Corneal thickness in glaucoma screening, diagnosis, and management
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Purpose of review
Variability in central corneal thickness (CCT) is a potent confounder of most tonometry techniques, especially Goldmann applanation tonometry. The Ocular Hypertension Treatment Study (OHTS) provided important information regarding predictive factors for the eventual development of glaucoma in patients at risk of the disease. Among the most striking of the OHTS’ findings was that CCT was a powerful predictor of glaucoma risk. In this review, studies subsequent to the OHTS report will be reviewed and placed in the context of what is known about CCT and its relation with tonometry and glaucoma risk.

Recent findings
Several well-designed studies have since expanded on this hypothesis, confirming that CCT bears an inverse relation with the risk of developing glaucoma damage. Other investigators have confirmed the presence of racial differences in CCT and pilot studies suggest that CCT may vary systematically in different forms of glaucoma.

Summary
The absence of a widely-accepted algorithm for the correction of IOP measurements should not prevent the widespread adoption of pachymetry as part of the comprehensive eye exam, as knowledge of an individual’s CCT provides valuable information about their glaucoma risk.

Keywords
glaucoma, tonometry, pachymetry, ocular hypertension, LASIK

“I do not object to having a patient of mine subjected to examination with a mechanical tonometer, but expect very little from this test since digital tonometry by an expert is a much more accurate test…”

Isador Schnabel (1842–1908) before the Vienna Ophthalmological Society, 1908

Introduction
Ever since the recognition by Bannister in the 16th century that certain forms of blindness were associated with a firm eye, ophthalmologists have been trying to measure intraocular pressure (IOP). The simultaneous explosion of ophthalmic knowledge and medical instrument-making in the 19th century led to mechanical tonometers of varied underlying principals and designs. These devices were met with almost uniform suspicion by the leaders of the day. More than a century later, it seems that perhaps their skepticism was well founded.

Goldmann applanation tonometry (GAT) gained widespread and rapid acceptance after its introduction in the 1950s. It was reasonably priced, based on easily understood physical principles, fit seamlessly into the workflow of the slit-lamp examination, and appeared to provide accurate, reproducible measurements. GAT’s status as a gold standard went largely unchallenged for 50 years, even though Professor Goldmann himself recognized various potential sources of error for the device in his first description of his tonometer. In particular, Goldmann and Schmidt acknowledged that their design assumptions were based on a central corneal thickness (CCT) of 500 µm and that the accuracy of their device would vary if CCT deviated from this value [1]. Given the paucity of published data at the time, 500 µm seemed a reasonable assumption for the average patient. We now know that CCT varies greatly among the general population, to a degree that impacts the accuracy of GAT in daily practice.

In 1975, Ehlers [2] cannulated 29 otherwise normal eyes undergoing cataract surgery and correlated corneal thickness with errors in GAT. He found that GAT most accurately reflected true intracameral IOP when CCT was 520 µm, and that deviations from this value resulted in an over- or underestimation of IOP by as much as 7 mm Hg per 100 µm. Numerous investigators have since demonstrated that CCT varies far more among otherwise normal individuals than Goldmann and Schmidt ever...
dramed; differences in CCT are seen among different racial and ethnic groups [3–5], and may lead to misclassification of patients with normal tension glaucoma and ocular hypertension [6,7].

**The Ocular Hypertension Treatment Study**
The importance of CCT in the management of glaucoma patients, particularly those with ocular hypertension, was recently driven home by findings from the Ocular Hypertension Treatment Study (OHTS) [8,9]. In the OHTS, patients were recruited who had untreated GAT measurements in one eye between 24 and 32 mm Hg on two separate occasions (the other had to be between 21 and 32 mm Hg), with no secondary cause of elevated IOP. The patients all had normal visual fields and optic nerves. CCT was measured approximately 2 years after enrollment was completed. Among the OHTS participants, 25% had CCT values greater than 600 µm [5]. If one uses Ehler’s correction of approximately 7 mm Hg/100 µm deviation from the nominal value of 520 µm, then as many as 50% of OHTS subjects had corrected IOP values upon entry less than 21 mm Hg! In a multivariate model of baseline characteristics predictive of which subjects would develop glaucoma, CCT proved to be the most potent [9].

The OHTS results demonstrate that many patients are being misclassified in terms of glaucoma risk on the basis of erroneous IOP estimates by GAT. Clearly, many individuals with elevated GAT measurements but no other findings suggestive of glaucoma probably have normal true IOPs and do not need treatment or even increased glaucoma surveillance.

**The Early Manifest Glaucoma Trial**
In contrast to the OHTS, which studied patients initially enrolled without glaucoma damage, the Early Manifest Glaucoma Trial (EMGT) studied subjects with glaucomatous damage documented at enrollment [10]. Like the OHTS, the EMGT measured CCT in all participants shortly after enrollment was completed. The EMGT randomized patients with primary open-angle glaucoma, normal tension glaucoma, and pseudoexfoliation glaucoma to either treatment with topical betaxolol, a β1 selective adrenergic antagonist, combined with argon laser trabeculoplasty, or to observation. As a safety measure for eyes with sustained IOP elevation greater than or equal to 35 mm Hg, delayed treatment was permitted for the observation group, as was the addition of latanoprost, a topical prostaglandin analog, after it became commercially available in 1996.

