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# Glaucoma in myopia: diagnostic dilemmas

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## ABSTRACT

Myopic eyes have an increased risk of glaucoma. However, glaucomatous changes in a myopic eye are often difficult to detect. Classic structural and functional investigations to diagnose glaucoma may be confounded by myopia. Here, we identify some of the common pitfalls in interpreting these structural parameters, and the possible solutions that could be taken to overcome them. For instance, in myopic eyes, we discuss the limitations and potential sources of error when using neuroretinal rim parameters, and retinal nerve fibre layer and ganglion cell-inner plexiform layer thickness measurements. In addition, we also review new developments and potential adjuncts in structural imaging such as the assessment of the retinal nerve fibre layer texture, and the examination of the microcirculation of the optic nerve head using optical coherence tomography angiography. For the functional assessment of glaucoma, we discuss perimetric strategies that may aid in detecting characteristic visual field defects in myopic glaucoma. Ultimately, the evaluation of glaucoma in myopia requires a multimodal approach, to allow correlation between structural and functional assessments. This review provides overview on how to navigate this diagnostic dilemma.

## INTRODUCTION

The epidemic of myopia is a growing public health concern, and is projected to affect 5 billion people globally (half of the world's population) by 2050.[1] In medium-income and high-income countries in East and Southeast Asia, the prevalence of myopia has increased markedly over the past half-century. In these countries, over 80%–90% of young adults, and nearly 40% of older adults aged 40 years and above are myopic.[2–4] Similar trends are also seen in the Western world.[1 5] This represents a significant health and societal burden due to reversible visual impairment from uncorrected refractive error, as well as irreversible visual loss from causes such as myopic macular degeneration, as well as potentially, glaucoma. Glaucoma is a leading cause of irreversible visual impairment and blindness, affecting more than 100 million people worldwide, making it also a global health problem.[6 7]

Myopia is a risk factor for glaucoma,[8–10] and the risk of glaucoma increases with age.[11] With the rising prevalence of both myopia and glaucoma in an ageing population, the occurrence of these two ocular conditions in the same patient is likely to increase. For example, a study by Pan *et al* demonstrated that eyes with high myopia had a sixfold increased odds of having primary open-angle glaucoma.[12] While the two conditions can coexist, there is often a diagnostic challenge to the clinician, since the detection of glaucomatous optic nerve damage in highly myopic eyes is difficult. Ophthalmoscopically, it may be hard to tell apart myopia from glaucoma (figure 1) for a combination of reasons. First, in highly myopic eyes, the colour contrast between the pink neuroretinal rim and the pale optic cup decreases due to an increased pallor in the rim. Second, the spatial contrast between the height of the neuroretinal rim and the bottom of the optic cup gets reduced by a flattening of the cup due to the enlargement and stretching of the optic disc and the lamina cribrosa. Third, the rotation of the optic disc may give rise to an oblique view of the optic nerve head (ONH). Fourth, the assessment of the retinal nerve fibre layer (RNFL) in the peripapillary region gets difficult due to the increased brightness of the underlying peripapillary tissue. Fifth, distinguishing between the myopia-related parapapillary gamma and delta zones, and the glaucoma-related histological beta zone (without delta and gamma zones) is often impossible on ophthalmoscopy alone. Thus, clinical assessment alone is often insufficient to diagnose myopic glaucoma. The use of objective structural parameters to identify glaucomatous change, combined with perimetry to detect corresponding visual field loss, therefore takes on an even greater importance in myopia. However, the application of structural imaging or visual field testing in glaucoma is fraught with multiple potential pitfalls in myopia. For instance, myopic eyes may be structurally distorted with posterior staphylomas (that make structural comparisons against a normative population difficult) or functionally abnormal with macular atrophy (where visual field defects may be attributable to either optic nerve or macula dysfunction). Thus, highly myopic eyes may be falsely overdiagnosed with glaucoma if care is not taken to distinguish between glaucomatous and myopic pathology.[13–15]

The aim of this review is therefore to discuss the structural and functional assessments for detecting glaucoma in myopic eyes, how these tests may be misinterpreted, and the potential solutions that could be used to overcome this diagnostic dilemma (table 1). In addition, a brief overview of the relationship between myopia and glaucoma, and the pathophysiology on how myopia might predispose towards glaucoma, will also be discussed.

## THE RELATIONSHIP BETWEEN MYOPIA AND GLAUCOMA

### Epidemiological associations

Various population-based cross-sectional epidemiological studies have consistently shown that myopia is positively associated with prevalent glaucoma;

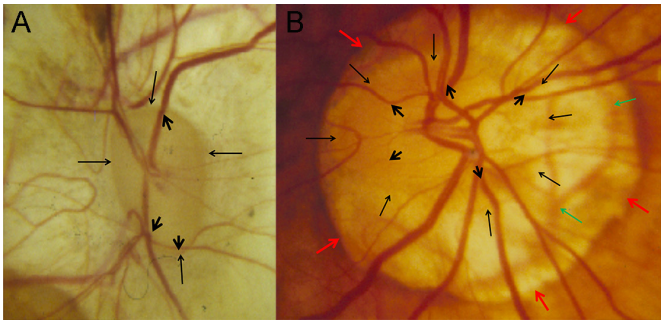


**Figure 1** Optic disc photographs of highly myopic eyes with and without glaucoma. (A) Advanced glaucoma in a highly myopic eye demonstrating loss of the neuroretinal rim. Long thin black arrows: optic disc border. Short thick black arrows: vessel kinking close to the optic disc border. (B) A highly myopic eye with myopic deformations to the optic nerve head, but without glaucoma. Long thin black arrows: optic disc border. Short thick black arrows: border between neuroretinal rim and optic cup as indicated by vessel kinking. Green arrows: peripapillary arterial circle of Zinn-Haller, which often indicates the border between the parapapillary gamma and delta zones. Red arrows: outer border of parapapillary gamma zone.

