Bruch's membrane opening-minimum rim width and peripapillary retinal nerve fibre layer thickness measurement in myopic eyes with glaucoma

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Abstract

Introduction: Optic nerve head imaging in myopic eyes with glaucoma is challenging due to atypical myopic optic disc morphology. Peripapillary retinal nerve fibre layer (pRNFL) and Bruch's membrane opening-minimum rim width (BMO-MRW) utilize different anatomical reference points to measure the retinal nerve fibre layer.
Purpose: To evaluate the diagnostic agreement between BMO-MRW and pRNFL in glaucomatous eyes with varying degrees of myopia.
Design: Prospective observational study.
Methods: Forty-three eyes diagnosed as primary open-angle glaucoma, normal-tension glaucoma, and primary angle-closure glaucoma with varying degrees of myopia were included in the study. Geometric measurement of the neuroretinal rim tissue was conducted with spectral domain optical coherence tomography (SD-OCT) using two different parameters: BMO-MRW and pRNFL. The classification of scan quality and diagnostic agreement between both methods were compared using an exact McNemar's test. The association between the summary classifications of quality

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scans with myopic degree was assessed with Fisher's exact test.

Results: BMO-MRW had a higher percentage of good quality image scans compared to pRNFL ($p = 0.004$). BMO-MRW was capable of obtaining equally good quality scans for glaucomatous eyes with various myopic degrees, whereas pRNFL demonstrated a significant statistical difference between mild, moderate, and high myopia ($p = 0.001$). pRNFL was difficult to identify in highly myopic eyes. By excluding poor quality scans, the diagnostic agreement between both modalities was 48.4% ($p = 0.002$). The observed agreement was higher in low myopia (66.7%), followed by moderate myopia (28.6%) and high myopia (16.7%).

Conclusion: Compared to pRNFL, BMO-MRW is a better diagnostic imaging modality in glaucoma, especially for eyes with high myopia. Scan quality must be considered when interpreting OCT result in daily clinical practice to yield more accurate and reliable results.

Pengukuran Bruch's membrane opening-minimum rim width (BMO-MRW) dan peripapillary retinal nerve fiber layer (pRNFL) pada mata rabun jauh dengan glaukoma

Abstrak

Pengenalan: Pengimbasan pangkal saraf optik di kalangan mata rabun jauh dengan glaukoma adalah sukar disebabkan ciri-ciri pangkal saraf optik yang luar biasa. pRNFL dan BMO menggunakan rujukan anatomi yang berbeza untuk mengukur ketebalan lapisan saraf retina.

Tujuan: Untuk mengenalpasti keseirasan diagnostik antara BMO-MRW dan pRNFL di kalangan mata glaukoma yang berbeza status rabun jauh.

Kaedah: Kajian pemerhatian prospektif.

Kaedah: Empat puluh tiga mata merangkumi glaukoma prima sudut buka, glaukoma tekanan normal dan glaukoma prima sudut tutup dengan status rabun jauh yang berbeza termasuk dalam kajian. Pengukuran geometrik tisu rim neuroretina dilakukan dengan Spectral Domain Optical Coherent Tomography (SD-OCT) dengan dua cara pengukuran yang berbeza iaitu BMO-MRW dan pRNFL. Klasifikasi kualiti pengimbasan dan keseirasan diagnosis kedua-dua kaedah pegimbasan dibandingkan dengan ujian statistik McNemar's. Pengiraan statistik Fisher's dijalankan untuk meninjau hubungan klasifikasi kualiti pengimbasan dengan status rabun jauh.

