



The thick and thin of the central corneal thickness in glaucoma

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Abstract

Central corneal thickness (CCT) is an important parameter in the assessment of any potential glaucoma patient. While it affects prognosis in ocular hypertension, its value in patients diagnosed with glaucoma is less certain. There are several biological factors and genetic components that may influence glaucoma progression, which have been associated with thinner CCT. The CCT itself can be affected by several factors including ethnicity, age, sex, glaucoma medications, genetics, and the subtype of glaucoma. Besides, there is variability in the measurement of CCT between different types of devices. These factors need to be considered in the evaluation of glaucoma patients' CCT and its effect on interpretation of intraocular pressure levels and risk stratification.

Introduction

Central cornea thickness (CCT) is an integral component in the workup of any new patient suspected of having glaucoma. It is part of guidelines promulgated, for example, by the American Academy of Ophthalmology, Canadian Ophthalmology Society, Asia-Pacific Glaucoma Society, European Glaucoma Society, and Australian National Health and Medical Research Council. The CCT can be influenced by many factors including: ethnicity, genetics, age, glaucoma treatment and the subtype of glaucoma. The measurement of CCT by the various types of devices are also not interchangeable. All these above factors need to be considered in the evaluation of a glaucoma patient's CCT and its effect on interpretation of intraocular pressure (IOP) levels and risk stratification.

Methods

An Ovid MEDLINE search was performed using the following resource: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946-Present (September 2017). A search using keywords “Central Corneal Thickness” OR “CCT” limited by human studies was performed. The results were filtered by those with a “Glaucoma” subject heading. From these results relevant studies were identified.

Measurement tools

CCT measurement

Owing to its general ease of use, repeatability, and modest cost, the most widespread method to measure CCT is ultrasound pachymetry (UP), which requires contact with the eye, necessitating the use of topical anesthetic and a cooperative patient. It may also be a source of infection or potential damage to the corneal epithelium. Specular microscopy (e.g., Topcon SP-3000P, Topcon Corporation, Tokyo, Japan), optical coherence tomography, rotating Scheimpflug camera (e.g., Pentacam, Oculus Inc., Wetzlar, Germany), optical low-coherence reflectometry (e.g., Lenstar, Haag-Streit AG, Koeniz, Switzerland), and slit-scanning optical pachymetry (OPT; e.g., Orbscan, Bausch & Lomb, Rochester, NY, USA) are other imaging techniques that are non-contact. Results from these OPT

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techniques are not interchangeable between devices and differ significantly compared with UP [1–5]; some devices overestimate [5, 6], while others underestimate [4, 7]. The presence of corneal haze and keratoconus may explain some differences in the measurements between devices [8, 9]. Even though in some studies the Pentacam, Orbscan, and the Galilei Dual-Scheimpflug (Ziemer Group, Port, Switzerland) were found to correlate with the UP [8–11], the UP and OPT are not considered interchangeable.

Intraocular pressure measurement

Devices and CCT

There are many devices available for measuring IOP, most of which can be influenced by variations in CCT. Goldmann Tonometry (GAT), the gold standard for IOP measurement, was developed based on a 500- μm -thick cornea [12]. However, with cannulation studies a CCT of 520 μm was found to be the most accurate with GAT [13]. There is a positive correlation between CCT and IOP in GAT [14, 15]. The Dynamic Contour Tonometry (Zeimer Ophthalmic systems AG, Port, Switzerland) in contrast appears to not be affected by differences in the CCT [16, 17]. The Ocular Response Analyzer (Reichert Inc., Depew, NY, USA), which takes into account corneal hysteresis, provides two IOP measures: Corneal Compensated IOP (IOPcc) and Goldmann correlated IOP (IOPg). The IOPg has been correlated with CCT in several studies [18, 19], but also has shown no correlation [20]. There is no association with CCT in IOPcc measurements [18–20]. In the Tonopen (Reichert Inc.), there may be negligible effect of CCT on the IOP readings [21, 22]. Rebound Tonometry (e.g., iCare, Helsinki, Finland) is affected by CCT [23, 24]; however, one study did show that it was affected by cornea hysteresis and cornea resistance rather than CCT [25]. The pneumotonometer can be significantly influenced by CCT [26]. The Diaton tonometer (Tonon GmbH, Munster, Germany) is independent of CCT as it is applied over the eyelid onto the sclera, so is influenced by variations in those structures instead.