a meta-analysis by Marcus *et al* in 2011 that incorporated 13 studies involving 48 161 individuals corroborated this finding: the pooled OR (95% CI) for glaucoma was 1.92 (1.54 to 2.38) for myopia overall (based on 11 studies), and 1.65 (1.26 to 2.17) and 2.46 (1.93 to 3.15) for low and high myopia, respectively (based on seven studies).[8] Subsequent cross-sectional studies have also reported a similar trend.[12 16 17] However, longitudinal population-based data regarding the association between myopia and incident glaucoma are scarce. In the Ponza eye study, high myopia was identified as a risk factor for 12-year incident glaucoma.[9] Similarly, in the Rotterdam study, participants with high myopia were more likely to develop glaucomatous visual field loss (HR (95% CI), 2.3 (1.2 to 4.5)) over 10 years.[10] However, this effect became less pronounced (1.5 (0.8 to 3.0)) with a longer follow-up of 20 years, and a higher mean age of the cohort.[18] This may possibly indicate that myopia may play a role in the development of glaucoma at a younger age.[19]

Data on myopia as a potential risk factor for the progression of myopia have come from mainly clinic-based studies (due to the low prevalence of glaucoma in the general population). A systematic review on the risk factors for glaucomatous visual field progression did not identify myopia as a risk factor.[20] Other studies that incorporated structural criteria for glaucomatous progression also have not found a strong association with myopia.[21–24] From a pathophysiological perspective, it is not certain why myopia may predispose towards the development, but not the progression of glaucoma. It is possible that the lack of association between myopia and glaucomatous progression may be related to the difficulty in detecting progression on structural or functional assessment. Alternatively, some cases of reported myopic glaucoma could be misdiagnoses, which therefore do not progress on longitudinal follow-up.

**Table 1** Considerations for glaucoma assessment in a myopic eye

| Clinical assessment | Considerations in myopia |
|---|---|
| Neuroretinal rim thickness | ► Neuroretinal rim thickness parameters may use the Bruch's membrane opening as a reference. However, in myopic eyes, the margin of the Bruch's membrane may be indistinct, or it may move away from the temporal optic disc border, thus introducing errors in neuroretinal rim thickness measurements in myopia. |
| Peripapillary RNFL thickness | ► Superotemporal and inferotemporal RNFL bundles tend to converge temporally with axial elongation.<br>► This may cause apparent false-positive thinning in the superior and inferior sectors of the RNFL deviation map, when compared against the normative database of non-myopic eyes.<br>► This effect may be reduced by incorporating a myopic database of eyes with longer axial lengths.<br>► However, refraction or axial length matching alone is insufficient; optic disc rotation may still contribute towards significant intereye variation in the RNFL thickness profile. |
| Macular GCIPL thickness | ► Where marked optic disc deformations make the structural assessment of the ONH difficult in myopia, in select cases, the macula may be less distorted—hence, the GCIPL may work as a complementary structural assessment in myopia in these instances.<br>► However, the macula is also frequently affected in high myopia. Myopic macular degeneration may for instance cause abnormal thinning (from patchy atrophy) or thickening (from retinoschisis) of the retinal layers.<br>► In the absence of macular disease, the axial elongation and stretching of the globe may also cause thinning of the macular GCIPL due to geometric reasons. Thus, false-positive pathological thinning may be recorded when using non-myopic databases for comparison. |
| RNFL texture | ► ROTA on optic coherence tomography is a new method of analysing RNFL abnormalities, which does not depend on normative databases for thickness measurements. However, as a new development, its performance in clinical settings is still unproven. |
| Microvasculature of the ONH | ► Various lines of evidence show that the blood supply around the ONH is reduced in both myopia and glaucoma. However, the clinical significance of this is uncertain. Furthermore, ocular blood flow is not established as a modifiable risk factor or therapeutic target for glaucoma, and the ideal method for assessing ONH vascular supply is also undetermined. |
| Visual field | ► Central or paracentral scotomas may be more frequent in myopic glaucoma, and these visual field defects are often missed on 24–2 perimetry. Hence, an alternative perimetric protocol, for example, one that combines 24–2 with 10–2 perimetry, may be better suited in myopia.<br>► The mode of optical correction (eg, trial lenses or contact lenses) of myopic refractive errors may also introduce artefacts in visual field assessment. Thus, if visual field defects are found using trial lenses, it may be advisable to repeat perimetry using contact lenses (and vice versa) to exclude the effect of artefacts. |
| IOP | ► In eyes that have undergone myopic refractive surgery (eg, laser-assisted in situ keratomileusis), the change in corneal properties may alter IOP measurements on Goldmann applanation tonometry. The use of other tonometers, such as the Pascal dynamic contour tonometer, may be more suitable in post-refractive surgery eyes. |
| Anterior chamber angle | ► Although primary angle closure in myopia is relatively uncommon, as myopia increases in prevalence, the absolute number of primary angle closure eyes with myopia will increase. These myopic angle-closure eyes may have similar anterior chamber parameters (but longer posterior segments) compared with emmetropic or hyperopic eyes. Thus, gonioscopy should be performed in all myopic eyes with glaucoma to exclude angle closure. |

GCIPL, ganglion cell-inner plexiform layer; IOP, intraocular pressure; ONH, optic nerve head; RNFL, retinal nerve fibre layer; ROTA, retinal nerve fibre layer optical texture analysis.

