Long-term change in central corneal thickness from a glaucoma perspective

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Aim: To investigate the longitudinal change in central corneal thickness (CCT) over 3 years in patients with glaucoma. **Materials and Methods:** The Chennai Glaucoma Follow-up Study, an offshoot of the Chennai Glaucoma Study, was designed to evaluate the progression of glaucoma. A cohort of participants in the Chennai Glaucoma Study that were suffering from glaucoma or were at a higher risk for glaucoma underwent comprehensive ophthalmic evaluation at the base hospital at 6-month intervals during the years 2004 to 2007. The CCT (average of 10 readings) was measured between 11 am and 1 pm on any given day using an ultrasonic pachymeter. Patients with a history of ocular surgery, corneal disease and usage of topical carbonic anhydrase inhibitor were excluded. No patient was a contact lens wearer. **Results:** One hundred and ninety-six patients (84 male, 112 female) met the inclusion criteria. We analyzed data from the right eye. The mean age of the patients was 59.97 ± 9.06 years. Fifty-nine (30.1%) of the patients were diabetic. The mean change in CCT (CCT at first patient visit – CCT at last patient visit) was 3.46 ± 7.63 μm. The mean change in CCT was 0.75 μm per year ($R^2 = 0.00$). Age, gender, intraocular pressure at the first patient visit and diabetic status had no significant influence on the magnitude of change in CCT. **Conclusion:** A carefully obtained CCT reading by a trained examiner need not be repeated for at least 3 years as long as the ocular and systemic factors known to affect the measurement of CCT are constant.

Key words: Central corneal thickness, glaucoma, pachymetry

Measurement of central corneal thickness (CCT) is important in the management of glaucoma for several reasons. CCT has been shown to be a strong risk factor for the conversion from ocular hypertension (OHT) to primary open angle glaucoma (POAG).[1] CCT can significantly affect intraocular pressure (IOP) measurement obtained using Goldmann applanation tonometry.[2-4] Measurement of CCT is also useful in the interpretation of clinical trials on glaucoma therapy. A review and meta-analysis describes the extensive research on the various methods of measurement of CCT and their relative accuracy and precision, normal range of CCT and factors responsible for change in CCT.[5] Several studies report on the long-term change in CCT.[6-9] All but one of them recommends to obtain more than one measurement of CCT before assessing the risk of glaucoma progression.[6-8] Nevertheless, the studies investigating long-term change in CCT are few and have inherent limitations.

The Chennai Glaucoma Follow-up Study, an offshoot of the Chennai Glaucoma Study, was designed to evaluate the progression of glaucoma. As a part of comprehensive ocular examination, CCT measurements were obtained. The characteristics of CCT in our population are recently reported.[10] This article reports the longitudinal change in CCT in glaucoma patients over 3 years.

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Materials and Methods

This study was approved by the institutional ethics review board. The methods and design of the Chennai Glaucoma Study are described in detail elsewhere.[11] Chennai city is our urban study area. People aged 40 years and above and residing at the target address for a minimum period of 6 months were eligible for inclusion in this study. Sample selection was performed using a multistage sampling procedure. Trained social workers performed the enumeration by a door-to-door survey. During the enumeration, demographic information was collected. A total of 3850 (response rate 80.2%) urban study patients underwent comprehensive ophthalmic examination at the base hospital. Written, informed consent was obtained from all patients who responded. Data were collected over the years 2001 to 2004.

The Chennai Glaucoma Follow-up Study was designed to evaluate the progression of glaucoma. Four hundred and fifty participants in the Chennai Glaucoma Study who were suffering from glaucoma, or were at a higher risk for glaucoma, were invited to the base hospital at 6-month intervals during the years 2004 to 2007. All patients underwent a comprehensive ophthalmic examination and diagnostic procedures during each visit. Corneal pachymetry was performed before applanation tonometry and gonioscopy.

The CCT was measured between 11 am and 1 pm on any given day using a DGH 550 Ultrasonic pachymeter (DGH Technology Inc., Exton, PA, USA) by one of the two observers (PR and SVR). Both observers had at least 4 years of experience in the technique. The agreement between them was good (weighted kappa = 0.87, 95% CI: 0.78-0.97, 95% limits of agreement: −10.9 to +8.5 μm). The ocular surface was anesthetized with 0.5% Proparacaine eye drops (Sunways, Mumbai, India). The measurement was made in auto mode

with the patient in supine position while he or she fixates on a distant target. The probe tip was placed perpendicular to the central cornea and applanated. Ten readings were obtained and an average of these readings was recorded in micrometers.