Hasil: BMO-MRW mempunyai peratusan kualiti pengimbasan yang lebih tinggi berbanding pRNFL (*p = 0.004*). BMO-MRW boleh mendapatkan kualiti pengimbasan yang bagus untuk semua katogori rabun jauh yang mempunyai glaukoma. Sebaliknya, pRNFL menunjukkan perbezaan statistik antara rabun jauh paras rendah, serdahana and tinggi (*p = 0.001*). pRNFL sukar dikenalpasti pada mata yang mempunyai paras rabun jauh yang tinggi. Keserasian diagnosa antara dua cara pengimbasan adalah 48.4% (*p = 0.002*). Keserasian adalah tinggi pada mata rabun jauh paras rendah (66.7%), diikuti dengan rabun jauh paras sederhana (28.6%) dan rabun jauh paras tinggi (16.7%).
Kesimpulan: BMO-MRW mempunyai ciri-ciri pengimbasan diagnosa yang lebih jitu berbanding pRNFL. Kualiti pengimbasan perlu diambilkira semasa mentafsir keputusan OCT untuk mendapatkan keputusan yang lebih tepat.

Kata kunci: Bruch's membrane opening-minimum rim width, glaukoma, optical coherence tomography, peripapillary retinal nerve fibre layer, rabun jauh,

Introduction

Medical imaging technology has advanced dramatically in recent years and enables improvement in non-invasive microscopic visualization of the ocular structures. These additional data can help clinicians in understanding the disease in more depth and aid in diagnosing glaucoma and providing better clinical care for patients. The impact of medical imaging in clinical practice is evidenced by the significant increased application of medical imaging in diagnosing and monitoring of glaucoma since the last decade.[1] Therefore, accuracy and measurement reproducibility of retinal nerve fibre layer (RNFL) measurement is crucial.

Myopia is a known risk factor for glaucoma.[2,3] The risk of developing glaucoma in myopia increases up to three-fold as the degree of myopia increased.[2,3] In addition, it is a challenge to diagnose glaucoma in myopic eyes due to atypical myopic optic disc morphology and myopic visual field defect. A study using optical coherence tomography (OCT) also revealed that the average RNFL thickness decreased with increasing ocular axial length and negative refractive power.[4] These myopic changes may mimic changes of the optic disc, visual field defects, and RNFL thickness in glaucoma. For these reasons, it is important for clinicians to be able to differentiate glaucoma progression from pure ocular myopic changes, especially in glaucoma patients with myopia. It has been shown that OCT technology is more accurate than conventional clinical assessment of optic disc margins in identifying glaucomatous optic discs in myopic eyes.[5]

Anatomically, Bruch's membrane is essential for the presence of retinal pigment epithelium cells and choriocapillaris. Bruch's membrane opening-minimum rim width (BMO-MRW) measures the minimum distance between Bruch's membrane

opening (BMO) and the internal limiting membrane (ILM) at the cross-section image of the optic nerve head.[6-9] On the other hand, peripapillary retinal nerve fibre layer (pRNFL) measures the peripapillary thickness of the uppermost hyper-reflective retinal layer, which represents the unmyelinated axons of ganglion cells. Studies have shown that both BMO-MRW and pRNFL are comparable in diagnostic performance.[10] However, we have observed a slight discrepancy, especially in highly myopic discs. The aim of this study was to evaluate the diagnostic agreement between BMO-MRW and pRNFL in glaucomatous eyes with varying degrees of myopia.

Materials and methods

Patients
This cross-sectional, observational study was conducted at the eye clinic, Department of Ophthalmology, Hospital Sultanah Bahiyah, Alor Setar, Malaysia. Inclusion criteria were myopic patients with primary open-angle glaucoma (POAG), normal-tension glaucoma (NTG), and primary angle-closure glaucoma (PACG). Exclusion criteria were concomitant ocular disease other than glaucoma and eyes with history of ocular surgery other than cataract surgery. pRNFL defect was classified according to OCT artefact as described by Liu *et al.*[12] This study was approved by the Ministry of Health Malaysia Medical Research Ethic Committee (identifier: NMRR-17-87834292). Written informed consent was obtained from all subjects and the study adhered to the tenets of the Declaration of Helsinki.