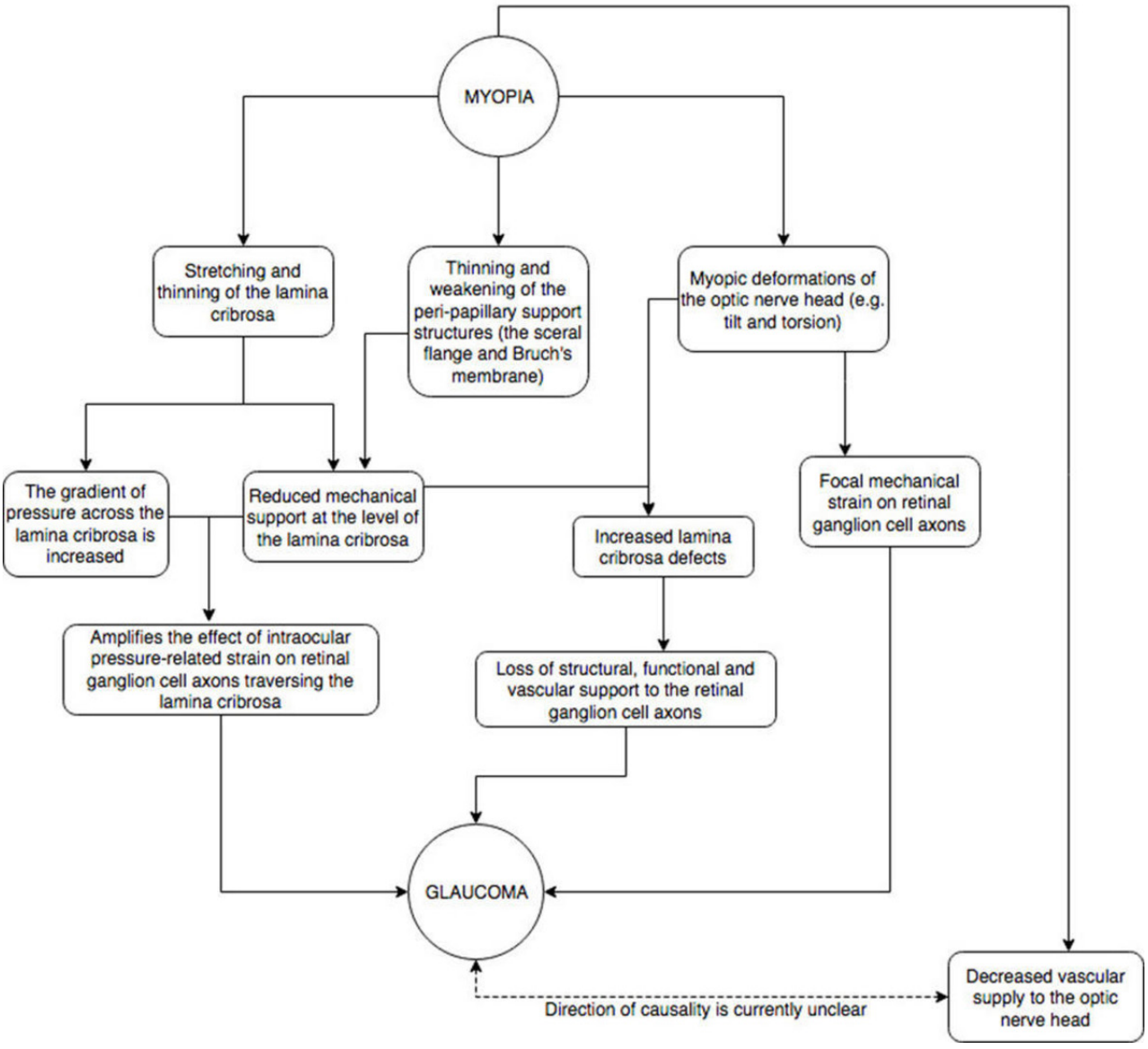


**Figure 2** Hypothetical pathogenic pathways that may link myopia to glaucoma.

### Pathogenic pathways and the role of the lamina cribrosa in myopic glaucoma

Although the exact mechanisms that link myopia to glaucoma are still uncertain, it is postulated that structural changes to the ONH in myopia may increase its susceptibility towards glaucomatous damage. A diagram of hypothetical pathogenic pathways is included in figure 2. Axial elongation of the myopic eye is associated with the stretching and thinning of the lamina cribrosa and the peripapillary scleral flange.[25] The loss of biomechanical support at and around the lamina cribrosa exposes retinal ganglion cell (RGC) axons to mechanical strain as they traverse the porous lamina cribrosa, down a pressure gradient (from a higher intraocular pressure (IOP), to a lower retrobulbar cerebrospinal fluid pressure).[26 27] In addition, myopic ONH deformations such as torsion and tilt may further increase strain at the lamina cribrosa.[28 29] This may lead towards lamina cribrosa defects, which have a pathogenic role in glaucoma.[30 31] In this schema, the susceptibility towards glaucoma may be related more to the mechanical stresses from myopic deformations of the ONH, rather than to elevated IOP. Recently, Sawada *et al* showed that in myopic eyes with lamina cribrosa defects, those with progressive visual field loss had a higher baseline IOP that that in non-progressive eyes.[32] This may suggest that in myopia, existing lamina cribrosa defects (which first develop in an IOP-independent manner) may become a focus of strain (that results in glaucomatous progression) only when exposed to higher IOP. This ties in with a prior study that reported IOP and severity of myopia to have synergistic effects on the risk of primary open-angle glaucoma.[33] It may also explain why in some cases (eg, where baseline IOP is low), myopia may not predispose towards further glaucomatous damage.[34 35]

## CLINICAL ASSESSMENT OF GLAUCOMA IN MYOPIC EYES

### Assessment of the neuroretinal rim thickness

A key aspect in the evaluation of the ONH includes the assessment of the neuroretinal rim, as this may often be thinned out diffusely or focally in glaucoma. In recent years, neuroretinal rim measurements using the Bruch's membrane opening (BMO) as a reference plane for optical coherence tomography (OCT) has supplanted rim assessments based on the clinical optic disc margin on confocal scanning laser tomography (the latter has been shown to lack a sound anatomical basis).[36] The BMO-minimum rim width (BMO-MRW), defined as the minimum

distance between the BMO and the internal limiting membrane, has demonstrated a higher sensitivity compared with peripapillary RNFL thickness measurements in diagnosing early glaucoma.[37] Thus, the BMO-MRW parameter may also be applied to the diagnosis of glaucoma in myopic eyes. In myopes, Malik *et al* demonstrated that it had a similar sensitivity (at 90% specificity) compared with RNFL parameters.[38] In non-glaucomatous but myopic eyes, the BMO-MRW parameter also had fewer false-positive readings compared with the parameter of average RNFL thickness.[39 40]