For the analysis, patients with a history of ocular surgery, corneal disease or usage of topical carbonic anhydrase inhibitor were excluded. We analyzed data from the right eyes. Glaucoma was classified according to the International Society of Geographic and Epidemiologic Ophthalmology classification.[12] Ocular hypertension was defined as eyes with an IOP of more than the 22 mmHg, with open angles on gonioscopy without evidence of glaucomatous optic neuropathy or a visual field defect. For each patient, we recorded the presence of diabetes mellitus (DM) based on self-reporting or current use of anti-diabetic medication (s) or random blood sugar level >200 mg/dL at the baseline visit in the Chennai Glaucoma Study.

All CCT data were reported as mean and standard deviation. Age group-related difference in the mean CCT at the first patient visit was tested using an analysis of variance. Gender- and diabetic status-related differences in the mean CCT at the first patient visit were assessed using the Student t-test. The change in CCT was analyzed with a univariate linear regression model that included age, gender, IOP at the first patient visit and diabetic status. Statistical significance was assessed at the $P < 0.05$ level for all parameters. Statistical analysis was carried out using SPSS software version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Two hundred and eighteen patients completed all six visits as per the schedule. Twenty-two patients were excluded from the analysis. The reasons for exclusion were pseudophakia (18 eyes), aphakia (one eye), central corneal scar (two eyes) and use of topical carbonic anhydrase inhibitors at any visit (two eyes; one of them also had a central corneal scar) in the right eye. No patient was a contact lens wearer. Data from the right eye of the remaining 196 patients were analyzed. There were 84 males (42.9%) and 112 females. The mean patient age was 59.97 ± 9.06 years (range, 42-82 years). Fifty-nine (30.1%) patients were diabetic. Table 1 shows the ocular diagnoses of patients at the first visit. The mean IOP at the first patient visit was 18.02 ± 4.89 mmHg (range: 7-40 mmHg). The average number of topical anti-glaucoma medications at the first (0.41 ± 0.66) and the last patient visits (0.44 ± 0.71) were comparable ($P = 0.66$, two-tailed t-test). The mean duration of follow-up was 2.42 ± 0.11 years (range: 2.18-2.92 years). Table 2 shows the age group-wise distribution of the mean CCT ± SD at the first patient visit. There were no significant differences in corneal thickness between the different age groups ($P = 0.46$, one-way ANOVA). Mean CCT at the first patient visit did not differ significantly between males (527 ± 34 µm) and females (525 ± 33 µm, $P = 0.63$, two-tailed t-test) and also between diabetics (525 ± 33 µm) and non-diabetics (526 ± 34 µm, $P = 0.94$, two-tailed t-test).

Fig. 1 is an error bar chart showing the mean value of CCT (µm) at each patient visit. Fig. 2 is a histogram of the difference in CCT (µm) between the first and the last patient visits. The mean change in CCT (CCT at first patient visit – CCT at last patient visit) was 3.46 ± 7.63 µm (range: −13 to 34 µm). The mean change in CCT was 0.75 µm per year ($R^2 = 0.00$).

The change in CCT was less than the 95% limits of agreement between the pachymetry operators (PR and SVR) in 146 (74.5%) eyes. The mean CCT variability (SD) in the remaining 50 (25.5%) eyes was 11.34 µm (9.05 µm). Only five (2.5%) eyes had >20 µm variability in CCT. The mean CCT variability (SD) in these five eyes was 25 µm (4.77 µm). In the univariate linear regression model, age ($P = 0.27$), gender ($P = 0.66$), IOP at the first patient visit ($P = 0.13$) and DM ($P = 0.95$) were insignificantly associated with the difference between the first and the last CCT measurements.

Discussion

CCT is a dynamic parameter. The ocular and systemic factors known to influence CCT are varied, and include age, gender, ethnicity, diurnal variation, contact lens wear, topical medication, corneal disease, ocular surgery, systemic disease (e.g. DM) as well as the technical factors (instrument, observer or technique related).[5] These variables were taken into consideration while evaluating the long-term change in CCT in this study.

