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Optical coherence tomography and optical coherence tomography angiography in glaucoma: diagnosis, progression, and correlation with functional tests

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***Abstract*:** The present review will summarize the most updated findings with regards to optical coherence tomography and optical coherence tomography angiography in glaucoma, highlighting their clinical use for detection and monitoring of the disease, and their correlation to functional tests (such as visual field) widely employed in the asset of modern glaucoma clinics.

Keywords: glaucoma, optical coherence tomography, optical coherence tomography angiography

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Introduction

Glaucoma is characterized by progressive retinal ganglion cell (RGC) axonal loss.[1–5]

Because RGC axonal thickness is greatest at the peripapillary retina,[6–8] optical coherence tomography (OCT) scans have been mainly used to measure the peripapillary retinal nerve fiber layer (pRNFL) thickness to estimate the glaucomatous structural loss. However, more recent studies demonstrated that glaucoma involves not only RGC axons but also their bodies and dendrites,[9–12] which are mainly located at the macula. Therefore, spectral domain-optical coherence tomography (SD-OCT) scans centered on the macula to measure various inner macular parameters (e.g. ganglion cell complex (GCC), ganglion cell-inner plexiform layer (GCIPL)) are also highly informative of glaucomatous damage, and, combined with optic nerve head (ONH) SD-OCT scans, provide the clinician with a comprehensive understanding of the disease stage.

In the last few years, optical coherence tomography angiography (OCTA) was introduced in the clinical practice, allowing to image the vascular component of this disease, and, possibly, its role in the pathogenesis of glaucoma. Several studies reported decreased OCTA vessel density (VD) both in the peripapillary area and at the macula, corresponding to the location of RGCs' neural loss in glaucoma.[13–16]

The present review will summarize the most updated findings with regards to OCT and OCTA in glaucoma, highlighting their clinical use for detection and monitoring of the disease and their correlation to functional tests (such as visual field) widely employed in the asset of modern glaucoma clinics.

Optical coherence tomography: detection of early glaucoma

It is well established that pRNFL is mainly affected in the inferior and superior quadrants in preperimetric and early glaucoma, whereas temporal and nasal quadrants are usually involved later on in the course of the disease.[17–22] Because of this pattern of pRNFL thinning, Wang and colleagues[23] reported that the pRNFL temporal quadrant thickness missed 77% of the eyes showing early GCIPL thinning, suggesting that pRNFL analysis may overlook early glaucomatous macular damage.

At the same time, many studies reported that early superior and inferior pRNFL defects are frequently associated with initial GCIPL changes, which are preferentially located at the inferior-temporal and superior-temporal macular sectors.[12,24–27]

Furthermore, it was shown that GCIPL parameters have similar diagnostic accuracy compared to the pRNFL ones in detecting early glaucoma.[28–31]

However, it remains unclear whether the glaucomatous damage becomes detectable at the macula or at the peripapillary region first. Kim and colleagues[32,33] explored the relationship between abnormal macular GCIPL thinning and corresponding pRNFL defects on the OCT deviation map. All cases of pRNFL thinning also showed macular GCIPL loss. However, there were several cases of inferior macular GCIPL loss that did not show corresponding pRNFL defects. Therefore, the authors suggested that inferior macular GCIPL changes could be detected statistically before pRNFL changes.[32,33] Triolo and colleagues showed in a cross-sectional study that macular GCIPL and pRNFL normalized thicknesses are affected in similar amount in early glaucoma (Triolo G et al. "Ganglion Cell–Inner Plexiform Layer or Retinal Nerve Fiber Layer: which one is affected first in Early Glaucoma?" Poster presented at: 2016 American Glaucoma Society annual meeting, Fort Lauderdale, Florida, USA). Interestingly, Marshall and colleagues.[34] have recently reported that GCIPL precedes pRNFL progression in patients with lower tension glaucoma, whereas patients with higher baseline intraocular pressure (IOP) showed pRNFL progression first.