Comparable to the BMO-MRW, the three-dimensional neuroretinal rim (3D-NRR) thickness is also a BMO-based neuroretinal rim parameter the use of which has been recently evaluated in myopia.[41] Kim *et al* reported that in groups of myopic eyes with and without glaucoma, the 3D-NRR thickness had a significantly lower false-positive rate than RNFL thickness (2.1% vs 26.9%, p<0.001). Using the internal normative database, 3D-NRR thickness consistently showed a better sensitivity and specificity in the diagnosis of myopic glaucoma compared with RNFL measurements. Furthermore, and most promisingly, 3D-NRR thickness seemed to improve specificity especially in regions where false-positive readings of RNFL thickness were most common in myopia (namely, the superior and inferior sectors, as discussed below).[41]

However, a major problem with using BMO-based parameters in the evaluation of the myopic ONH is that the margin of Bruch's membrane (BM) may often move away from the temporal optic disc border.[42 43] The latter may be defined by the peripapillary border tissue of the choroid (Jacoby) and of the peripapillary scleral flange (Elschnig) as continuation of the optic nerve pia mater. Using the BM margin as optic disc border thus leads to a falsely large optic disc size in OCT-based measurements, and potentially to a false decrease of the neuroretinal rim (and RNFL) thickness measurements due to geometrical reasons. Notably, in Kim *et al*'s study, eyes with a large peripapillary gamma zone and delta zone or indistinct BMO margin were excluded from the analyses.[41] This circumvented a major limitation of this technology. Zheng *et al* recently demonstrated that in high myopia, around 30% of eyes may have indiscernible BMO in at least one meridian.[44] Furthermore, the BMO was indistinct most frequently at areas where glaucomatous neuroretinal rim loss was most common.[44] Thus, the use of BMO-based parameters may potentially be ill-suited in highly myopic eyes.

### Assessment of the RNFL thickness

Another common use of OCT imaging is to evaluate the peripapillary RNFL thickness in the assessment of glaucoma. However, in myopic eyes, the superotemporal and inferotemporal RNFL bundles tend to get closer together temporally, since the angle kappa between the temporal vascular arcades decreases with longer axial length due to the elongation of the fovea-optic disc distance.[45] It causes more temporally located superior and inferior peaks (or 'humps') of the RNFL thickness profile.[13] The angle between the superotemporal and inferotemporal RNFL bundles was shown to decrease by 3.3° for every 1 mm increase in axial length.[13] Due to the temporalisation of the RNFL bundles in myopia, when compared against the normative database (calibrated for non-myopic eyes), highly myopic non-glaucomatous eyes may appear to have abnormally thickened RNFL temporally, but abnormally thinned out RNFL inferiorly and superiorly.[13] In a study of healthy non-glaucomatous eyes, Yamashita *et al* showed that increased axial lengths were associated with increased odds of false-positive RNFL thinning at 5 and 6 o'clock (inferiorly), and 12 o'clock (superiorly).[14] The angle kappa and the position of the temporal vascular arcades[45] may thus have to be taken into account in the interpretation of the RNFL thickness profiles in myopic eyes (as in any eye). Thus, when the OCT deviation map shows abnormally thinned RNFL in the superior and inferior quadrants in a myopic eye, and the RNFL thickness peaks are moved in the temporal direction, the possibility of this being a false-positive result should be considered (figure 3). Conversely, as myopic eyes have thicker RNFL in the temporal quadrants, there is also a possibility of missing a papillomacular bundle defect, which is more common in myopia.[46 47]

