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Macular versus Retinal Nerve Fiber Layer Parameters for Diagnosing Manifest Glaucoma

A Systematic Review of Diagnostic Accuracy Studies

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Topic: Macular parameters have been proposed as an alternative to retinal nerve fiber layer (RNFL) parameters to diagnose glaucoma. Comparing the diagnostic accuracy of macular parameters, specifically the ganglion cell complex (GCC) and ganglion cell inner plexiform layer (GCIPL), with the accuracy of RNFL parameters for detecting manifest glaucoma is important to guide clinical practice and future research.

Methods: Studies using spectral domain optical coherence tomography (SD OCT) and reporting macular parameters were included if they allowed the extraction of accuracy data for diagnosing manifest glaucoma, as confirmed with automated perimetry or a clinician's optic nerve head (ONH) assessment. Cross-sectional cohort studies and case-control studies were included. The QUADAS 2 tool was used to assess methodological quality. Only direct comparisons of macular versus RNFL parameters (i.e., in the same study) were conducted. Summary sensitivity and specificity of each macular or RNFL parameter were reported, and the relative diagnostic odds ratio (DOR) was calculated in hierarchical summary receiver operating characteristic (HSROC) models to compare them.

Results: Thirty-four studies investigated macular parameters using RTVue OCT (Optovue Inc., Fremont, CA) (19 studies, 3094 subjects), Cirrus OCT (Carl Zeiss Meditec Inc., Dublin, CA) (14 studies, 2164 subjects), or 3D Topcon OCT (Topcon, Inc., Tokyo, Japan) (4 studies, 522 subjects). Thirty-two of these studies allowed comparisons between macular and RNFL parameters. Studies generally reported sensitivities at fixed specificities, more commonly 0.90 or 0.95, with sensitivities of most best-performing parameters between 0.65 and 0.75. For all OCT devices, compared with RNFL parameters, macular parameters were similarly or slightly less accurate for detecting glaucoma at the highest reported specificity, which was confirmed in analyses at the lowest specificity. Included studies suffered from limitations, especially the case-control study design, which is known to overestimate accuracy. However, this flaw is less relevant as a source of bias in direct comparisons conducted within studies.

Conclusions: With the use of OCT, RNFL parameters are still preferable to macular parameters for diagnosing manifest glaucoma, but the differences are small. Because of high heterogeneity, direct comparative or randomized studies of OCT devices or OCT parameters and diagnostic strategies are essential. *Ophthalmology 2016;■:1–11 © 2016 by the American Academy of Ophthalmology.*

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Glaucoma is a chronic optic neuropathy characterized by a slow progressive degeneration of retinal ganglion cells (RGCs) and their axons, which leads to structural alteration to the optic nerve head (ONH) and retinal nerve fiber layer (RNFL), and to functional damage to the visual field.[1] The structural assessment of glaucomatous damage can be achieved subjectively by biomicroscopy or stereophotography, as well as objectively by imaging technologies such as optical coherence tomography (OCT).[2,3]

Optical coherence tomography is a well-established, noninvasive, noncontact imaging modality that allows for highly reproducible cross-sectional images of the retina.[4–6] It is widely used as an add-on test for glaucoma detection, and peripapillary RNFL analysis represents the scanning protocol most used for routine patient management.[7–9] Peripapillary RNFL analysis offers clear advantages considering that the surrounding ONH area comprises the axons of all RGCs from the entire retina, but it suffers from

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flaws that are mainly related to intersubject variability of ONH size and shape found in those with glaucoma and in healthy individuals.[10,11]

Since Zeimer et al[12] suggested that retinal thickness changes in the macula could be indicative of glaucoma status, macular parameters are increasingly proposed as an alternative or a complementary analysis to peripapillary RNFL thickness to diagnose glaucoma. The rationale behind this hypothesis is based on anatomic evidence.[12–17] Up to 50% of all RGCs are located in the macular region, where up to 7 layers of RGC bodies can be found. The RGC body has a larger diameter than its axon and therefore is potentially easier to detect. Moreover, the macular area is characterized by less intersubject anatomic variability.

