ocular hypertension was defined as intraocular pressure greater than 21 mm Hg or use of intraocular pressure-lowering medication, with a cup:disk ratio of less than 0.5, and with no glaucomatous visual field defect in the baseline phase of the Rotterdam Study.

The diagnosis of primary open-angle glaucoma was based on the presence of a glaucomatous visual field defect on kinetic Goldmann perimetry in the same baseline phase combined with either a vertical cup:disk ratio of 0.5 or greater, or a difference in cup:disk ratio of 0.2 or more between both eyes, or an intraocular pressure measurement greater than 21 mm Hg, or use of intraocular pressure-lowering medication, and with open and normal anterior chamber angles without any other abnormality that could explain the visual field defect.¹²

Only one eye per person was used in the analyses. In subjects without primary open-angle glaucoma and in bilaterally affected patients with primary open-angle glaucoma, a random choice was made between

TABLE 1. Characteristics of the Study Population*

	Control Subjects	Subjects With Ocular Hypertension	Patients With POAG
N	352	13	30
Age (years) (SEM)	72.0 (1.21)	65.1 (2.34)	64.7 (0.35)
Age range (years)	55.1–90.2	64.7–72.1	69.7–88.5
Women (%)	43.4	37.5	51.1
Body mass index (kg/m ²) (SEM)	25.7 (0.60)	27.1 (1.13)	26.1 (0.17)
Systolic blood pressure (mm Hg) (SEM)	137.2 (4.10)	158.9 (7.64)	139.2 (1.16)
Diastolic blood pressure (mm Hg) (SEM)	72.2 (2.12)	79.9 (3.96)	73.8 (0.60)
Left eyes (%)	63.8	36.9	51.1

*All figures (when appropriate) are adjusted for age, sex, or both. See Subjects and Methods for descriptions of the groups.

POAG = primary open-angle glaucoma.

the right and left eyes. In monocular primary open-angle glaucoma, the affected eye was used in the analysis. Mean central corneal thickness was calculated for the entire group and also for right and left eyes separately in men and women. The Student *t* test and linear regression were used for comparing means between groups. The effect of central corneal thickness on intraocular pressure was evaluated with linear regression analysis. All analyses were performed with the BMDP statistical package.¹³

RESULTS

IN TABLE 1, THE GENERAL CHARACTERISTICS OF THE 395 subjects are given. The control subjects were significantly older than the other groups, but other characteristics were comparable. The mean central corneal thickness in the control subjects was 537.4 μ m (95% confidence interval [CI], 533.9 to 540.9 μ m; range, 427 to 620 μ m). Figure 1 shows the distribution of the central corneal thickness in the 365 randomly selected subjects (control subjects and patients with ocular hypertension).

There was no significant difference in corneal thickness between right and left eyes (mean differ-

FIGURE 1. Distribution of central corneal thickness (CCT) in the 365 randomly selected subjects (control subjects [*n* = 352] and patients with ocular hypertension [*n* = 13]). The ordinate indicates the percentage of men and women with central corneal thickness as indicated on the abscissa.

ence, 4.22 μ m; 95% CI, -2.68 to 11.3 μ m; *P* = .23; maximum difference, 42 μ m) or between men and women (mean difference, 4.39 μ m; 95% CI, -2.52 to 11.3 μ m; *P* = .21). Central corneal thickness did not change significantly with age (0.061 μ m per year; 95% CI, -0.46 to 0.58 μ m; *P* = .82), and it was similar for right and left eyes and for men and women. All corneal thickness measurements were performed during daytime (8:30 AM to 4 PM), and there was no association between central corneal thickness and time of examination.

The mean central corneal thickness in the subgroups, and the differences in corneal thickness with the control subjects, are given in Table 2. In the ocular hypertension group, we saw a slightly, although not significantly, higher central corneal thickness than in the control subjects (+16.0 μ m; 95% CI, -2.6 to +34.6 μ m; *P* = .093). In the primary open-angle glaucoma group, the mean central corneal thickness was significantly lower than in the control subjects (-21.5 μ m; 95% CI, -34.1 to -8.8 μ m; *P* = .001). Past surgical or different medical treatments in the primary open-angle glaucoma group had no effect on the central corneal thickness.

We examined the association between intraocular

TABLE 2. Central Corneal Thickness and Intraocular Pressure of One Eye per Subject in the Different Subgroups

	No.	Mean CCT			Difference With		Mean IOP	SE	95% CI	Difference With	
		(μm)	SE	95% CI	(μm)	P Value				(mm Hg)	P Value
Control subjects	352	537.4	1.80	533.8, 540.9	—	—	14.6	0.16	14.3, 15.0	—	—
Patients with ocular hypertension	13	553.4	8.50	534.8, 571.9	+16.0	.093	18.7	1.26	16.0, 21.4	+4.05	.000
Without IOP-lowering treatment	5	562.3	9.08	537.1, 587.5	+25.0	.100	23.6	0.51	22.2, 25.0	+8.96	.000
With IOP-lowering treatment	8	547.8	12.6	517.8, 577.7	+10.4	.390	15.6	0.91	13.5, 17.8	+0.98	.347
Primary open-angle glaucoma*	30	515.9	6.70	502.2, 529.6	-21.5	.001	14.3	0.75	12.8, 15.8	-0.35	.549
All subjects	395	536.3	1.73	532.9, 539.7	—	—	14.8	0.16	14.4, 15.1	—	—

*All subjects with primary open-angle glaucoma were monitored and under treatment at the time of this study.