To reduce these diagnostic problems, Biwas *et al* built a custom normative database from 180 non-glaucomatous eyes with high myopia.[48] Compared with the in-built database, the new myopic database showed superior specificity and sensitivity in detecting abnormal RNFL measurements.[48] Although this highlights the importance of improving our current (non-myopic) normative databases, it may not be sufficient to simply include data from eyes with high myopic refractive errors. In a study that compared eyes with titled discs against eyes with refractive error-matched non-tilted discs, it was found that horizontal disc tilt (ie, a rotation of the optic disc around the horizontal axis) still contributed towards significantly thicker temporal RNFL profiles, and a poorer diagnostic ability in evaluating temporal RNFL thickness.[49] Thus, besides refractive error and axial length, structural peculiarities of the optic disc, such as the optic disc rotation around the vertical, horizontal and sagittal axes, may also have to be factored in when assessing the peripapillary RNFL in a myopic eye.

### Assessment of the ganglion cell-inner plexiform layer thickness

The RGCs of the peripapillary RNFL are mainly located in the central 4.5 mm-diameter region of the macula, which histologically is defined as the region with an at least double-layered RGC.[50] Therefore, besides RNFL thickness, the macular ganglion cell-inner plexiform layer (GCIPL) thickness has emerged as an additional important structural parameter in glaucoma.[51] In the context of myopia, where optic disc changes may make assessment of the peripapillary RNFL thickness challenging, GCIPL thickness provides an alternative method for detecting structural glaucomatous change. For instance, Shin *et al* showed that although the vertical cup-to-disc ratio and RNFL measurements may be affected by the optic disc rotation, the macular GCIPL was not.[49] Along the same lines, in highly myopic eyes, Nakano *et al* showed that subjective interobserver agreement was excellent for serial OCT macular vertical scans (in assessing for thinning of the macular ganglion cell layer), but poor for optic disc photos (in looking for glaucomatous change).[52] Recently, a 'GCIPL hemifield test' has also been described, which detects GCIPL thickness differences across the temporal raphe on an OCT macula scan.[53] In highly myopic eyes, the GCIPL hemifield test showed a large area under the receiver operator curve and a high sensitivity and specificity in diagnosing glaucoma.[53]

However, GCIPL assessment in myopia is not without its limitations. First, the GCIPL hemifield test works by detecting a hemifield difference across the temporal raphe; this may therefore be less useful when there is bipolar thinning of both the superior and inferior RNFL. Second, the premise of evaluating the macular GCIPL is that the macula region may be less distorted in eyes in which the ONH is deformed and difficult to assess in myopia—however, this may not be true. Recent studies