Diagnosis of glaucoma
In this study, glaucoma was defined clinically by documented evidence of progression in characteristic glaucomatous changes in the optic nerve head and visual field. Visual field assessment was performed with the Swedish Interactive Threshold Algorithm (SITA) program 24-2 standard automated perimetry using the Humphrey Field Analyzer (Humphrey Instruments Model Model 740; Carl Zeiss Meditec, Dublin, CA, USA). The visual field changes were considered to be glaucomatous if the changes fulfilled the Anderson criteria and the criteria were met on at least two consecutive visual field tests.[29] The three criteria were Glaucoma Hemifield Test (GHT) outside normal limits; a cluster of three or more non-edge points in a location typical for glaucoma, all of which were depressed on the pattern deviation plot at a p < 5% level and one of which was depressed at a p < 1 % level; and a corrected pattern standard deviation (PSD) p < 5 %. Patients with visual field defects due to other ocular pathologies were excluded from the study. Findings were verified independently by two fellowship-trained glaucoma consultants (AMS and CTW). We excluded patients with vision worse than 6/12 and epiretinal membrane as these are associated with OCT segmentation artefacts.[12]

Myopic status

Myopic status was defined as low myopia (-0.5 D to < -3.0 D), moderate myopia (-3.0 D to -6.0 D), and high myopia (> -6.0 D).

Optic nerve head RNFL measurement

The thickness of optic nerve head RNFL was measured by spectral domain optical coherence tomography (SD-OCT) (Spectralis with Glaucoma Module Premium Edition Software; Heidelberg Engineering, Heidelberg, Germany) with two different methods of scanning: BMO-MRW and pRNFL thickness at the same visit. A single experienced operator measured pRNFL and BMO-MRW. Pharmacology pupillary dilatation was not required, and the scanning room was darkened for mydriatic pupillary effect. Participants had a short break of 10 minutes between sessions. pRNFL was measured in a 6° peripapillary circle with radial pattern comprising 24 angularly equidistant, high-resolution 15° B-scan, centred on the optic disc centre and aligned with the fovea. Meanwhile, the BMO-MRW scan was done around the optic disc area with autodetection of BMO by the OCT software. As variation in relative foveal position would affect the sectoral neuroretinal rim analysis,[13] foveal positioning and eye tracking systems were activated as a reference to minimize intra-individual and inter-individual variability.[6,8,14] Variation of optic nerve head global thickness for each modality was compared to determine the agreement between both modalities. The entire OCT scans were checked for accuracy of segmentation results using the Heidelberg Eye Explorer Software tool (Software version 6.0.11.0, Heidelberg Engineering, Heidelberg, Germany). Segmentation errors were manually refined to achieve an accurate delineation of the anterior RNFL border (between the ILM and vitreous) and posterior border of the RNFL (between the ganglion cell layer and RNFL). OCT artefacts that required manual correction were: incorrect segmentation of the anterior RNFL; posterior RNFL misidentification; incomplete segmentation; and decentred scan where the optic nerve head was 10% off-centre of the peripapillary circular scan. The BMO point at each segmentation was examined to ensure the correct location was measured. Incorrect locations were manually realigned. The OCT glaucoma classification for each scan (normal, borderline, or abnormal) was subsequently exported. Global OCT glaucoma classification was used for analysis.

Poor quality scans in our study were defined as error of RNFL layer delineation where manual correction was impossible. The errors were: a portion of RNFL across its entire thickness was completely black or indistinguishable from background noise; cut edge artefact was defective where lateral edge of RNFL was truncated abruptly; peripapillary atrophy-associated artefacts; or any condition where identification of the RNFL layer was impossible. Motion artefacts attributed to patient movement during scanning and poor signal defined as quality score less than 15 were excluded from our study. In addition, failing to identify three consecutive BMO points was defined as poor quality of BMO in our study.

Statistical analysis

The comparison of scan quality classification, as well as the diagnosis classification by pRNFL thickness and BMO-MRW were performed using exact McNemar's test. Fisher's exact test was used to assess the association between the summary of scan quality classification with the patient's myopic status. A generalized McNemar or Stuart–Maxwell test was used to determine whether the classification of the optic discs (*i.e.*, within normal limits, borderline, or outside normal limits) among glaucoma patients with myopia by BMO-MRW and pRNFL thickness had the same distribution. All *p*-values reported were two sided, and a *p*-value of less than 0.05 was considered significant. Data were analysed using Stata software (Stata/SE 14, College Station, TX, USA).