Eligible subjects were from 50 to 80 years of age, with newly diagnosed, previously untreated chronic open-angle glaucoma. The diagnosis of glaucoma required repeatable visual field defects in at least one eye and included primary open-angle glaucoma, normal-tension glaucoma, and pseudoexfoliation glaucoma. The study outcome is glaucoma progression as measured by quantitative visual field criteria and optic disc changes as determined by a disc reading center. The identification of subjects took place in Malmö and Helsingborg, Sweden. A total of 255 patients were enrolled with randomization concluded in April 1997.

The primary outcome result, with median follow-up of 6 years, was published in October 2002 [11]. The treatment group maintained a mean IOP reduction from baseline of 25%, whereas the observation group maintained its baseline IOP through the course of follow-up. Progression was less frequent in the treatment group (45%) compared with the observation group (62%) and occurred later. The median time to progression was 66 months in the treatment and 48 months in the observation groups. The EMGT provided unequivocal evidence that reducing the IOP makes a difference in slowing glaucomatous damage. It thus corroborates the major conclusion of OHTS, but at a more advanced stage of the disease process, and it reaffirms the primary role of IOP in the pathogenesis of glaucomatous damage.

In a publication analyzing baseline risk factors for progression of glaucoma among EMGT participants, Leske et al. reported that CCT was not a significant predictor of progression [12••]. This seeming contradiction of the OHTS findings is best understood by recognizing the following.

1. The OHTS used IOP as its primary entry criterion (at least from the standpoint of recruitment and screening), with normality of visual fields and optic nerves confirmed afterwards. If the influence of CCT as a predictive factor is primarily as a confounder of IOP measurement, then the entry criteria for OHTS and its study design is perfectly set up to demonstrate that CCT causes a misclassification of risk—thus the powerful effect CCT had in predicting who went on to get glaucoma.

2. In contrast, the EMGT was a population-based study, with patients recruited based on the presence of damage regardless of IOP. This study design eliminated the recruitment bias an IOP cutoff can cause. Indeed, a large portion of the subjects were those whom many would consider as having normal tension glaucoma. Thus, at the outset, the EMGT started with patients who had demonstrated the propensity to sustain damage at whatever their true IOP might be; errors in IOP measurement become less important in such a situation. It may be that if and when we have a correction algorithm and apply it to the EMGT data, a dose–response relation between true IOP and progression would be demonstrated. Finally, the EMGT was a relatively small sample (at least compared with the OHTS) and may not have
the statistical power to find such a relation. The EMGT investigators have published few details on the range and distribution of CCTs they measured in their racially homogeneous population; it is quite possible it was far narrower than what was found in the OHTS. If there is an effect of CCT on progression rates in established disease, the EMGT might be too small, and the range of IOPs and CCTs too narrow, to detect it.

Central corneal thickness as a glaucoma risk factor
The OHTS convincingly demonstrated that CCT plays an important role in risk stratification among patients in whom glaucoma was of concern. Medeiros et al. have provided additional support of a role for CCT in risk determination. They assessed a large cohort of ocular hypertensive individuals with a battery of structural and psychophysical tests and followed them longitudinally, looking for reproducible signs of early glaucoma. Patients with frequency doubling technology perimeter defects had thinner corneas than those with normal results [13••]. Similarly, patients with reproducible short wavelength automated perimeter defects, an indicator of early glaucomatous damage, had thinner corneas than subjects with normal short wavelength automated perimeter testing [14••].

Central corneal thickness differences among racial groups
Several investigators recently provided further evidence that African-American subjects, as a group, tend to have thinner corneas than their white counterparts. Nemesure et al. [15], following a CCT survey of participants in the Barbados Eye Survey, reported that black participants had thinner corneas (mean thickness 529.8 µm) than white participants (545 µm). No relation between IOP and CCT was found in this population-based survey. Shimmyo et al. [16] performed a retrospective biometric review of patients at a large refractive surgery center, also finding that African-American patients had thinner corneas than white patients seeking refractive surgery; they found no difference in CCT among white, Asian, and Hispanic patients in their population. This is in contrast to the findings of the population-based Los Angeles Latino Eye Study [17], which found CCTs among their Hispanic patients intermediate between values reported for African-American and white populations.

Central corneal thickness differences among glaucoma syndromes
Are different glaucoma syndromes associated with differences in CCT? Normal-tension glaucoma is associated with thinner CCTs than primary open-angle glaucoma, but this may simply represent a misclassification of patients with primary open-angle glaucoma as having normal-tension glaucoma on the basis of tonometry error and therefore may not represent a true biologic association. In an intriguing small study of 26 eyes in Japanese patients with pseudoexfoliation syndrome, Inoue et al. [18] recently found corneas thinner than age-matched controls without pseudoexfoliation, regardless of whether glaucoma was present.

