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Macula assessment using optical coherence tomography for glaucoma diagnosis

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Abstract

Optical coherence tomography (OCT) is an interferometry-based imaging modality that generates high-resolution cross-sectional images of the retina. Circumpapillary retinal nerve fiber layer (cpRNFL) and optic nerve head assessments are the mainstay of glaucomatous structural measurements in OCT. However, because these measurements are not always available or precise, it would be useful to have another reliable indicator. The macula has been suggested as an alternative scanning location for glaucoma diagnosis. Using time-domain (TD-) OCT, macular measurements have shown to provide good glaucoma diagnostic capabilities. With the adoption of spectral-domain OCT, which allows a higher image resolution than TD-OCT, segmentation of inner macular layers becomes possible. These layers are specifically prone to glaucomatous damage and thickness measurements show a comparable performance to that of glaucomatous cpRNFL measurements. The role of macular measurements for detection of glaucoma progression is still under investigation. More sophisticated measurement and analysis tools that can amplify the advantages of macular measurements are expected. For example, improvement of image quality would allow better visualization, development of various scanning modes would optimize

Competing Interest
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Kyung Rim Sung; conception and design, acquisition of data, analysis and interpretation of data, drafting the article, critical revision, final approval of the version
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macular measurements, and further refining of the analytical algorithm would provide more accurate segmentation. With these achievements, macular measurement can be an important surrogate for glaucomatous structural assessment.

Introduction

Glaucoma is an optic neuropathy that is characterized by progressive loss of the retinal ganglion cells (RGCs) and their axons in the retinal nerve fiber layer (RNFL), thinning of the neuroretinal rim in the optic nerve head (ONH), and visual field (VF) deficit. During clinical evaluation, examining the ONH and surrounding area, focusing on features suggesting neural tissue loss, assesses the glaucomatous structural changes. Complicating this assessment is the high variability of the ONH size and shape even among healthy subjects: a wide range of optic disc and cup sizes, variable size and configuration of the blood vessels, variable angle of penetration into the eyeball of the optic nerve (titled disc), and peripapillary changes, such as atrophy and others. Taking into consideration this marked variability of ONH size and shape, it is not surprising that the ability of detecting glaucoma, especially at an early stage of the disease, varies considerably among clinicians. In the last two decades, a few ocular imaging devices have been introduced to allow micron scale quantification of ocular structures. Optical coherence tomography (OCT) is an interferometry-based ocular imaging modality that generates high-resolution cross-sectional images of the retina. This device has been shown to be valuable in the diagnosis and monitoring of retinal diseases and glaucoma.[1–7] Clinical utility of OCT in glaucoma is predominantly based on assessment of the circumpapillary RNFL[8–12] because it allows a thorough sample of all retinal axons as they approach the ONH. However, the variability of ONH size and shape described above, along with pathologic features, such as large peripapillary atrophy, papilledema, and others, might affect the reliability of the circumpapillary RNFL measurements. Zimmer et al. first suggested imaging of the macula as a potential location for glaucoma evaluation.[13] In this manuscript, we review the clinical significance, previous works, and future direction of macular imaging by OCT in glaucoma.

Why is macular imaging by OCT meaningful in glaucoma?

Compared to the ONH, the macula is a relatively simple structure that is devoid of large vessels. It has multiple cellular and plexiform layers and a central depression (fovea) devoid of RGCs. The macula offers several potential physiological and anatomical advantages for glaucoma evaluation. Firstly, the retinal nerve fiber is composed of the RGC axons, and therefore assessment of the RGCs may be a more direct method for measuring glaucomatous damage than circumpapillary RNFL thickness. Additionally, the macula is the only place in the retina where more than a single RGC body exists in the ganglion cell layer. Because the cell body is substantially larger than the soma of the cell, this might improve the ability to detect damage to these cells.[13–16] Furthermore, within the macula, more than 50% of the RGCs of the entire retina are located; thus scanning of the macula allows sampling of the majority of the RGCs. The macula shape, more specifically the RGC layer, is generally less variable among healthy individuals than other diagnostically important structures, such as the RNFL and ONH. Sensitivity of the RGCs could potentially be higher than that of the RNFL because changes in this layer would more likely be the result of a pathologic process rather than of normal variation.[17]