Artifact and correction

On the basis of the cannulation studies of Ehlers et al., a deviation of 100 μm from the “ideal” CCT of 520 μm introduces an error of 7 mmHg [13]. To account for this deviation, several methods have been devised including linear correction factors [27, 28], nonlinear models [29], and more intricate mathematical models, taking into account the lesser significance of CCT at lower IOP [30]. Unfortunately, these correcting methods introduce other errors into the interpretation of the IOP results. In addition, the

adjusted IOP is unlikely to improve tonometry as a screening tool for open angle glaucoma (OAG) in at-risk populations [31] and is not necessary in population-based assessment [32]. Therefore, attempting to “correct” IOP based on CCT does not provide any benefit in the assessment or management in the glaucoma or glaucoma suspect patient.

IOP correction factors are based on structurally normal corneas with no pathology. Thicker edematous cornea will result in artefactually lower GAT readings owing to reduced rigidity. In comparison, a thinner cornea with scarring may have an artefactually higher reading due to increased rigidity. The increased rigidity in the cornea after cornea crosslinking has been postulated to explain the increase in IOP observed in keratoconus patients after 1 year, despite no change in their CCT [33].

Prognostic factors and associations

Ocular hypertension and glaucoma suspect

The Ocular Hypertension Study (OHTS) identified a thinner CCT as an important predictive factor for development of primary open angle glaucoma (POAG) from ocular hypertension (OHTN) [34]. In this study, a patient with a CCT of 555 μm or less had a threefold increased risk of developing glaucoma within 5 years compared with someone with a CCT greater than 588 μm . This study was limited by having only 7% of patients with CCT less than 526 μm , while more than 25% had a CCT greater than 600 μm . Even though this distribution could overestimate the significance of CCT, CCT is still considered an important risk factor.

The prediction model from OHTS has been supported by data from the European Glaucoma Prevention Study (EGPS). The pooled OHTS-EGPS-predictive model confirmed CCT as a significant predictor for glaucoma, with every 40 μm decrease in CCT associated with a twofold increased risk of developing glaucoma over 5 years [35]. There was no evidence that its predictive value could be attributed to any other risk factors and is therefore considered to be independent.

Glaucoma

In patients with established glaucoma, the predictive role of CCT is not as well proven in management or long-term prognosis. However, patients with advanced damage are more likely to have a thin CCT [36].

Population-based studies, including groups from West Africa and East Asia, have shown no difference in CCT between glaucomatous and non-glaucomatous eyes [14, 37–40]. However, in the Los Angeles Latino Eye Study, those

with thin CCT had a significantly higher prevalence of POAG than those with normal or thick corneas [32]. There are several studies showing an association of a thinner CCT (range: 522 ± 35 to $537.5 \pm 33.0 \mu\text{m}$) in normal tension glaucoma (NTG) compared with those with POAG [36], OHTN [36, 40], or normal eyes [41–43]. No association between NTG and a thinner CCT has been reported [44].

Pseudoexfoliation syndrome (PXF) and pseudoexfoliation glaucoma (PXG) patients have been reported to have thinner CCT [36, 41, 45] or similar CCT compared with normal controls [46]. Palko and Sheybani looked at studies examining corneal alterations in PXF or PXG and found no consistent trend of an effect on CCT [47].

Pigment dispersion syndrome (PDS) and CCT have not been well reported and were excluded from the OHTS study. These patients were included in the EGPS, but as such a tiny cohort were excluded from the pooled OHTS–EGPS analysis. Only a few studies have included PDS and there is no significant difference in CCT for this group compared with normal or POAG eyes, limited by the smaller cohort of patients [36, 48].

Confusingly, patients with primary angle closure (PAC) or PAC glaucoma have been reported with thinner CCT compared with controls (range: 509.7 ± 27.4 to $525.9 \pm 5.0 \mu\text{m}$) [41, 49]. Kniestedt et al. found no association in their cohort [36].

Biological factors

Association between the thin CCT and thin lamina has been proposed. A thin lamina might have less rigidity than a thicker one and could be more susceptible to displacement by IOP fluctuations, leading to increased loss of adjacent axons [50]. Lesk et al. found that their surrogate marker for lamina cribrosa (LC) displacement was greater in patients with thinner CCT [51]. In contrast, Nicolela et al. found that IOP changes of 5 mmHg in range did not have a measurable effect on optic disc topography and no association with thin CCT [52]. This finding was supported in a subsequent study by Omodaka et al. [53]. The disparity may be explained by the duration and severity of glaucoma, which could influence the compliance of the lamina in response to IOP changes [54]. Other studies have found no relationship between CCT and the LC [55, 56].