The laser in situ keratomileusis–thinned cornea
A million laser in situ keratomileusis (LASIK) procedures are performed each year among mostly young to middle-aged myopes. Myopia is a strong risk factor for the development of glaucoma [19], and many of the patients undergoing LASIK today are destined genetically to develop glaucoma in the coming decades. Although we do not yet know how to correct a GAT measurement made on a LASIK-thinned cornea, it is clear that in many cases GAT will grossly underestimate IOP. The problem will arise 10 or 15 years from now when patients neglect to inform their ophthalmologist that they had LASIK years ago in 2003, and a GAT measurement of 18 mm Hg is regarded as normal despite a 425-µm cornea. Unless pachymetry becomes a part of the routine eye examination (or tonometry technologies independent of CCT are developed and widely disseminated), patients like this will fall through the cracks.

One promising new technology that may prove useful is the dynamic contour tonometer. This device consists of an electronic strain gauge embedded in a contoured plastic tip. When in contact with the cornea, the tonometer tip creates a tight-fitting shell on the corneal surface without anplation of corneal tissue. The assumption is that the tonometer compensates for all forces exerted on the cornea, allowing the strain gauge to measure IOP largely independently of corneal properties. Preliminary data with the device suggest that it is more accurate in LASIK-thinned corneas than GAT [20•].

Implications for clinical practice
Confronted with the expanding evidence that CCT is an important ocular parameter that should be measured in clinical practice, ophthalmologists understandably wonder how to obtain the measurements and what to do with the information. Newer technologies such as optical coherence tomography [21] and partial coherence interferometry [22] seem likely to become part of a future biometric workstation. In the meantime, ultrasonic pachymeters are reasonably priced (less than US$3000), extremely accurate, and easy to use: the acquisition of CCT data can safely be delegated to technical personnel in a busy clinical practice. How to use CCT measurements in daily practice, however, is not as straightforward; there is wide disagreement among investigators as to whether there is an adequately validated correction algorithm; without a validated algorithm, the argument goes, clinicians cannot use the data.

The question of whether such an algorithm exists is, in my opinion, not particularly important in daily practice.
Indeed, the clinician should be cautious in rigidly extrapolating any algorithm into practice. For example, Ehlers’ oft-quoted study [2] was based on a small number of eyes (29) that included a relatively narrow range of CCTs (450 to 590 μm). The interested reader is referred to a detailed exploration of the mechanic characteristics of the cornea and the role of CCT in GAT error by Orssengo and Pye [23] in which a mathematical and engineering model closely approximates Ehlers’ and other published cannulation data.

A general recommendation supported by the data so far is that one can take far better care of patients simply by categorizing corneas as thin, average, or thick, just as it is important to recognize that optic discs come in small, medium, and large, allowing the clinician to interpret disc configurations accordingly.

**Conclusion**

The story of corneal thickness is but the tip of the iceberg. The Goldmann tonometer simply measures the force needed to deform the cornea in a standardized manner. IOP is derived from the force measurement indirectly, based on a number of assumptions about corneal deformability. Corneal deformability in turn represents a summation of the cornea’s curvature, elastic properties, surface tension, and the IOP. Although CCT is probably the major component of corneal elasticity, it is likely not the only component. The mix of collagen types, corneal hydration, packing density of collagen fibrils, the extracellular matrix, and other factors undoubtedly vary among individuals; in some patients these other factors may dwarf the effect of CCT on the accuracy of IOP estimation. A LASIK flap can be lifted easily a year or more after the procedure. Does this flap slide over its bed during applanation, altering corneal rigidity in ways we can’t imagine? Might the potent IOP-lowering effect of the prostaglandin analogues result not only from their impressive effects on outflow but also through an effect on the corneal extracellular matrix (and thus the cornea’s deformability and elastic properties)? No one knows. Finally, some have proposed that the risk relation of CCT and glaucoma represents not just an artifact of GAT but also a biomechanical relation between CCT and the support structures of the optic nerve. These hypotheses are pure speculation at this point but seem worthy of serious investigation in coming years.

We now grudgingly recognize that our ability to accurately measure IOP is far weaker than we’ve ever imagined; we have spent half a century believing that a flawed one-time measurement told us enough about our patients on which to base clinical decision-making. A failure to question whether our measurement techniques were sufficiently accurate to guide patient care has led us to propose a variety of hypotheses to explain the outliers—patients who did not seem to fit the mold of a pressure-sensitive disease. As new technologies are developed to measure IOP with greater precision (and on a continuous basis), it seems likely that a much tighter dose–response relation between glaucoma damage and IOP will be found. Incorporating corneal thickness into our thinking is but the beginning of this transformation.

**References and recommended reading**

Papers of particular interest, published within the annual period of the review, have been highlighted as:

- Of special interest
- Of outstanding interest

Corneal thickness and glaucoma


An initial evaluation report of a promising new tonometry technique.