Results

A total of 43 eyes, of which 26 (60.5%) were POAG, 12 (27%) were NTG, and 5 (11.6%) were PACG, were included in our study. Mean age of patients was 63 ± 12.9 years of

Table 1. Demographic data

	Degree of myopia, *n* (%)			*p*-value[a]
	Low (*n* = 19)	Moderate (*n* = 8)	High (*n* = 16)	
Age, years*	70.16 (7.70)	50.38 (16.20)	60.88 (11.09)	< 0.001b
Gender				
Female	6 (31.6)	5 (62.5)	6 (37.5)	0.390
Male	13 (68.4)	3 (37.5)	10 (62.5)	
Ethnicity				
Malay	11 (57.9)	5 (62.5)	5 (31.3)	0.269
Chinese	8 (42.1)	3 (37.5)	9 (56.3)	
Siamese	0 (0.0)	0 (0.0)	2 (12.5)	
Glaucoma				
POAG	9 (47.4)	6 (75.0)	12 (75.0)	0.237
NTG	6 (31.6)	1 (12.5)	4 (25.0)	
PACG	4 (21.1)	1 (12.5)	0 (0.0)	

NTG: normal-tension glaucoma; PACG: primary angle closure glaucoma; POAG: primary open-angle glaucoma
*Numerical data reported as mean (standard deviation)
[a]Fisher's exact test
[b]One-way ANOVA. Post-hoc Bonferroni tes

age. Twenty-six (60%) males and 17 (40%) females were included in the study. There was no statistically significant difference between the study group (Table 1).

Scan quality
BMO-MRW had a higher percentage of good quality scans compared to pRNFL. Up to three-quarters of the eyes with poor quality scans using pRNFL obtained good quality scans when performed with BMO-MRW. However, there were no poor quality scans in BMO-MRW for eyes with good quality scans with pRNFL. Only three eyes were classified as poor quality with both modalities. There was a statistically significant different in image quality obtained using BMO-MRW and pRNFL (p = 0.004) (Table 2).

On further analysis, all three poor quality scans with both modalities were highly myopic eyes. BMO-MRW obtained equally good quality scans for different myopic degrees. On the other hand, 10 out of 12 cases of poor-quality scans using pRNFL occurred in highly myopic eyes. pRNFL demonstrated a significant statistical difference between different myopic degrees (p = 0.001) (Table 3). However, there was no difference between myopic degrees when using BMO-MRW (Table 3). Hence, good quality scans were able to be obtained by using BMO-MRW in glaucomatous eyes with different degrees of myopia (Table 3). RNFL was difficult to identify in highly myopic glaucoma eyes as compared to low and moderately myopic glaucomatous eyes by pRNFL. pRNFL failed to obtain a good quality scan in 12 cases. However, good quality scans were obtained in 9 of 12 cases by BMO-MRW.

Table 2. Scan quality: pRNFL and BMO-MRW

		BMO-MRW, n (%)		*P*-value[b]
		Good quality	**Poor quality**	
pRNFL	**Good quality**	31 (72.1)	0 (0.0)	0.004
	Poor quality	9 (20.9)	3 (7.0)	

BMO-MRW: Bruch's membrane opening-minimum rim width; pRNFL: peripapillary retinal nerve fibre layer
[b]Exact McNemar's test

Table 3. pRNFL and BMO-MRW: scan quality by myopic degree

Parameter	Scan quality	Myopic status, I (%)			*P*-value[c]
		Low (n = 19)	**Moderate** (n = 8)	**High** (n = 16)	
pRNFL	Good	18 (41.9)	7 (16.3)	6 (14.0)	0.001
	Poor	1 (2.3)	1 (2.3)	10 (23.2)	
BMO-MRW	Good	19 (44.2)	8 (18.6)	13 (30.2)	0.129
	Poor	0 (0.0)	0 (0.0)	3 (7.0)	