95% CI = 95% confidence interval; CCT = central corneal thickness; IOP = intraocular pressure.

pressure and central corneal thickness only in the subjects without intraocular pressure-lowering treatment. Intraocular pressure rose with increasing central corneal thickness (0.19 mm Hg per 10 μm ; 95% CI, 0.09 to 0.28 mm Hg; $P = .0001$) (Figure 2). This regression coefficient did not change after adjustment for age and gender. Conversely, the corneal thickness increased by 2.23 μm per 1.0-mm Hg increase in intraocular pressure (95% CI, 1.13 to 3.34 μm ; $P = .0001$).

DISCUSSION

THE MAIN FINDINGS IN OUR POPULATION-BASED STUDY are that the mean central corneal thickness we found in normal eyes (537.4 μm) is similar to that reported in clinic-based studies and that it is positively associated with intraocular pressure. In clinical studies, the mean central corneal thickness varied from about 520 μm using optical pachymetry^{4,6,7,14} to 540 μm with ultrasound.^{9,15} Patients with ocular hypertension in the present study had a slightly higher corneal thickness than did control subjects; on the other hand, patients with primary open-angle glaucoma had a significantly lower central corneal thickness than did the control subjects. Age had only a small and nonsignificant inverse relation to corneal thickness, which agrees with other studies,^{6,7,15} and similarly, there were no differences between sexes.^{6,7}

Central corneal thickness was similar in right and left eyes. Previous studies with optical pachymetry^{6,16}

FIGURE 2. Association between central corneal thickness and intraocular pressure (IOP) as measured with applanation tonometry in the 352 control subjects and in five patients with ocular hypertension, all without intraocular pressure-lowering treatment. — = the linear regression line; - - - = the borders of the 95% confidence interval; + = control subject; ♦ = subject with ocular hypertension.

did show a systematic right-left difference. This may be because of a measurement error in the optical method when the measurement is not perpendicular to the cornea. Such a measurement error does not occur with the ultrasound pachymeter used here because this gives a reading only when the probe is perpendicular to the cornea. Indeed, other studies using ultrasound pachymetry also could not find a right-left difference.^{9,10}

In the ocular hypertension group, central corneal

thickness was slightly higher than in control subjects, which has also been found by others.¹⁷⁻¹⁹ In the primary open-angle glaucoma group, however, central corneal thickness was significantly lower than in control subjects, in contrast to the findings in other studies, possibly because of too low a power or the use of the less accurate optical pachymetry in those studies.^{7,18-20}

As expected from the literature,^{6,21} we found that central corneal thickness and intraocular pressure were positively related. On the other hand, a negative relation between central corneal thickness and intraocular pressure was found in a study of 45 subjects with unilateral retinal detachment.⁵ However, eyes with a retinal detachment often show flare in the anterior chamber and vitreous, pointing to a breakdown of the blood-retina barrier and to release of inflammatory mediators. These may have influenced the corneal thickness in that study,⁵ as was also confirmed by Ytteborg and Dohlman.²²

It is still not clear whether the relation between intraocular pressure and corneal thickness is artifactual rather than real. It may be caused by a measurement error in applanation tonometry because of differences in corneal thickness, as anticipated by Goldmann himself.³ Another possible explanation is a physiologic effect of intraocular pressure on the cornea, resulting, for example, in an increase of collagen fibers or rigidity in the cornea or a combination of both. Based on our data, we cannot prove or reject any of these possibilities. To do so, invasive measurement of intraocular pressure is necessary.²¹

The diagnosis of ocular hypertension, and of high-tension and low-tension primary open-angle glaucoma, is usually made on the basis of the arbitrary intraocular pressure cutoff point of 21 mm Hg, a point based on statistical grounds and convention rather than on causative factors. Our findings on central corneal thickness, showing a definite relation with intraocular pressure values, may have an impact on values around the "magic" 21 mm Hg. Many patients with increased intraocular pressure but without other glaucomatous features might merely have a thicker cornea but not be at higher risk for glaucoma.

In conclusion, the mean central corneal thickness in the normal eyes of this elderly population was 537.4 μm , and thickness showed a maximal differ-

ence between eyes of 193 μm . In an individual, the maximum difference between right and left eyes was 42 μm . Mean central corneal thickness was slightly higher in subjects with ocular hypertension and significantly lower in patients with primary open-angle glaucoma. As measured by applanation tonometry, intraocular pressure is positively related to central corneal thickness. From this study, we cannot conclude whether this is only because of measurement errors or also because of a direct effect of the intraocular pressure on the corneal thickness. Because of the variation in central corneal thickness in this population, the measured intraocular pressure can be an underestimation or an overestimation of the actual hydrostatic intraocular pressure and thus can be a confounder in the subdivision between normal and increased intraocular pressure—and, therefore, a confounder also between normal-pressure and hypertensive primary open-angle glaucoma at an absolute cutoff point of 21 mm Hg.

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