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Is Corneal Thickness an Independent Risk Factor for Glaucoma?

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The Ocular Hypertension Treatment Study (OHTS) showed that central corneal thickness (CCT) was a significant predictor of which patients with ocular hypertension are at higher risk for converting to glaucoma.[1] Eyes with CCT of 555 μm or less had a 3-fold greater risk of developing glaucoma compared with eyes that had CCT of more than 588 μm. In a multivariable model including age, baseline intraocular pressure (measured by Goldmann tonometer), optic disc topography (cup/disc ratio) and visual field (pattern standard deviation), CCT retained its statistical significance as a predictor of glaucoma development, with a hazard ratio of 1.82 for each 40μm thinner CCT.

The results of this report have been mistakenly interpreted by some as demonstrating that CCT is an independent risk factor for the development of glaucoma. As Goldmann applanation tonometry (GAT) measurements ultimately depend on CCT, it is impossible in the original model to completely disentangle the effects of both. For example, consider two patients with the same baseline GAT IOP of 24mmHg, but with corneal thicknesses of 520μm and 560μm. The adjusted hazard ratio for CCT in the OHTS multivariable model would tell us that the risk for developing glaucoma for the one with the thin cornea would be 82% higher. However, it is impossible to determine, from the original analysis, whether the increased risk is due to a true independent effect of corneal thickness *per se*, or simply due to the effect of CCT on GAT measurement error. In fact, using a correction formula proposed by Ehlers et al[2], the patient with the thinner cornea would have “corrected” IOP close to the measured value of 24mmHg. In contrast, the “corrected” IOP would be 2.8mmHg lower at approximately 21mmHg for the patient with the thicker cornea. So, the increased risk could ultimately be due just to the fact that the first patient actually has a higher “true” IOP. On the other hand, some authors have suggested that the predictive effect of CCT is not fully accounted for by its induced GAT measurement error, but rather that there is a possible association between corneal thickness and structural measures possibly related to glaucoma risk, such as scleral or lamina cribrosa thickness.

Whether corneal thickness is a true independent risk factor for glaucoma has remained an unanswered question. In the current issue of Ophthalmology, Brandt et al.[3] attempt to shed light on this issue. They evaluated whether the OHTS prediction model could be improved by correcting IOP for CCT using previously published formulas. The rationale of the authors was that if the influence of CCT on GAT fully explains the role of CCT as a predictive factor, than inclusion of CCT-corrected IOP values in the model would cause CCT to become non-significant. They show that models with CCT-corrected IOP do not perform better than the original model, as evaluated by *c*-statistics and calibration chi-squares. Additionally, CCT remains a statistically significant predictor in the multivariable model including CCT-corrected IOP. Based on these results, the authors conclude that the influence of corneal thickness as a prognostic factor for POAG is not entirely from its effect on IOP measurement error, but rather that CCT is a biomarker for structural and physical factors involved in the pathogenesis of glaucoma.

Although the results of Brandt and colleagues provide important clarification for the role of CCT as a risk factor for glaucoma development, caution should be exercised when

concluding that they demonstrate that CCT is indeed a true biomarker or independent risk factor for glaucoma. A close analysis of the data actually suggests a decrease in the predictive ability of CCT when CCT-corrected IOP values were included in the model. The hazard ratios for CCT decreased from 1.84 in the original model to 1.38 in the model which included IOP corrected by the Ehlers formula, for example. More importantly, it is likely that the correction formulas used by the authors did not fully capture the corneal-induced error on tonometric measurement. It has been shown that other factors besides corneal thickness may influence tonometric readings, such as corneal elasticity and viscoelasticity, and the formulas used by the authors do not fully take into account these factors.[4] The only way to fully evaluate the independent role of CCT as a prognostic factor would be to include in the predictive model IOP measurements obtained by a perfectly cornea-independent tonometer. As it does not require corneal applanation, dynamic contour tonometry (DCT) measures have been proposed to be largely independent of corneal influence and agree closely with manometric readings.[5] Therefore, the inclusion of DCT measurements along with corneal thickness in a predictive model for glaucoma might provide a better assessment of the true independent value of CCT compared to the simple incorporation of CCT-corrected GAT values.

Brandt et al. concluded that the available formulas to correct IOP measurements do not improve the accuracy of prediction models for development of glaucoma. Although this conclusion is technically correct and expected, it should not be used to indicate that CCT provides an additional independent contribution to the prediction model besides its effect in correcting IOP. In fact, a close analysis of the data actually suggests just the opposite interpretation. The predictive abilities were similar between the original OHTS model including CCT and the models which did not include CCT, but only CCT-corrected IOP. This could actually imply that CCT is relatively unimportant for the final predictive ability of the multivariable model, as long as one includes CCT-corrected IOP. For example, the model including IOP values corrected by the Ehlers formula (but excluding CCT) had a predictive ability almost identical to the original OHTS model. Such a result would hardly indicate a major true independent contribution of CCT as a prognostic factor for development of glaucoma.

In conclusion, the results of Brandt et al suggest that the use of CCT correction formulas for GAT measurements is probably of little value in clinical practice. Instead of attempting to use these formulas, clinicians are probably better off incorporating risk information as provided by validated predictive models for glaucoma development.[6, 7] However, the conclusion that CCT is a true independent risk factor for glaucoma is not validated at this time and requires further investigations.

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