Peripapillary RNFL and macular GCIPL thicknesses, although extensively utilized, are not the only OCT parameters used for early diagnosis of glaucoma. For instance, the Bruch's membrane opening derived minimum rim width (BMO-MRW) is another measurement that showed similar accuracy in diagnosing early glaucomatous changes.[35–37] More recently, Zheng and colleagues[38] found that among all the parameters taken into account in the study, the supero-temporal and infero-temporal pRNFL and BMO-MRW thicknesses below the fifth percentile yield the best diagnostic performance for glaucoma detection, with Retinal Nerve Fiber Layer Thickness (RNFLT) attaining higher sensitivities than MRW at the same specificity. Surprisingly, BMO-MRW assessment could fail to reveal abnormality even in eyes with confirmed visual field (VF) defects and RNFL abnormalities. Furthermore, integrating RNFLT assessment to BMO-MRW assessment increased the sensitivity of BMO-MRW assessment without compromising the specificities, whereas integrating BMO-MRW assessment to RNFLT assessment did not improve the diagnostic performance. This finding underscores the higher importance of pRNFL thickness analysis in the diagnostic evaluation of glaucoma.

Optical coherence tomography: glaucoma progression

Because of its objective nature and low test–retest variability, structural SD-OCT is a valuable tool to estimate disease progression.[39]

It is commonly believed that structural OCT is useful only in the pre-perimetric and early stages of the disease, while it is of limited help in advanced glaucoma. This belief is based on the results of several studies showing that pRNFL thickness has greater sensitivity than VF test in eyes with early glaucoma, but not in those with moderate to advanced disease.[40–43] The pRNFL thickness hits the floor earlier than functional measures, usually at mean deviation (MD) values between −8 and −10 dB, preventing recognition of further worsening.[40,41] This is certainly true but applies only to global pRNFL thickness, and recent studies demonstrated that other structural OCT parameters may provide useful information even in patients with advanced disease, where the detection of progression has limitations even with other techniques, due to the minimal residual rim to monitor and the high VF variability in the low sensitivity range.[44,45]

Lee and colleagues[46] recently reported that eyes with advanced glaucoma have preserved regions of pRNFL, which may be used to monitor disease progression. However, it must be kept in mind that quadrants or clock-hours thicknesses are characterized by higher test–retest variability, and, therefore, a greater structural change is required to distinguish true progression from fluctuation.[39] Furthermore, glaucoma follows characteristics patterns of OCT progression, whose recognition at the thickness and total deviation maps may help the clinician discriminating between variability and progression.[47,48]

Compared to peripapillary OCT parameters, macular OCT measures reach the floor later on

and may be useful to monitor patients along the entire spectrum of the disease, including advanced stages.[42,49–51] Belghith and colleagues[49] were the first to report that mGCIPL thickness may detect progression in advanced glaucoma better than optic nerve measures, such as pRNFL, and further studies corroborated these findings. In the Advanced Imaging for Glaucoma Study, Zhang and colleagues[42] investigated the utility of pRNFL and macular GCC measures to detect progression in all the spectrum of glaucoma severity and found that pRNFL had little utility in patients with advanced glaucoma as opposed to GCC thickness, which retains high sensitivity throughout all the course of disease. Shin and colleagues[50] showed that Glaucoma Progression Analysis (GPA) of the GCIPL may be used to track glaucoma progression better than that of pRNFL. In a cohort of patients with advanced glaucoma, Lavinsky and colleagues[51] compared the rates of changes of VF MD, visual field index (VFI), pRNFL, and mGCIPL and found that all the indices but pRNFL rate detected a significant negative rate of change.