Although glaucomatous macular changes are difficult to detect clinically, OCT allows accurate quantitative assessment. Imaging of this region is easier and less prone to eye motion artifacts because, unlike ONH imaging, macular imaging does not require eccentric fixation. Eccentric fixation is known to affect OCT measurements.[18] Recent development of spectral domain (SD-) OCT technology allows image acquisition at faster speeds than were

possible with conventional time domain (TD-) OCT. As a result, more scans can be acquired and combined to create 3D macular images.[19] Due to the relatively slow acquisition rate of TD-OCT, the conventional scanning pattern used for the macula was six evenly distributed radial scans with interpolation between neighboring scans. The interpolation mostly affected the outer part of the macula, where the scans are further apart, which is also the location of most glaucomatous damage. SD-OCT scans either employ a raster scan pattern or a denser collection of radial scans with less interpolation than what was employed for TD-OCT images.

Macula thickness performance with TD-OCT

Several studies evaluated the diagnostic capability of the macular thickness.[1–7] Some reports compared the diagnostic abilities of macular thickness, RNFL thickness, and ONH parameters. Using an early version of TD-OCT, Giovannini et al. showed that volumetric analysis of the macula correlated significantly with glaucoma status.[2] Greenfield et al. reported that macular thickness changes correlated with changes in visual function and circumpapillary RNFL in glaucoma and may be a surrogate indicator of RGC loss.[3] Wollstein et al. reported that macular thickness, as measured by OCT, was capable of detecting glaucomatous damage and corresponded with the circumpapillary RNFL thickness; however, circumpapillary RNFL thickness had a higher sensitivity and specificity for detection of VF abnormalities.[1] Leung et al. also showed that circumpapillary RNFL thickness outperformed both total macular and macular NFL thickness in terms of glaucoma detection and visual function correlation.[6] Medeiros et al. reported that RNFL and ONH measurements had better discriminating performance than macular measurements when assessed by a later version of TD-OCT.[7] Study outcomes comparing RNFL and macular thickness measurements are summarized as Table 1. These studies indicated that although macular thickness has good glaucoma diagnostic capabilities, circumpapillary RNFL measurement performance is superior. One possible explanation might be due to the use of the total macular thickness, which contains all retinal layers. Some of the retinal layers are not involved in the glaucomatous process and thus may reduce the sensitivity and specificity of diagnosis. This leads to concrete efforts in further segmenting the macula to allow quantification of individual retinal layers.

Segmentation of macular layers

The macula is composed of multiple layers organized from innermost to outermost: inner limiting, nerve fiber, RGC, inner plexiform, inner nuclear, outer plexiform, outer nuclear, and the retinal pigment epithelial (RPE) layers. Glaucoma primarily affects the axon and body of RGCs, which constitutes the inner retina.

Differentiation of individual retinal layers by ocular imaging requires a high level of resolution and an advanced segmentation algorithm. Ishikawa et al. developed a customized segmentation algorithm for macular segmentation using TD-OCT images.[16] They demonstrated comparable glaucoma diagnostic capability of the inner retinal layers with circumpapillary RNFL. Moreover, inner retinal layer thickness was statistically significantly better in discriminating between healthy and glaucomatous eyes than total macular thickness. Wang et al. measured the RGC layer thickness in glaucomatous eyes with an SD-OCT device, using a computer-aided manual segmentation procedure.[20] They reported that it was feasible to obtain local measurements of RGC thickness that corresponded to functional findings.