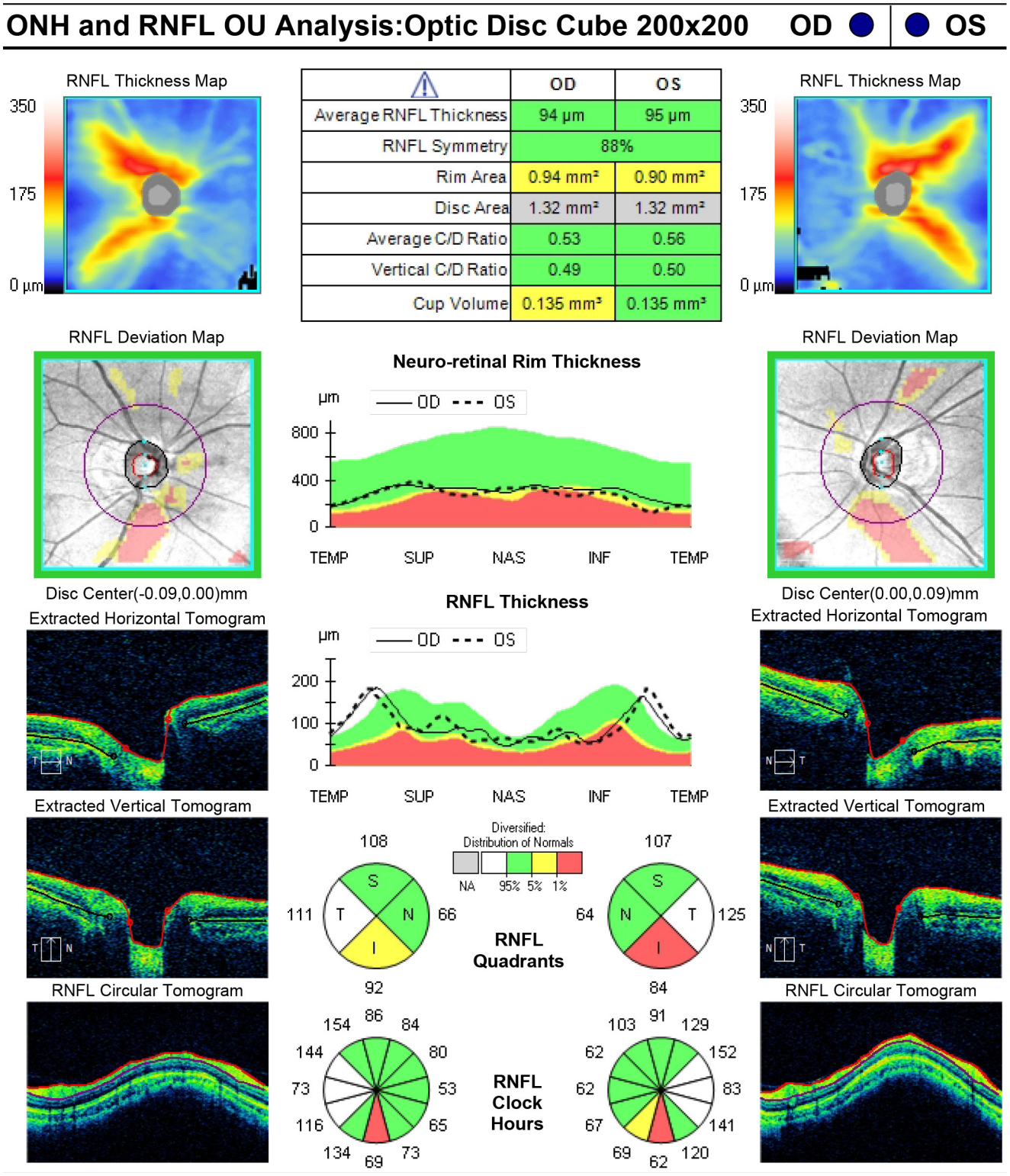


**Figure 3** Printout of optical coherence tomography examination (Cirrus-HD software V.6.0; Carl Zeiss Meditec, Dublin, CA, USA) of the optic nerve head (ONH) and peripapillary retinal nerve fibre layer (RNFL). Both eyes have high myopia with temporalisation of the superotemporal and inferotemporal RNFL bundles. This is shown graphically on the RNFL thickness profile. The superior and inferior temporal humps are both displaced temporally such that it lies above the 95th percentile of thickness in that location. Therefore, on the RNFL quadrant and clock hours sector map, the temporal sectors of both eyes are classified as having supranormal thickness. However, the temporal displacement of the RNFL peaks also results in the bottom of the peaks residing in the location where the population-average RNFL is normally thickest (as seen on the thickness profile). Therefore, despite the superotemporal and inferotemporal RNFL bundles having a good quality signal on the thickness map, the deviation map shows apparent thinning inferiorly (and to a lesser degree, superiorly) on the deviation map, in locations nasal to the healthy superotemporal and inferotemporal RNFL bundles. The thin (or borderline) inferior sectors on the RNFL quadrant/clock hour maps are therefore false-positive results.

have suggested that the contour of the posterior globe determines the eventual ONH configuration.[28 54] Thus, irregularities at the macular region may similarly confound GCIPL assessment in high myopia. Third, similar to the RNFL assessment, false-positive thinning on the GCIPL deviation map is also more common with longer axial length.[55] With longer axial length or a greater optic disc-fovea distance, the stretching of the globe may result in a thinner macula.[56 57] Hence, the use of a myopic database for GCIPL assessment, as is present on the RS-3000 spectral domain-OCT (Nidek, Gamagori, Aichi, Japan), may likewise be necessary.[58] Fourth, the presence of myopic macular degeneration may also cause abnormalities to the macular ganglion cell layer independent of glaucoma. For instance, patchy atrophy at the macula may cause thinning of the retina due to retinal atrophy and/or the stretching of the overlying retinal layers as the edges of the underlying BM defect move apart; conversely, there may also be cystoid thickening of the inner retinal layers with macular retinoschisis.[59] Lastly, segmentation errors in macular GCIPL are more common in myopic eyes.[60]

### Assessment of the RNFL texture

In healthy eyes, the normal RNFL has fine and bright striations that radiate from the optic disc and follow an arcuate distribution in the inner retina. Therefore, its reflectance pattern may be used to judge the health of the RNFL. As opposed to measuring the thickness of the peripapillary RNFL (or the macular GCIPL), which relies on the comparison against population-specific normative databases, studying the texture of the RNFL in the evaluation of glaucoma does not require normative data. This may therefore be particularly suited for analysing myopic eyes, where obtaining normative data is difficult, since myopic eyes may exhibit a wide range of axial lengths and various degrees and directions of optic disc rotations. This texture analysis of the RNFL has previously been explored using retinal photographs, and can be evaluated qualitatively or semiquantitatively.[61 62] As the striations of the RNFL may be seen on photographic images, loss of these fibres can be identified after postprocessing with custom software. A similar approach may also be conducted using OCT. On widefield swept source OCT, Leung *et al* found that RNFL optical texture analysis (ROTA) localised RNFL abnormalities that would be missed by conventional RNFL thickness analysis; furthermore, ROTA was also able to discern different levels of RNFL damage in advanced glaucoma that would not be feasible with conventional RNFL thickness analysis.[63] Lastly, ROTA across the peripapillary and macular region showed a similar sensitivity and significantly higher specificity in diagnosing glaucoma compared with the combined peripapillary RNFL and macular GCIPL thickness analysis.[63] Since ROTA does not require comparison against normative databases, its potential application in diagnosing/monitoring glaucoma in myopia is promising. The development of ROTA for use in commercially available OCT machines is underway.