There is no consensus on which macular measure (e.g. thickness of GCC, ganglion cell layer (GCL), GCIPL, or full macular thickness (FMT)) best monitors glaucoma progression. A real change must exceed the test–retest variability to be detectable. Previous studies have shown that within-session variability, rather than between-session variability, is responsible for most of the total test–retest variability in macular OCT imaging, and variability is low and uniform (approximately 3 µm) regardless the macular measure considered.[52,53] As the relative variability is related to normal layer thickness, thinner outcome measures (i.e. GCL and GCIPL) have higher relative variability than thicker ones (i.e. GCC and FMT).[52,53] In addition, thinner measures are limited by narrower dynamic ranges and increased variability in severe glaucoma, likely related to segmentation errors which are more frequent with thinner retinal layers.[54] In yet unpublished studies, GCC was the best outcome measure to monitor glaucoma progression along the entire disease spectrum and provided the best longitudinal structure–function relationship with central VF (Nouri- Mahdavi et al. "Comparison of rates of progression of macular OCT parameters in glaucoma." Paper presented at: 2018 ARVO annual meeting, Honolulu, HI, USA. Mohammadzadeh et al. "Longitudinal structure-function relationship in the macula." Paper presented at: 2019 ARVO annual meeting, Vancouver, Canada).

Although MRW is a promising measure to diagnose patients with early glaucoma, few studies suggest that it may perform worse or, at least, equal to pRNFL to monitor disease progression. Bowd and colleagues[55] estimated the measurement floor of macular GCIPL, pRNFL, and MRW and found that the latter two hit similar measurement floor, which is reached far before macular GCIPL. Gardiner and colleagues[56] compared pRNFL and MRW in terms of signal-to-noise ratio, which indicates how well a method discriminates a true change from variability; they found that MRW measure has a lower signal-to-noise ratio, and, therefore, it may require a larger magnitude of change than pRNFL to identify significant progression. The conclusions of these theoretical studies were confirmed by Belghith and colleagues,[49] who showed that both mGCIPL and pRNFL detect more progression than MRW in a cohort of patients with advanced glaucoma. Future studies need to clarify whether MRW can be useful to monitor early glaucoma.

Optical coherence tomography angiography: detection of early glaucoma

OCTA has provided insights into the relationship between neuronal and vascular changes in glaucomatous eyes. Initially, the attention was focused on the peripapillary VD in patients with established glaucoma, and capillary dropouts in these areas corresponding to pRNFL defects were thoroughly demonstrated.[13–16,57] The diagnostic ability of peripapillary VD has been shown to be lower or, at best, equal to pRNFL thickness, and it is still uncertain how this measure may improve the clinical care of glaucoma patients.[16,57,58]

More recently, OCTA-based studies have also investigated the macular region and found that glaucomatous eyes have a significantly lower superficial vascular complex (SVC) VD at the macula than healthy eyes. In contrast, no significant difference was found in VD of the intermediate and deep capillary plexuses at the macula.[59–61] The SVC has been found to supply blood to the nerve fiber layer and GCL. Thus, these studies suggested that vascular changes associated with glaucoma occurred preferentially among the vessels that feed the superficial layers of the retina. Similar findings have also been reported in preperimetric glaucoma.[61,62]

Takusagawa and colleagues,[59] noticed that a macular area with low perfusion in the SVC corresponded in shape, size, and location to areas of detectable GCC thinning and VF defects. This indicates that there is an intimate correspondence between vascular and structural defect.

Whether macular OCTA parameters are useful in the early diagnosis of glaucoma patients is still under debate. Same studies demonstrated high diagnostic performance of macular OCTA parameters in detecting glaucoma, comparable to those typical of the pVD.[59–61] In a previous study, we compared diagnostic properties of structural OCT and OCTA at the peripapillary and macular regions, and we found that structural parameters (i.e. pRNFL and macular GCIPL) had the best diagnostic performance, followed by radial peripapillary capillaries VD, and, far beyond, macular SVC VD.[16] In this study, high correlation was reported between peripapillary VD and pRNFL, but not between macular VD and mGCIPL in glaucomatous patients. Richter and colleagues[63] also reported that peripapillary superficial retinal layer VD has higher diagnostic abilities compared to macular parameters. Wan and colleagues[64] evaluated the diagnostic performance of macular OCT and OCTA in a large cohort of Chinese patients and, once again, found that macular OCTA performed considerably worse than structural measures. In a study by Park and colleagues,[65] macular OCTA parameters had an area under the receiver operating characteristic (ROC) curve to discriminate between early glaucoma and healthy controls ranging between 0.50 and 0.60, which is slightly better than tossing a coin. Taken together, these findings may suggest that macular OCTA alone may have a limited role in the diagnosis of early glaucoma patients.

