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## **Original Article**

# Effect of high myopia on glaucoma diagnostic parameters measured with optical coherence tomography

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#### ABSTRACT

**Background:** We examined the influence of high myopia on conventional spectral-domain optical coherence tomographic parameters and assessed the macular ganglion cell complex thickness to macular outer retinal thickness ratio as a new optical coherence tomography parameter.

Design: Prospective cross-sectional study.

- **Participants:** Sixty normal and 30 highly myopic eyes (refractive error more than –6 D).
- **Methods:** We used the RTVue-100 to measure macular ganglion cell complex and circumpapillary retinal nerve fibre layer thickness, global loss volume, and focal loss volume and then calculated the ganglion cell complex thickness to macular outer retinal thickness ratio.
- Main Outcome Measures: Each parameter was compared between the two groups. Using the area under receiver operating characteristics curve, the classification abilities of optical coherence tomography parameters were examined in highly myopic eyes.
- **Results:** Between normal and highly myopic eyes, we found significant differences in ganglion cell complex and retinal nerve fibre layer thickness, global loss

volume and focal loss volume. The new ratio parameter was not significantly different between groups (55.74% *vs.* 54.50%). The area under receiver operating characteristics curve was 0.775 (P < 0.01) for retinal nerve fibre layer thickness, 0.721 (P < 0.01) for ganglion cell complex thickness and 0.588 (P > 0.05) for the new ratio parameter.

- **Conclusions:** Although refractive status significantly affected conventional optical coherence tomography parameters, the new ratio parameter may not be influenced by refractive error. Therefore, a normative database for healthy highly myopic eyes may not be necessary if ratio parameter is used.
- **Key words:** axial length, ganglion cell complex, high myopia, optical coherence tomography, ratio.

#### INTRODUCTION

The risk of glaucoma in myopic eyes is higher than in non-myopic eyes.<sup>1</sup> However, myopic disc structure may vary widely making images of them difficult to interpret; myopic discs may mask early glaucomatous damage. Spectral-domain (SD) optical coherence tomography (OCT) has enabled automatic measurements of macular ganglion cell complex (GCC) thickness. This includes the thickness of the nerve fibre, ganglion cell and inner plexiform layers.<sup>2</sup>

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The RTVue-100 OCT (Optovue Inc., Fremont, CA, USA) is a new SD-OCT system that attempts to recognise glaucoma damage using GCC thickness and global loss volume (GLV).<sup>3-5</sup> However, average GCC thickness decreases in myopia, as axial length increases.<sup>6,7</sup> Therefore, GCC thickness of both glaucomatous and myopic eyes is thinner than in healthy, emmetropic eyes. In eyes with both glaucoma and myopia, it is difficult to determine whether GCC thickness is decreased because of myopic changes or because of glaucomatous damage; this has limited the use of SD-OCT to diagnose glaucoma in myopic patients. We recently found a positive relationship between GCC thickness and outer retinal (OR) thickness in healthy Japanese eyes8 and introduced new OCT diagnostic parameters.<sup>8,9</sup> These included the GCC/OR thickness ratio (G/O ratio) and the GCC/total retinal thickness ratio (G/T ratio). We reported a G/O ratio of 55.7% in healthy eyes and 45.1% in eyes with primary open-angle glaucoma (POAG) and that the area under the receiver operating characteristics curve (AUROC) for the G/T ratio was significantly higher than circumpapillary (cp) retinal nerve fibre layer (RNFL) thickness in early stage of glaucoma.<sup>8,9</sup>

Here, we evaluate how high myopia influences both conventional OCT parameters and the new OCT ratios in healthy eyes. Using the receiver operating characteristic (ROC) curve, we analysed the performance of the OCT result, which classified non-glaucomatous highly myopic individuals as abnormal.

#### **METHODS**

Potential participants were examined between October 2012 and June 2013 at the Department of Ophthalmology of Toho University Ohashi Medical Center in Tokyo, Japan. The Institutional Review Board for Human Research at the Toho University Ohashi Medical Center approved the study and its consent form (authorization number 12–77), which followed the tenets of the Declaration of Helsinki. After written informed consent was obtained, participants were enrolled.