BMO-MRW: Bruch's membrane opening-minimum rim width; pRNFL: peripapillary retinal nerve fibre layer
[c]Fisher's exact test

Table 4. Agreement between BMO-MRW and pRNFL*

Myopic status	pRNFL	BMO-MRW n (%)			Observed agreement[d]	Kappa, K (SE)[d]	p-value[d]
		IN	BL	OUT			
Low	IN	5 (27.8)	3 (16.7)	0 (0.0)			
	BL	0 (0.0)	1 (5.6)	0 (0.0)			
	OUT	2 (11.1)	1 (5.6)	6 (33.3)	66.7%	0.48 (0.16)	0.001
pRNFL Moderate	IN	1 (14.3)	1 (14.3)	0 (0.0)			
	BL	1 (14.3)	0 (0.0)	0 (0.0)			
	OUT	1 (14.3)	2 (28.6)	1 (14.3)	28.6%	0.03 (0.20)	0.445
High	IN	1 (16.7)	0 (0.0)	0 (0.0)			
	BL	0 (0.0)	0 (0.0)	0 (0.0)			
	OUT	2 (33.3)	3 (50.0)	0 (0.0)	16.7%	0.09 (0.08)	0.137

*Twelve cases of pRNFL were excluded due to poor quality and unable to be identified, either with one parameter or both (missing in myopic degree of 1 low case, 1 moderate case, 10 high cases). The frequencies and percentages are reported based on available information.
IN: Within normal limits (above the 5th percentile of eyes in the reference database).
BL: Borderline (between 1st and 5th percentile of eyes in the reference database).
OUT: Outside normal limits (below the 1st percentile of eyes in the reference database).
[d] Kappa (K) was interpreted as poor agreement: < 0.00; slight agreement: 0.00–0.20; fair agreement: 0.21–0.40; moderate agreement: 0.41–0.60; substantial agreement: 0.61–0.80; almost perfect agreement: 0.81–1.00, according to Landis and Koch (1977).

Diagnostic agreement

Further analysis was performed after excluding poor quality scans and including only good quality scans. The diagnostic agreement between BMO-MRW and pRNFL which adhered to the criteria of "above 5th percentile", "between 1st and 5th percentile", and "below 1st percentile" of the reference database as interpreted by OCT was 48.4% (15/31) (p = 0.002) (Table 4). By reconsidering only "below the 1st percentile" of eyes in the reference database as abnormal, as has been practiced clinically, the diagnostic agreement increased to 67.8% (21/31) (p = 0.754). The observed agreement was higher in low myopia (66.7%), followed by moderate myopia (28.6%), and high myopia (16.7%) (Table 4).

Discussion

SD-OCT technology allows good visualization of the optic nerve head. Termination of Bruch's membrane can be easily identified in most cases. This is because the axons of the optic nerve exit the eye through the BMO. Thus, BMO is the best reference point for RNFL measurement.[15] BMO-MRW measures the shortest distance between BMO and ILM, allowing measurement of the oblique insertion of RNFL regardless of the severity of tilted optic disc in myopic eyes. On the contrary, pRNFL measures RNFL thickness at a fixed circumference around the optic disc. In our study, we found some differences between the two modalities according to degree of myopia.

Scan quality

We observed better quality imaging of RNFL in glaucomatous optic disc of varying myopic degrees using BMO-MRW as compared to pRNFL, especially in highly myopic patients. pRNFL failed to obtain a good quality scan in the 12 cases. However, good quality scans were obtained in 9 of 12 cases by BMO-MRW. Both modalities produced poor quality scans in the same three highly myopic eyes. Hwang *et al.* found that 7% of detected BMO locations were not consistent, which was associated with high myopia.[16] Inconsistency was found at the beta zone of the peripapillary zone of the optic disc. This was due to neural retinal thinning secondary to both glaucomatous changes and high myopia. For the same reason, high myopia was associated with failed accurate delineation of retinal layers of pRNFL automated scans.[12,17] Furthermore, advanced stage of glaucoma was shown to be associated with artefacts in RNFL scans.[12] This is likely due to reduced RNFL refractivity, which leads to algorithm failures.[12]