Early studies conducted with time-domain OCT showed that macular analysis is capable of differentiating healthy individuals from those affected by glaucoma, but that overall its diagnostic accuracy was inferior to that of RNFL thickness.[18–21] This could be explained at least in part by the fact that time-domain OCT macular analysis involves the entire macular thickness, thus including inner retinal layers that are directly affected in glaucoma, as well as outer layers that are, as far as we know, not involved in the glaucomatous process and have larger variability among individuals.[22]

With the advent of spectral domain OCT (SD OCT), some of these limitations have been overcome. Spectral domain OCT allows for image acquisition at a faster speed, with higher axial resolution and raster pattern scan with less interpolation and 3-dimensional volumetric reconstruction.[23,24] These technical improvements along with the development of new postacquisitional software algorithms allow automatic multiple segmentation of the entire macular thickness. Spectral domain OCT is able to selectively analyze the innermost layers of the retina, including the RNFL, ganglion cell layer, and inner plexiform layer, which comprise the axons, bodies, and dendrites of RGCs, respectively.[25] Several studies have shown that segmented analysis focused on the innermost macular layers has better diagnostic ability compared with total macular thickness assessment.[26,27]

Despite a large amount of evidence sparsely collected, whether OCT assessment of glaucomatous damage in the macula has better diagnostic ability than peripapillary RNFL remains unclear.

To achieve a comprehensive synthesis of the existing evidence, we conducted a systematic review and meta-analysis with the aim of comparing the diagnostic accuracy of macular parameters, specifically the ganglion cell complex (GCC) and ganglion cell inner plexiform layer (GCIPL) thickness, with that of RNFL thickness for detecting manifest glaucoma, measured using any SD OCT device.

Methods

Our main objective was to compare the diagnostic accuracy of macular GCC/GCIPL layer damage seen on OCT, hereafter referred to as "macular parameters," with that of RNFL parameters for diagnosing manifest glaucoma.

A large number of macular and RNFL parameters have been investigated in studies of the accuracy of glaucoma diagnostic tests. Therefore, to achieve our primary objective, we preliminarily assessed which macular or RNFL parameter is more accurate for detecting glaucoma.

This review largely relies on the evidence base selected by another systematic review conducted by Cochrane Eyes and Vision, which aims to investigate the accuracy of RNFL and ONH OCT parameters for diagnosing manifest glaucoma.[28] Therefore, readers should refer to that review as an evidence synthesis of the overall accuracy of OCT, as well as of the sources of heterogeneity between studies. The protocol for this review has been registered and is available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015024717.

Eligibility Criteria for Considering Studies for Review

We included all studies that evaluate the sensitivity and specificity of OCT for diagnosing glaucoma, which allow for the extraction of true positives, false positives, false negatives, and true negatives. We included both single studies assessing macular parameters and comparative studies assessing both macular parameters and RNFL parameters in the same patients. There was no language restriction in selecting studies.

Detection of manifest glaucoma using OCT alone may be of interest in primary care settings, such as by optometrists as an add-on test or by ophthalmologists who are not glaucoma specialists and use OCT as a triage test. Thus, the patients in the studies that were included in this review should have been a consecutive series of patients with risk factors for glaucoma, such as family history of glaucoma or mild ocular hypertension, who were screened by means of OCT to assess the need for referral to ophthalmologists. However, we knew from the Cochrane review[28] that almost all studies in this field are case-control studies, and we allowed the inclusion of studies with this type of design.

We considered only studies that evaluated the more recent version of OCT with SD technology. We extracted data on all parameters obtained using standard commercial software measuring macular and RNFL morphology. We accepted all definitions of glaucoma given by the study authors, and we classified studies as using perimetry alone, optic disc assessment alone, or both as the reference standard.

In addition, we excluded studies investigating patients with pathologic myopia, as defined by the investigators; studies measuring peripapillary RNFL thickness only or full macular rather than GCC/GCIPL layer thickness; and studies not providing useful data to form a 2×2 cross-tabulation of index and reference tests, such as studies presenting mean and standard deviation in normal subjects and those with glaucoma or studies measuring correlation between imaging and other variables, for example, between functional and anatomic parameters.

Search Methods for Identifying Studies

We used search strategies developed by the Cochrane Eyes and Vision Group for a related review, which are reported in Appendix A (available at www.aaojournal.org), including the Cochrane Library, MEDLINE, EMBASE, MEDION, and ARIF. We manually searched the reference lists of the included studies. Searches are current to February 2015.

Study Selection

Two pairs of review authors (E.L., M.M., G.V., S.D.) independently examined the titles and abstracts identified by the electronic