A Method to Estimate the Amount of Neuroretinal Rim Tissue in Glaucoma: Comparison With Current Methods for Measuring Rim Area

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• PURPOSE: To test whether the minimum rim area assessed by spectral domain optical coherence tomography (SD-OCT), based on the shortest distance from the Bruch membrane opening (BMO) to the inner limiting membrane, corresponds more closely to retinal nerve fiber layer (RNFL) thickness and visual field mean deviation (MD) than current rim measures in early glaucoma.

• DESIGN: Prospective cross-sectional study.

• METHODS: We studied 221 participants with non-endstage glaucoma or high-risk ocular hypertension and performed standard automated perimetry. We received SD-OCT and confocal scanning laser ophthalmoscopy (CSLO) scans on the same day. Rim area measured by CSLO was compared with 3 SD-OCT rim measures from radial B-scans: horizontal rim area between BMO and inner limiting membrane within the BMO plane; mean minimum rim width (BMO-MRW); and minimum rim area (BMO-MRA) optimized within sectors and then summed. Correlations between these measures and either MD from perimetry or RNFL thickness from SD-OCT were compared using the Steiger test.

• RESULTS: RNFL thickness was better correlated with BMO-MRA ($r = 0.676$) or BMO-MRW ($r = 0.680$) than with either CSLO rim area ($r = 0.330$, $P < 0.001$) or horizontal rim area ($r = 0.482$, $P < 0.001$). MD was better correlated with BMO-MRA ($r = 0.534$) or BMO-MRW ($r = 0.546$) than with either CSLO rim area ($r = 0.321$, $P < 0.001$) or horizontal rim area (0.403, $P < 0.001$). The correlation between MD and RNFL thickness was $r = 0.646$.

• CONCLUSIONS: Minimum rim measurements from SD-OCT are significantly better correlated to both RNFL thickness and MD than rim measurements within the BMO plane or based on the clinical disc margin. They provide new structural parameters for both diagnostic and research purposes in glaucoma. (Am J Ophthalmol 2014;157:540–549. © 2014 by Elsevier Inc. All rights reserved.)

UNDERSTANDING THE RELATIONSHIP BETWEEN structural and functional damage in glaucoma has been a key aim for many years.[1–7] For example, in the United States, the National Eye Institute and the Food and Drug Administration indicated that structural measures could be used as endpoints in clinical trials for glaucoma treatments if they demonstrated a strong correlation with functional measures, with $R^2 \approx 0.9$.[8] While this may seem unrealistic, better understanding of this relationship would aid attempts to combine structural and functional measures to improve assessment of disease stage and progression.[9,10] However, advances on this front have been limited by 2 key factors. First, inter-individual variability in both structural and functional measures is considerable. The non-neural (vascular and glial) component of both the optic nerve head rim tissue and the retinal nerve fiber layer varies with individuals, and the manner in which each changes with age and disease may differ.[11] In normal, healthy human eyes, there is little correlation between retinal nerve fiber layer (RNFL) thickness and contrast sensitivity,[12,13] and in healthy eyes of nonhuman primates there is little correlation between RNFL thickness and total optic nerve axon count.[14] Second, both structural and functional tests contain significant intra-individual inter-test variability. For example, when visual field sensitivity measured by standard automated perimetry has declined to 15 dB, test-retest variability is reported to have a standard deviation of up to 8 dB,[15] so the 95% confidence interval for retest sensitivity covers the majority of the perimeter's effective dynamic range. This means that even if the underlying structure-function association were perfect, its strength would be masked by this substantial variability.[16]

Much previous work has relied on performing functional testing with standard automated perimetry and structural testing with confocal scanning laser ophthalmoscopy (CSLO). Recently, Reis and associates have demonstrated that CSLO does not measure the neuroretinal rim area accurately because important subsurface structures are not readily identifiable on CSLO scans.[17] They showed that "the basis for current rim measurements lacks a solid

AJO.com Supplemental Material available at AJO.com

Accepted for publication Nov 6, 2013.

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0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2013.11.007

anatomical foundation because (1) the clinical DM (disc margin) is not a consistent outer border of the rim tissue and (2) the orientation of neural tissue in the optic nerve head is not accounted for."[18] This could be a significant contributing factor to the variability of the structure-function relation when structure is assessed using CSLO. Improving the structure-function relation therefore requires new and improved testing methodologies that have stronger links to anatomy and hence lower variability, for structural as well as functional testing.