Diagnostic agreement

The observed diagnostic agreement was higher in low myopia, followed by moderate myopia and high myopia in our study. Normal eyes with high myopia of -6 D and greater have been shown to have a substantial proportion of false positive

errors.[18] A previous study demonstrated lower sensitivity of both BMO-MRW and pRNFL thickness in myopic eyes (71% at 90% specificity).[10] Sensitivity was higher after excluding subjects with myopia exceeding -6 D.[10] The reported area under the curve for pRNFL in myopic eyes ranges from 0.84 to 0.98.[19-22] Shoji *et al.* found that pRNFL measurement was significantly related to refractive error and glaucoma.[20] However, BMO-MRW showed a lower rate of false positives compare to pRNFL.[23] In our study, the lowest agreement was observed in highly myopic eyes.

Causes of poor quality scans
Two major factors contribute to the difference in the quality of scan obtained. The first factor is the variation in scanning technology. The second factor is the anatomical variation of optic discs due to degree of myopia.

Scanning method
BMO is a stable fixed opening through which all axons exit the eye. BMO-MRW precisely determined the BMO at each point of the optic nerve head margin. Conversely, pRNFL measures RNFL in a fixed circular peripapillary area. Although circular scans can be done in three different circular areas in a pRNFL scan, inter-circular variations occur due to anatomical variations in myopic eyes.

Anatomical variation and changes in myopic eye
Anatomically, the optic nerve head can be regarded as an aperture with three-layers: the innermost aperture of Bruch's membrane, a central aperture in the choroid bordered by the peripapillary border tissue, and an external aperture of peripapillary sclera covered by fenestrated lamina cribrosa. These three apertures fit perfectly with each other. However, the position of these three apertures moves as the globe elongates in axial myopia. Thus, tilting of the optic nerve is observed in myopic eyes where the temporal portion of the optic nerve has a greater rotation compared to the nasal portion in the process of globe elongation. Rotation of the optic nerve causes shifting of the RNFL entering the optic nerve head. In addition, high myopia of -8.0 D or more has been shown to have larger optic disc size with increasing myopia.[24] This is due to enlargement of the optic nerve head as a result of the expansion and stretching of the optic nerve canal and lamina cribrosa.

Th peripapillary region of highly myopic optic discs shows prominent peripapillary atrophy involving the outer retina, retinal pigment epithelium, and choroid. Therefore, evaluation of glaucoma in myopic eye is challenging as the measurement of RNFL thickness in this area is not accurate.[25-27] RNFL distribution is thinner on average in the superior, nasal, and inferior sectors of highly myopic eyes. The temporal RNFL is thicker, with temporal shift in superior and inferior peak area [27].

Conus temporalis or myopic crescent is a moon-shaped feature that develops at the temporal disc border of myopic eyes due to atrophic changes and elongation of the eye.

The limitation of normative data in myopic eyes in commercially available OCT must be considered. As such, the eye with and without myopia cannot be compared with the same set of normative references.

Limitations
There are limitations in our study. A larger sample size would have provided a better overview of the results presented. However, we were unable to proceed further due to various technical issues. The study was conducted in a limited time frame due to financial and resource constraints. Secondly, there were no normal controls in our study. We may extend our study to include normal myopic subjects in the future. Third, the current inclusion of refractive error in our study was based on objective refraction. It would be desirable to include axial length in future studies.

Conclusion

BMO-MRW is a better diagnostic imaging modality than pRNFL for glaucoma, especially for highly myopic eyes. Scan quality must be considered when interpreting OCT results in our daily clinical practice.

Declarations

Authors' contributions
CTW: study design, data collection, article writing, critical revision, final approval; TJP: proofreading; THA: statistics; FJ: supervision, AMS: supervision.

Ethics approval and consent to participate
This study was approved by the Ministry of Health Malaysia Medical Research Ethic Committee (identifier: NMRR-17-87834292). Written informed consent was obtained from all subjects and the study adhered to the tenets of the Declaration of Helsinki.

Consent for publication
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