There is no definitive correlation between Heidelberg retina tomography (Heidelberg, Germany) optic disc parameters and CCT. The Singapore Malay Eye Study found that a thinner CCT was associated with smaller rim area and a greater cup to disc area in subjects with POAG [57]. Similarly, the Tajimi study in Japan found a thinner CCT associated with a larger cup volume [58]. However, in other population-based studies there was no significant relationship with any optic disc parameter [15, 59]. Some hospital-

based studies have found CCT associated with optic disc area [60–62], nasal rim area [63], as well as no significant correlation of CCT and disc size [62].

Siegfried et al. found an inverse correlation between CCT and partial pressure of oxygen in the anterior chamber angle [64]. The theory is that thin CCT may increase trabecular exposure to oxidative damage.

Genetic associations

The CCT phenotype is a highly heritable trait based on twin studies [65–67]. There is, however, no single genetic determination for CCT [68]. Genome-wide association studies have identified many CCT-associated loci [69–73], but only the FNDC3B genetic locus has been associated with POAG in a meta-analysis [69]. In addition, the combined genetic effect of these loci explain only a small amount of heritability. The meta-analysis found that genes associated with CCT are involved in collagen and extracellular matrix metabolism, collagen fibril organization, and myosin binding.

Ethnic groups

Measured average CCT varies between the different ethnic groups, with African Americans and Japanese having thinner CCT consistently compared with other groups [36, 41, 74]. Patients with Indian descent were reported with both thinner [75] and similar CCT [76]. The method of measuring CCT does vary between studies with some using UP and others OPT. As mentioned earlier, these are not interchangeable; therefore, comparing between the two is not accurate. Therefore, as there is no comparison group for the Mongolian patients, their OPT thinner CCT finding is harder to compare [77]. Caucasian, Hispanic, Latino, Chinese, Filipino, Korean, Malay, and Iranian populations have thicker CCT compared to those listed above, as is illustrated in Table 1 [36, 40, 41, 76, 78–82]. Overall, ethnicity should be considered when interpreting CCT, given the variations.

In the OHTS and EGPS, Caucasian patients were the most represented race, with the African American group the second most in OHTS. The African American group had a thinner CCT compared with the Caucasian subjects [83]. In patients with African descent, the Barbados Eye Studies showed that decreased CCT is associated with an increased risk of developing POAG over 9 years (odds ratio (OR) 1.41 95% confidence interval 1.01–1.96 per $40 \mu\text{m}$ lower) [84].

Systemic

There is a positive relationship between CCT with both serum glucose and HbA1c levels. In several studies, some population-based, diabetes mellitus (DM) is associated with

Table 1 Average central cornea thickness ($\mu\text{m} \pm \text{SD}$) by ethnic group

Study	Caucasian	Hispanic	Latino	African American	Chinese	Filipino	Japanese	Korean	Indian	Asian	Other	Method
Aghaian et al., 2004 [41]	550.4 \pm 3.2	548 \pm 3.6		521.0 \pm 3.9	555.6 \pm 3.4	550.6 \pm 3.8	531.7 \pm 4.1		540.4 \pm 33.6	548 \pm 2.8	540.9 \pm 33.6 ^h	UP
Chua et al., 2014 [76]					552.3 \pm 33.4							UP
Eysteinsson et al., 2002 [78]	527 \pm 39										495 \pm 32 ^f	OPT ^a
Foster et al., 1998 [77] ^d												OPT ^b
Hahn et al., 2003 [79]			546.9 \pm 33.5									UP
Kniestedt et al., 2006 [36]	549 \pm 39			518 \pm 30						538 \pm 32	541 \pm 28 ^e	UP
La Rosa et al., 2001 [80] ^d	558.0 \pm 34.5			531.0 \pm 36.3								UP
Lee et al., 2007 [40]								550.3 \pm 3.5				UP
Nemesure et al., 2003 [81]	545.2 \pm 45.7			529 \pm 37.7							537.8 \pm 34.0 ^g	UP
Pakravan et al., 2017 [82]											543 \pm 37 ^o	UP
Shimmyo et al., 2003 [91]	552.59 \pm 34.48	551.10 \pm 35.54		535.46 \pm 33.39						549.79 \pm 32.3		UP
Sng et al., 2016 [14]				533.9 \pm 34.0								UP
Suzuki et al., 2005 [90]							517 \pm 29.8					UP
Tomidokoro et al., 2007 [74]							521 \pm 32					OPT ^c
Vijaya et al., 2010 [75]									511.4 \pm 33.5			OPT ^c