Manufacturers of SD-OCT devices incorporated automatic macular segmentation analysis into their operating system. Ganglion cell complex (GCC) was designated for thickness measurements from the internal limiting membrane to the inner nuclear layer, which is

composed of RGCs, along with their axons and dendrites. Other manufacturers segmented the inner retina into the ganglion cell inner plexiform layer (GCIPL). Cho et al. examined the relationship between VF mean sensitivity (MS) and macular GCC thickness, and reported a similar level of correlation as with circumpapillary RNFL thickness.[21] Rao et al. also demonstrated that the strongest structure-function association among the various macular measurements using SD-OCT was found to be the inner retinal thickness.[22]

Assessing the diagnostic performance of GCC thickness, Seong et al. reported that GCC thickness was comparable to circumpapillary RNFL thickness in terms of glaucoma diagnostic capability.[23] Sakamoto et al. compared macular RNFL images obtained by 3D SD-OCT with those obtained by color and red free fundus photography. They found that more macular RNFL defects were detected on 3D SD-OCT images than on color fundus photographs.[24] Kim et al. classified glaucoma into three disease severity groups based on VF's mean deviation. They reported that the macular GCC and circumpapillary RNFL thicknesses showed similar diagnostic performances in detecting early, moderate, and severe glaucoma.[25] Kotera et al. showed that the mean macular inner retinal thickness was significantly thinner in suspected glaucoma and preperimetric glaucomatous eyes than in the healthy eyes, while mean total retinal and macular NFL thicknesses were not.[26] This report might point out the utility of macular inner retinal measurements as an early indicator of glaucomatous change.

Assessing covariability associated with macular inner retinal thickness, Kim et al. showed that thin GCC thickness correlated with older age and longer axial length.[27] Similarly, Mwanza et al. reported that thinner GCIPL was associated with thinner RNFL, older age, longer ocular axial length, and male sex.[28]

Taken together, published studies indicated that the segmented macular inner retinal layer thickness performs better than the total macular thickness and similar to (but not better than) the circumpapillary RNFL thickness in glaucoma diagnosis.

Clinical application

In clinical practice, situations where glaucomatous changes were detected in the circumpapillary RNFL without corresponding damage in the macula or vice versa have been encountered. Na et al. classified cases according to whether they were better diagnosed by macular thickness or circumpapillary RNFL measurement.[29] Overall, more eyes were diagnosed by circumpapillary RNFL than by macular measurements. Eyes with exclusive macular damage tended to have larger ONH sizes than eyes that had solely abnormal circumpapillary RNFL measurements. It was suggested that this difference in diagnostic capability was due to measuring circumpapillary RNFL thickness in a fixed-sized circumpapillary diameter (3.4 mm), which brought the sampling circle closer to the disc margin in a larger ONH. Since RNFL thickness measured close to the disc margin tends to be thicker, this might mask early glaucomatous structural abnormality.

The papillomacular bundle has been shown to be resistant to glaucomatous damage until the end stage of the disease. Thus, measurement of the posterior pole macular thickness may be a strategy to measure advanced glaucomatous function. However, progressive RNFL loss is not easy to detect in advanced glaucoma because most of the RNFL is already lost at this stage. Sung et al. reported that more than half of their advanced glaucoma participants (VF mean deviation < −10 dB) could not be evaluated by photographic assessment of the ONH and RNFL because these structures exhibited advanced glaucomatous abnormalities that precluded clinical assessment of structural changes.[30] The participants showed a much higher rate of progression in macular thickness than with circumpapillary RNFL thickness and a better agreement with progression by VF.

Glaucoma is typically described as causing a focal abnormality, especially in early stages of the disease. In order to exploit this in a fashion similar to the one employed by the glaucoma hemifield test in VF, Um et al. categorized the posterior-pole macular area into five regions in each hemifield.[31] The difference between corresponding locations was compared to the difference between these locations in healthy eyes. The asymmetry in hemifield macular thickness showed better glaucoma diagnostic capability than the average circumpapillary RNFL thickness in early glaucomatous eyes.