### Assessment of the microvasculature of the ONH

A further consideration in evaluating the ONH in myopia involves studying its vasculature. Various lines of evidence suggest that the blood supply to the ONH is altered with myopia. On histology, it has been shown that the distance of the peripapillary arterial circle of Zinn-Haller to the optic disc border is considerably increased with longer axial lengths.[64] This may be of pathogenic significance as the circle of Zinn-Haller is the main arterial source for the lamina cribrosa blood supply.[65] On *in vivo* imaging using OCT angiography,[66] the peripapillary vessel density[67 68] and choroidal thickness[69] in highly myopic eyes were also found to be lower compared with normal eyes. Interestingly, both the parapapillary gamma zone (peripapillary sclera without overlying choroid, BM and deep retinal layers) and delta zone (no blood vessels of at least 50 mm diameter within the central gamma zone) are related to axial elongation, but only the size of the delta zone (but not gamma zone) is associated with glaucoma.[70] This may suggest that the paucity of larger vessels around the ONH may be associated with myopic glaucoma.

Similar to myopia, it has also been demonstrated that there is a reduction in ocular blood flow (for instance, at or around the ONH[67 71 72] or retrobulbar vessels[73] in glaucoma). However, whether these vascular changes are a cause or consequence of glaucoma is debatable. Decreased ocular blood flow could arise in glaucoma because increased IOP reduces the ocular perfusion pressure (defined as the difference between arterial blood pressure and IOP).[74] Alternatively, the reduced ONH circulation could be due to a diminished metabolic demand due to glaucomatous ONH degeneration.[72 75 76] To examine this second possibility, a recent OCT-angiographic study analysed the topographic pattern of the parapapillary deep-layer microvasculature dropout in glaucoma.[77] It was found that the microvasculature dropout did not follow the territory of the retinal vessels (which would suggest that the reduced ocular perfusion in glaucoma is an effect of primary vascular change), but instead corresponded to the location of RNFL defects—suggesting that the loss of capillaries was secondary to RNFL atrophy.[77]

Understood in this context, recent studies that have demonstrated reduced ocular perfusion in myopia are of an undetermined significance in its relation to glaucoma. For instance, although the peripapillary vessel density in highly myopic eyes was found to be significantly lower compared with normal eyes, the reduction in peripapillary vessel density in myopia is generalised[67 68] (this may reflect a thinner retina in an elongated eye with decreased retinal function[78] and metabolic requirements[79])—in contrast, in glaucoma, focal retinal vessel defects show a spatial concordance with the location of functional[71 76] or structural[72 80] deterioration (that may be a consequence or cause of RNFL atrophy). Thus, the role of measuring ocular blood flow in myopia or glaucoma—and how best to do so[81]—remains to be established. Furthermore, ocular blood flow does not seem to be a modifiable risk factor for glaucoma or a therapeutic target yet.[82]

### Assessment of the visual field

Besides structural assessment, visual field testing forms the second arm in the evaluation of glaucoma. In highly myopic eyes with structurally suspicious optic discs, the presence of a corresponding visual field defect may help clinch a diagnosis that otherwise might have been missed. However, as myopic macular degeneration can also cause visual field defects, where there is a macular lesion and a suspicious optic disc, it may be challenging to determine if the visual field defect is due to glaucoma or not. In these situations, although the diagnosis of glaucoma may be equivocal at baseline, the progression of visual field loss despite stable macular findings may eventually allude to the coexistence of a worsening optic neuropathy. Alternatively, the pattern or location of progressive visual field defects may also offer a clue. Myopic maculopathy affects the central visual field; therefore, if the central visual field defect is worsening, but the area of suspicion on the optic nerve is at the superior or inferior rim, then it might be wise to look closely for structural progression at

the macula (due to myopia) rather than at the optic nerve (from glaucoma). Thus, monitoring the trend of visual field function alongside structural imaging (eg, peripapillary RNFL thickness, or even disc photographs) for functional-structural agreement is key in the clinical management of myopic glaucoma, as with any other type of glaucoma. However, there are few specific considerations to be taken into account in the visual field assessment of the myopic eye.

First, the pattern of visual field loss in myopic glaucoma may differ from non-myopic glaucoma. In non-myopic glaucoma, early visual field defects are typically Bjerrum area defects and nasal steps. As these defects progressively enlarge or merge, they may encroach on fixation. Thus, the central visual field is often spared until a late stage. However, in myopic glaucoma, there may more often be early central or paracentral scotomas,[47] due to increased RNFL defects involving the papillomacular bundle.[46 47] For instance, Hangai *et al* described three patients in whom dense scotomas at or near fixation were missed on the 24-2 perimetry, but were picked up on 10-2 perimetry.[15] As the 24-2 SITA programme only tests five points placed within 5° from fixation, this test strategy has poor performance in detecting central or paracentral visual field defects.[83 84] A different perimetric protocol in screening for glaucomatous visual field defects in highly myopic eyes, which combines 24-2 perimetry with 10-2 perimetry, may therefore be warranted.

Second, myopic refractive error itself can also alter the outcome of visual field testing. In high myopia, high-powered minus lenses may cause prismatic deviation in extra-axial test points, leading to variable testing of the peripheral visual field among myopic eyes.[85] Furthermore, the use of either trial lenses or disposable contact lenses for optical correction may also influence the results of perimetry—in a study by Aung *et al*, some myopes demonstrated a spurious focal visual field defect on one method of correction, but not the other.[86] Thus, if visual field defects are found in myopes on perimetry using trial lenses, it may be advisable to repeat the test using contact lenses, and vice versa.

### Assessment of the anterior segment and IOP

Lastly, the assessment of the IOP and the anterior segment angle in myopia is also noteworthy for two reasons.