Reports on CCT and age have been inconsistent. Few studies[13,14] did not find a significant difference in mean CCT with increasing age and agreed with our cross-sectional analysis [Table 2]. The sample size of the later study[14] was inadequate to answer the study question. Power analysis might be one explanation to the conflicting reports of association between CCT and age. The non-homogeneous nature of the study groups, e.g. inclusion of study patients with ocular disease, is another issue. A large-scale analysis of 352 normal individuals over the age of 55 years revealed no statistically detectable change with age.[15] On the other hand, the cross-sectional finding of the Barbados Eye Study showed an association between thinner corneas and increasing age.[16] Aghaian *et al.* showed a 3-µm decrease in CCT per decade of age in a cross-sectional study of multiracial patients.[17] Foster *et al.* found a 5-6 µm decrease in CCT per decade of age in a cross-sectional study of Mongolian patients.[18] Another cross-sectional study in Latinos showed a decrease in CCT of 2.9 µm per decade.[19] Our recent publication on CCT in 6754 phakic patients over 40 years of age reported a significant ($P < 0.001$) decrease in CCT with increasing age.[10] Weizer *et al.*[8] demonstrated a longitudinal decrease in mean CCT over 8 years. However, the change in CCT was statistically significant for the right eyes and not for the left eyes.[8] CCT decreased at a mean rate of −0.74 ± 3.5 µm between the first

Table 1: Diagnoses of patients at the first visit

Diagnosis	Number of patients (%)
Primary angle closure glaucoma	23 (11.7)
Primary angle closure	2 (1)
Primary angle closure suspect (status post-YAG peripheral iridotomy)	86 (43.9)
Primary open angle glaucoma	25 (12.8)
Primary open angle glaucoma suspect	23 (11.7)
Ocular hypertension	31 (15.8)
Pseudoexfoliation glaucoma	6 (3.1)
Total	196 (100)

YAG indicates yttrium aluminum garnet
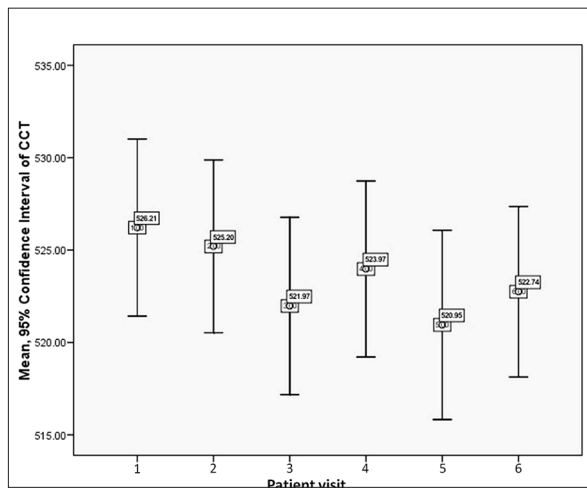
Figure 1: Error bar chart showing the mean value of central corneal thickness (μm) at each patient visit

Figure 2: Histogram of the difference in central corneal thickness (μm) between the first and the last patient visits

Table 2: Age group-wise distribution of the mean CCT at the first visit

Age group (years)	Frequency	Mean (SD) CCT in μm with 95% CI P (one-way ANOVA)=0.46
40-49	28	525.82 (31.59) (514.12-537.52)
50-59	64	531.64 (35.18) (523.02-540.26)
60-69	74	523.21 (32.61) (515.78-530.64)
>70	30	522.40 (37.13) (509.11-535.69)

ANOVA: Analysis of variance, CCT: Central corneal thickness, CI: Confidence interval, SD: Standard deviation

and the second CCT measurements 3.8 ± 0.8 years apart in the Ocular Hypertension Treatment Study.[9] However, the observed difference in CCT per decade was small in most of the studies,[9,10,16,17,19] and may not be clinically significant. Moreover, most of the studies[10,13-19] on the relationship between CCT and age are cross-sectional. This study design may not provide definite information about the cause-and-effect relationship.

We did not find a gender difference in the mean CCT at the first patient visit. Besides, gender did not affect the magnitude of change in CCT over 3 years. The effect of gender on CCT remains poorly defined. Some studies agree with our findings.[7,15] Some observed thinner corneas in women.[20] And yet, the CCT values in the ocular hypertension treatment study [9] and in the meta-analysis[5] were higher in women.

Several studies have examined the effect of DM on CCT. Ozdamar et al.[21] found a significantly greater CCT in diabetics (564 ± 30 μm, n = 100) compared with a healthy group (538 ± 35 μm, n = 145). In a population-based cross-sectional study, persons with diabetes (n = 748) had, on average, 6.50 microns thicker corneas than those without diabetes (n = 2491) after controlling for age, IOP, body mass index and axial length.[22] CCT was shown to be significantly higher for diabetes of over 10 years' duration than for diabetes of less than 10 years' duration.[23] On the other hand, CCT
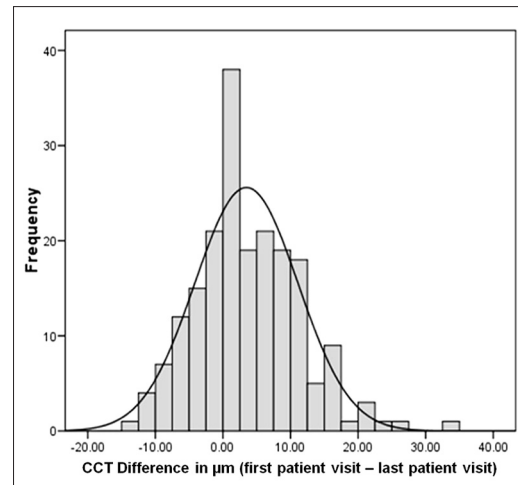
measured by Scheimpflug imaging did not differ significantly between patients with DM type 1 and 2 and healthy controls in another cross-sectional study.[24] In our study, mean CCT at the first patient visit did not differ between diabetics and non-diabetics. DM had no significant influence on the magnitude of change in CCT over 3 years. However, bias due to self-reporting of DM may have influenced the result. Additional information is needed to further clarify the influence of DM on CCT.