It still needs to be clarified whether the vascular changes at either optic disk or macula are a cause or a consequence of the glaucomatous loss of RGCs and their axons. The fact that the vascular abnormalities detected on OCTA resemble in shape and location the macular GCIPL and pRNFL defects[59] may suggest that the vascular density is reduced because of the loss of neural tissue, and not the other way around. Furthermore, the fact that the superficial vascular retinal component is selectively affected in glaucoma, and not the deeper plexuses, again suggests that the mechanism is more likely to be somehow related to the neural tissue degeneration rather than being a cause of it. However, longitudinal studies based on OCT and OCTA investigating the very early stage of the disease are needed to elucidate on this topic. These will certainly provide a broader understanding of the pathogenesis of glaucoma and its vascular component.

Optical coherence tomography angiography: glaucoma progression and structure–function correlation

The role of OCT-A in monitoring the disease progression across the glaucoma spectrum is still uncertain. Kim and colleagues[66] reported that OCT-A is characterized by wider dynamic range than both VF and structural OCT and, therefore, it could be useful to detect progression in severe glaucoma, where VF and structural OCT are limited by high test–retest variability and floor measurement, respectively. Park and colleagues[67] have shown that baseline reduction in peripapillary choroidal VD was associated with higher odds of VF progression in a cohort of Korean glaucomatous patients. This finding, however, is not surprising as peripapillary atrophy (especially beta) is a well-known risk factor for glaucoma progression and is histologically associated with the loss of choriocapillaris.[68,69] Currently, there is a lack of longitudinal studies investigating the role of OCT-A in the follow-up of glaucoma patients, and there is no evidence that its use in this context may improve the clinical care.

There are few studies investigating the structure–function relationship between VF and OCTA. Ghahari and colleagues[70] showed that the severity of VF damage is related to both macular and peripapillary VD, along with mGCIPL and pRNFL, and each 1 dB reduction of MD value is associated with a 0.43% and 0.46% reduction in peripapillary and macular OCTA values, respectively. Whether the structure–function relationship is stronger with either OCTA or structural OCT is still uncertain. Yarmohammadi and colleagues[71–73] reported that structure–function correlation between peripapillary OCTA parameters and VF MD was higher than the one between pRNFL and VF MD, and OCTA measures could anticipate VF changes in patients with POAG. Penteado and colleagues[74] also found a significant association between decreased macular VD and 10–2 VF MD in patients with glaucoma. On the contrary, Wan and colleagues[64] found that structure–function relationship is much weaker with OCTA than structural OCT.

Conclusion

The advent of clinical OCT has greatly revolutionized the care of glaucoma patients, and this technology has constantly evolved with instruments with better resolution and the introduction of novel parameters.

Peripapillary RNFL has an established role in both the early diagnosis and identification of glaucoma progression, but its measurement floor prevents its usage from monitoring eyes with moderate-to-advance disease. Macular OCT has emerged as a complementary imaging modality to pRNFL. In the glaucoma diagnosis, it fares no worse than pRNFL, and it may be the first sign of OCT damage in some phenotypes of disease, such as normal-tension glaucoma patients. Since macular measures hit the floor later than pRNFL, they may provide useful information also in patients with advanced disease.

Other imaging measures have been welcome with great, perhaps exaggerate, enthusiasm, but their real utility in clinical practice is far from being established. BMO-MRW has a solid rationale and may have some role to diagnose early glaucoma, but it may be of limited utility in the identification of glaucoma progression. OCTA may provide insight into the disease pathogenesis, but it does not offer any clear advantage over structural OCT at the present time.

All these imaging measures provide the clinician with a large amount of information, which may be sometimes discordant. The mental integration of various OCT measures along with the whole clinical picture may allow a better disease evaluation and overcome the limitations of individual parameters.

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