First, although IOP and central corneal thickness (CCT) are not significantly different in myopic compared with non-myopic eyes,[87 88] the accurate measurement of IOP may be difficult in a subset of patients with myopia who have undergone laser-assisted in situ keratomileusis (LASIK) or other types of refractive surgery.[89] In these procedures that alter CCT, the anterior corneal curvature and other biomechanical properties of the cornea, common forms of tonometry (including Goldmann applanation tonometry) may not be accurate.[89 90] Studies have shown that the values of IOP measurements decrease with a thinning and flattening of the cornea.[91 92] However, newer methods of tonometry such as the Pascal dynamic contour tonometer (which is less affected by changes in corneal thickness, curvature, rigidity and morphology) have been shown to improve the validity of IOP measurement in post-LASIK eyes.[89]

Second, although it is well recognised that myopia is a protective factor against primary angle closure,[93] it should not be assumed that all patients with myopia must have open angles. As the prevalence of myopia increases, although the relative association between myopia and primary angle closure may remain unchanged, the absolute number of patients who have angle closure but are myopic will increase. For instance, among angle-closure patients recruited from a tertiary eye centre in Singapore (where the prevalence of myopia is high),[2 3] 22% of all subjects were myopic.[94] Notably, in this study, there were no significant differences in the anterior chamber depth, lens thickness or lens vault between myopic and non-myopic participants.[94] Thus, gonioscopy should be performed in any patient suspected of glaucoma, regardless of myopic refractive status, in particular in East Asian patients.

## CONCLUSIONS

Structural imaging using OCT has emerged as a cornerstone in the diagnosis and management of glaucoma.[37 51] However, a fundamental weakness of using the thickness of an anatomical layer as a biomarker for glaucoma is that it requires a comparison against a normative database. This weakness becomes especially apparent in the assessment of myopic eyes, as the shape of the globe in myopes may differ greatly from emmetropes, as well as from each other.[95 96] The fact that investigators are working towards building myopic-specific databases (based on axial length-matched or refraction-matched data) is encouraging[48 58] (as it indicates an awareness of the limitations of existing one-size-fits-all non-myopic databases); however, it might be too simplistic an approach. Not all eyes with the same refractive error or the same axial length are equal. First, refractive error itself does not differentiate between axial, corneal or lenticular refractive components—only the former might directly affect the configuration of the ONH. Second, axial length is not synonymous with axial elongation; an eye with a high axial length may be simply be large in proportion with the rest of the eye's optical components.[97] Accordingly, in a refraction-matched study that compared eyes with tilted discs against eyes with non-tilted discs, myopic disc tilt was still demonstrated to confound the evaluation of peripapillary RNFL thickness.[49] Therefore, the ideal structural evaluation of thickness parameters in myopic eyes should take into account refractive error and axial length, and features of the ONH such as the optic disc rotation around the three principal axes, and even the configuration of the posterior globe.[28] Future research directions may include the use of large datasets and advanced algorithms (eg, from artificial neural networks)[98] to uncover and piece together multiple patterns of association. Alternatively, one might forgo the use of normative databases altogether. ROTA uses this unique approach by analysing not the thickness, but the texture of the RNFL.[63] This concept sounds promising, especially for myopic eyes—however, as a new development, real-world data on this technology are currently lacking.

Despite the many recent advances in structural imaging, one should not neglect the role of functional testing in glaucoma. Besides the fact that maintaining vision is the primary goal of glaucoma management, the detection of visual field loss or progression remains key in the diagnosis and management of glaucoma, especially in myopia. However, visual field testing may be complicated in myopia as there are often situations in which visual field defects may be missed on 24-2 perimetry (as myopic glaucoma may preferentially affect the central/paracentral visual field, which 24-2 has poor performance in assessing).[15 83 84] Alternatively, visual field defects may also often be detected in myopic eyes, that can be difficult to attribute to either a retinal or optic nerve cause. Therefore, future directions of research—that may help differentiate between visual loss from a myopic retinopathy versus an optic neuropathy—may be to explore objective functional tests (eg, electrophysiology,[99] pupillometry[100]) to detect glaucoma-specific dysfunction of the visual pathway.

In conclusion, the evaluation of glaucoma in a myopic eye requires a multimodal approach. Although the question: 'which

is the best structural assessment for myopic glaucoma?' may be of interest, there is no simple answer to this. So far, no studies have undertaken a head-to-head comparison of all investigations within the same subject pool. Furthermore, it is likely that the most appropriate investigation would vary according to each clinical scenario. For instance, where one specific test is deemed unreliable in a specific myope, another test could be used instead (eg, where GCIPL may be affected by macular disease, peripapillary RNFL assessment might be preferred). Thus, understanding the limitations and potential sources of error of each test (table 1) may allow the clinician to identify false positive or negative reports when they occur. Ultimately, if the results from different structural and functional tests correspond with each other, this may facilitate the diagnosis of glaucoma (eg, inferior peripapillary RNFL thinning, inferior GCIPL hemifield thinning, and superior arcuate visual field defect). Nevertheless, the development of better diagnostic strategies will help in the earlier and more accurate diagnosis of myopic glaucoma. Furthermore, it is hoped that the continual improvement in our ability to detect and define glaucomatous damage in a myopic disc may help to provide a deeper understanding of glaucoma as a multifaceted and multifactorial disease.

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