Progression detection

Clinical utility of ocular imaging devices could be further amplified by detecting disease progression in glaucoma. Most OCT progression studies conducted so far were confined to circumpapillary RNFL measurements and only a few studies evaluated macular thickness measurements. Medeiros et al. reported that circumpapillary RNFL thickness outperformed macular thickness and optic disc parameters in detecting glaucoma progression using TD-OCT.[32] Needless to say, measurement repeatability is of paramount importance in progression detection. Mwanza et al recently demonstrated higher measurement reproducibility of macular ganglion cell layer thickness by use of SD OCT.[17] Recently, Na et al reported the glaucoma progression detection capability of macular ganglion cell layer thickness. According to their results, ganglion cell layer thickness showed similar sensitivity to RNFL or total macular thickness in terms of agreement with progression determined by optic disc/RNFL photographic or VF assessment.[33]

The denser scanning and improved measurements reproducibility offered by SD-OCT hold promise to improve detection of structural progression. However, more studies to confirm this hypothesis are yet to be published.

Limitation

In the mean time, a limitation of using macular thickness measurements for glaucoma diagnosis should be also considered. One of the factors that may affect macular measurements for glaucoma detection and the relationship with functional tests is the spatial summation within central vision. Within the macula, the spatial summation becomes a significant factor affecting the structure-function relationship, which subsequently affects diagnostic performance as many studies use visual field defects as the definition of glaucoma.

Future directions

To enhance the clinical utility of macular measurements obtained by OCT in glaucoma diagnosis, image quality itself must be improved because the analytic outcome depends heavily on image quality. Reduced image quality substantially affects the segmentation of the retinal layers and reliable and repeatable measurements. In particular, segmentation of inner and outer macular layers demands high quality image. Enhanced image quality facilitates precise segmentation of various cellular layers of the macula. By recent development of SD-OCT technology, image resolution has been improved. By use of SD-OCT, Mwanza et al showed the test-retest standard deviation of GCIPL thickness was 1.43 μm. There has been an effort made to improve image quality using various techniques. Nakano et al suggested that speckle noise was the primary artifact in OCT images, and a speckle noise-reducing technique was adopted by using eye-tracking and averaging, which allowed clearer visualization and measurement of the macular ganglion cell layer.[34] Development of various applications of scanning modes to optimize macular measurements is warranted, as is further refining of the analytical algorithm for accurate segmentation.

Conclusion

Circumpapillary RNFL and ONH assessments are the mainstay of glaucomatous structural measurements. However, because these measurements cannot always be obtained, it would be useful to have another reliable indicator for glaucomatous structural assessment by OCT. Several studies show that the macular inner retinal layer acts comparably to circumpapillary RNFL in glaucoma diagnosis. Investigations are ongoing into its use for detection of glaucoma progression. More sophisticated measurement and analysis tools that can amplify the advantages of macular measurements are expected. With these achievements, macular measurement can be an important clinical surrogate for glaucomatous structural assessment.

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Table 1

Comparison of macular and circumpapillary retinal nerve fiber layer (RNFL) thickness measurement for glaucoma detection using optical coherence tomography (OCT)

Authors	OCT device	Main finding
Wollstein et al	Prototype OCT	RNFL thickness had higher sensitivity and specificity for the detection of visual field abnormalities than macular thickness
Leung et al	Stratus OCT	RNFL thickness outperformed both total macular and macular NFL thickness in terms of glaucoma detection and visual function correlation
Medeiros et al	Stratus OCT	The RNFL parameter inferior thickness was significantly better than the macular thickness parameter
Na et al	Cirrus OCT	RNFL thickness measurements were generally superior to those of macular thickness
Seong et al	RTVue OCT	Macular inner retinal thickness showed glaucoma discrimination ability comparable to that of RNFL thickness in patients with early visual field defects In eyes with advanced or peripheral defect, RNFL measurement showed a better glaucoma diagnostic ability than did MIRL measurement
Huang et al	RTVue OCT	Average RNFL thickness is the optimal individual OCT parameter to detect perimetric glaucoma Simultaneous evaluation on disc morphology, RNFL, and macular inner retinal thickness can improve the diagnostic accuracy in diagnosing glaucoma.
Nakatani et al	Topcon 3D OCT	For the diagnosis of early glaucoma, macular parameters had high discriminating power and high reproducibility comparable with RNFL parameters