In most of the studies, CCT measurements were obtained over the working day. The few studies documenting diurnal variation in CCT have shown significantly increased readings when measured before 11 o'clock.[25-27] CCT measurement between 11 am and 2 pm has been shown to approximate the mean diurnal CCT.[28]

Wickham et al.[6] evaluated the measurement of CCT in a cohort of 51 glaucoma patients over a 3-month period. A single, trained observer performed all ultrasonic pachymetry measurements. The study showed a significant fluctuation in corneal thickness (9.6 ± 26.9 μm). But, a systematic bias toward increased corneal thickness being recorded at the second examination cannot be ruled out. In 32% of the patients, the difference in CCT values was sufficient to recategorize glaucoma risk in both eyes.

Weizer et al.[8] examined 64 eyes of 39 available patients from a previously identified cohort of 109 patients. The mean length of time between the two examinations was 8.2 years (range 4.7-8.5 years). The study patients had open angle glaucoma, ocular hypertension, glaucoma suspect status or normal ocular examination. The mean CCT decreased significantly by 17 μm in the right eyes (P < 0.002) and by 23 μm in the left eyes (P < 0.001). However, CCT was measured by different operators using different ultrasound pachymeters. A variation of ≥ 15 μm between two repeated measurements has been demonstrated in nearly a quarter (304 out of 1377, 22%) test–retest interobserver evaluations.[29] Additional limitations of the study[8] were an inability to control the time of day for CCT measurement, performing contact pachymetry immediately following applanation tonometry and a small sample size.

Shildkrot *et al*.[7] studied 98 eyes of 98 patients. The mean inter-test period was 276 ± 124 days (range 35-610 days). Measured CCT values differed by >20 microns in 20 eyes (20.4%) and by >40 microns in five eyes (5%). The study was not designed to be a true reproducibility study and the goal was to mimic routine clinical practice. The technicians performing CCT varied over time and the time of CCT measurement was not adjusted to match the previous measurement. The authors suggest that a single measurement of CCT may not suffice for the long-term patient follow-up. However, the difference in the measured CCT values reflects both the reliability of ultrasound pachymetry and the variability of corneal thickness, if any, over the follow-up interval.

Only a few studies have evaluated the variability of ultrasound pachymetry. Most of them involved small sample sizes. The reported 95% limits of agreement between observers were −22 to +24 μm[30] and −20 to +17 μm.[31] The intraclass correlation coefficients of the interobserver evaluations were 0.89 to 0.95 in one study.[29] However, a variation of ≥15 μm between two repeated measurements was demonstrated in 22% test–retest interobserver evaluations in the same study.[29] Measurements of CCT may also vary due to the limitations of the equipment used and the experience of the operator. In contact ultrasound pachymetry, inexperienced users may exert excessive applanation and record erroneous readings. The anterior and posterior curvatures of the human cornea are not concentric.[32] Therefore, the angle of the probe and the exact location of applanation can influence the accuracy of pachymetry. In a clinical setting, measurements of CCT will be taken by different observers with different degrees of experience under varying conditions. A repeat measurement of CCT, if erroneous, can potentially mislead an examiner. A properly measured CCT by one of the trained operators under identical conditions showed a modest age-related rate of change in our study. The 95% confidence intervals of mean CCT at the first (521-530 μm) and the last patient visits (518-527 μm) were overlapping [Fig. 1]. We, therefore, suggest that a properly measured CCT reading need not be repeated for at least 3 years as long as the ocular and systemic factors known to affect the measurement of CCT are constant. Limitations in availability of resources in developing countries deserve additional consideration.

Conclusion

A carefully measured CCT by a trained examiner should suffice in calculation of the risk of glaucoma progression and taking management decision. The CCT reading need not be repeated for at least 3 years as long as the ocular and systemic factors known to affect measurement of CCT are constant.

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