UP ultrasound pachymetry, OPT optical pachymetry

^a NidekEAS1000 (Nidek, Fremont, CA, USA)

^b Depth Measuring Device I (Haag-Streit, Bern, Switzerland)

^c Specular-type pachymeter (SP-2000P; Topcon, Tokyo, Japan)

^d Right eye presented

^e Hispanic, Arab, native Indian

^f Mongolian

^g Mixed (African American + White)

^h Malays; o-Iranian

a thicker CCT [59, 81, 85, 86]. However, no association has also been reported [87]. In addition, metabolic syndrome [85] and an increased body mass index [85, 87, 88] are correlated with an increased CCT. Chronic kidney disease that often present in those with DM has also been found to be associated with increased CCT [85]. No association has also been reported [89].

Sex

The role of sex on CCT is variable as there are reports of no differences between the sexes [40, 41], females having thicker CCT than males [83] and males having thicker CCT than females [14, 39, 79, 87, 90].

Age

There is a significant inverse correlation between age and CCT, decreasing ~2–10 μm per decade [14, 38, 40, 41, 75, 77, 79, 81, 83, 90]. This rate, however, may not be clinically significant. While most studies have agreed on the decrease over time, there are also those that show no significant association of CCT with age [91, 92].

Treatment

Topical medications

Topical glaucoma medications are the mainstay of treatment for glaucoma. Depending on the class of medication, they could cause thinning, thickening, or no change to the CCT.

Prostaglandin analogue (PGA) topical drops can decrease, increase, or not affect CCT. The decrease appears to occur most significantly in the first 1–2 years of treatment and mostly in NTG patients (range: 8.6 ± 5.2 to $14.24 \pm 8.18 \mu\text{m}$) [93–95]. This appears reversible following cessation [96]. An increase in CCT can also occur as reported in brimatoprost and latanoprost [97]. Iester et al. showed no change to CCT in their Italian Glaucoma Register study [98]. No factor has been identified to explain the difference; however, many of those reporting a decrease have had more NTG patients.

Carbonic anhydrase inhibitor topical drops have been shown to cause irreversible corneal decompensation and increased CCT in eyes with underlying cornea endothelial disease [99]. In healthy corneas there was no effect on the endothelium [100]. In POAG, an increase [101] and no change [98] in CCT both have been reported.

Beta-blocker (BB) topical drops have shown a reversible increase in CCT, with no change to the endothelium [102]. The theory is that cornea homeostasis is interrupted by the

inhibition of the endothelium pump-leak mechanism by the medication, resulting in an increase in CCT [103].

Alpha2-Adrenergic topical drops cause a reversible increase over 2 days [104].

Response to treatment

In OHTN a thicker CCT is associated with a less significant decrease in IOP after starting ocular hypertensive medications [105, 106]. Likewise, glaucoma patients with a thicker CCT have a worse IOP response than those with a thinner CCT [107, 108]. Brandt et al. reported that this reduced response to treatment is more obvious with PGAs than by BB [109]. However, no association was shown between ocular penetration of travoprost and CCT [110]. This study is limited by short-term exposure though; therefore, it cannot report on the effects of chronic use on corneal permeability.

Treatment of OHTN and POAG with selective laser trabeculoplasty (SLT) showed a significantly greater reduction in eyes with thin CCT ($<555 \mu\text{m}$) over a 30-month period [111].

Conclusion

The CCT of a patient with OHTN, glaucoma suspect, or established glaucoma can be influenced by many different factors: ethnicity, glaucoma treatment, age, and subtype of glaucoma. Thinner CCT is found more often in patients with NTG and angle closure, African American and Japanese patients, those with more advanced glaucoma and is an independent risk factor in OHTN. Its predictive value in established glaucoma is not proven; however, it is important in interpreting IOP results and risk stratification. Despite many proposed mathematical models, correcting GAT IOP does not provide any benefit in the assessment or management of glaucoma. The use of devices that measure IOP independently of CCT would help to overcome its influence; however, they are still not widely incorporated into general clinical practice. The association of CCT with biological factors and genetics in glaucoma will hopefully become clearer as the research expands in these areas.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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