Recently, optical coherence tomography (OCT) has been developed. It has been widely used to measure RNFL thickness at a specific angular eccentricity from the center of the optic disc. The RNFL thickness and retinal nerve fiber layer cross-sectional area measures from CSLO are suboptimal because they are based on the vertical distance between the tomographically determined retinal height and a reference plane, and hence are actually measures of relative height rather than the true thickness of any retinal layer. By contrast, the RNFL thickness measure is the distance between the anterior and posterior borders of the highly reflective nerve fiber layer so should reflect the targeted anatomy better.

OCT can also be used to perform scans through the optic nerve head. OCT reveals subsurface structures that are not evident using previous techniques, such as CSLO or stereophotography. Time-domain OCT has been shown to improve the correlation between global RNFL thickness and functional measures from 0.33 (using CSLO) to 0.48 (using OCT).[19] The more recent development of spectral-domain OCT (SD-OCT) could improve this relationship even further, given its greater axial resolution and that its faster speeds can reduce motion artifact within denser scan patterns. Better methods to quantify SD-OCT images are being developed. Povazay and associates suggested that rim could be better defined as the area of a surface extending from the Bruch membrane opening (BMO) to the inner limiting membrane.[20] Strouthidis and associates demonstrated, using SD-OCT, that this rim parameter was both reliable and sensitive in a longitudinal study of nonhuman primates with experimental glaucoma[21] and in studies of acute intraocular pressure elevation.[22] Reis and associates also measured this using SD-OCT, and showed that it reflected the anatomy of the optic nerve head better than the clinically visible disc margin.[18] This would prevent the problem noted above, whereby current clinical measurements of the rim were not consistently referenced to any given anatomic structure.[23] By removing this large source of anatomic variability, this type of SD-OCT–based assessment of the neuroretinal rim should be more easily comparable among individuals, improving the ability to detect the presence of glaucomatous damage[24] and its progression.

Different variants of neuroretinal rim assessment are considered in this article, as detailed in the Methods section. First, a horizontal rim area measurement is considered, giving the most direct analogous measurement to current rim assessment. For example, this is the same method used by the Cirrus SD-OCT instrument (Carl Zeiss Meditec, Dublin, CA, USA) to generate a rim area measurement.[25,26] Second, a mean minimum rim-width measurement from BMO (BMO-MRW) is considered, along an angle that varies in radial scans, in order to represent the minimum distance from the BMO to the inner limiting membrane within each radial scan around the optic nerve head rim, similar to the technique proposed by Povazay and associates[20] and Chen.[27] Unlike the clinical disc margin, BMO is an actual anatomic boundary of the neuroretinal rim tissue. BMO-MRW therefore represents an accurate estimate of the minimum width of the neural tissues relative to each BMO point within the plane of each radial B-scan. Finally, this minimum rim width is used to estimate the minimum rim area (BMO-MRA) through which the axons must pass. This adjusts for the fact that the BMO-MRW will be related to disc size and not just the number of axons.

This study compares current disc-margin–based rim area measurements from CSLO with these new BMO-based measurements from SD-OCT.[17,18] The starting point for the comparison is the principle that a sound measurement of the neuroretinal rim should correlate well with RNFL thickness (since the same axons compose both) and with function (since glaucomatous loss of RNFL thickness is associated with concomitant loss of function). This article aims first to determine whether horizontal or minimum measurements of the rim based on BMO as assessed by SD-OCT are better correlated with RNFL thickness than are the current rim area measurements based on CSLO. Second, the article aims to determine whether these new measures of optic nerve head neuroretinal rim tissue also result in a stronger correlation between visual field mean deviation (MD) and optic disc rim structure.

METHODS

• **PARTICIPANTS:** Data from 221 participants with nonendstage glaucoma (ie, with remaining measurable visual function) or with ocular hypertension plus risk factors for glaucoma were taken from the ongoing Portland Progression Project, a prospective study of the course and risk factors for glaucomatous progression.[28] All protocols were approved and monitored by the Legacy Health Institutional Review Board and adhere to the Health Insurance Portability and Accountability Act of 1996 and the tenets of the Declaration of Helsinki. All participants provided written informed consent for their participation in the study once all of the risks and benefits of their involvement were explained to them.

At study entry, participants had either a clinical diagnosis of early glaucoma, or they had ocular hypertension