All participants underwent complete ophthalmologic examination with review of their medical and family history. We performed visual acuity testing (including refraction), slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry and dilated stereoscopic fundus examination. Visual field (VF) sensitivity was determined using a Humphrey Field Analyzer (Humphrey–Zeiss Systems, Dublin, CA, USA) with 24-2 Swedish Interactive Threshold Algorithm standard automated perimetry. The VF was considered to be reliable when fixation losses

were <20% and both false-positive and falsenegative rates were <15%. Anderson's criteria were used to define abnormal VF results and included glaucoma hemifield test outside normal limits, pattern standard deviation (PSD) probability <5% or a cluster of  $\geq 3$  adjacent non-edge points in typical glaucomatous locations. All depressed points on the pattern deviation plot needed to be at a significance of P < 0.05, with one at P < 0.01. Axial length was measured with the IOLMaster (Carl Zeiss Meditec, Jena, Germany) and non-cycloplegic refraction was performed using an auto ref/keratometer (ARK-530; Nidek, Aichi, Japan). The refraction was further refined subjectively by experienced ophthalmologists. Refraction data was converted to spherical equivalent (SE), which was calculated by adding the spherical refractive error (in dioptres [D]) to one-half of the cylindrical refractive power. Participants were excluded if they had a history of intraocular surgery or retinal laser procedures. We also excluded subjects with a possible history of elevated intraocular pressure (IOP) (e.g. iridocyclitis, ocular trauma), other intraocular eye disease, family history of glaucoma in a first-degree relative, diabetes or any other diseases that could affect the VF (e.g. pituitary lesions, demyelinating disease). Subjects were healthy individuals who had an IOP of <21 mm Hg, a normal optic nerve head (ONH) appearance, normal open anterior chamber angles, normal VF test results, a bestcorrected decimal visual acuity  $\geq 1.0$ , an SE between +1.00 and -12.00 D, and a cylindrical refractive error ≤3.00 D. The ONH appearance was considered normal if all of the following were met: symmetrical vertical cup-to-disc (C/D) ratio <0.7, uniform neuroretinal rim, and no visible RNFL defects nor optic nerve changes (e.g. diffuse or localized rim thinning, disc haemorrhage, vertical C/D ratio >0.2 different from the fellow eye). Subjects with myopic macular degeneration, obvious posterior staphyloma, obvious tilted discs or peripapillary atrophy extending outside the measurement circle of the OCT were excluded. Subjects were divided into two categories: normal (SE >-6.00 D) and highly myopic (SE  $\leq$ -6.00 D). Only one eye from each participant was included in analyses. When data from both eyes was eligible for analysis, the eye with the higher signal strength index (SSI) was selected.

## Macular parameters and retinal nerve fibre layer imaging

The OCT measurements were obtained using the RTVue-100 (software version 4.0.5.39), as previously described.<sup>10</sup> Following pupil dilation, a skilled operator obtained high-quality OCT images. Only scans with an SSI higher than 45 were used in analyses. The GCC scan algorithm consists of collecting 15

vertical line scans covering a 7 mm  $\times$  7 mm square region. The computer then created a 6 mm  $\times$  6 mm map, which corresponds to approximately 20° on the VF map. The GCC scanning protocol was used for GCC, macular total retina and OR thickness measurements. All measurements were calculated in three ways: global average, superior hemisphere average and inferior hemisphere average.

The ONH protocol was used for cpRNFL thickness measurements. By using OCT-generated (video baseline protocol) fundus pictures, we were able to manually trace ONH contours. The RNFL thickness was automatically measured on a 3.45-mm-diameter circle centred on the optic disc. The ONH protocol scan ring did not pass over the area of peripapillary atrophy, and RNFL thickness measurements represented mean thickness of a 360-degree area. For each scan pattern, two image series were saved, but only the one with the higher SSI was further used in study analyses.

### Global loss volume, focal loss volume and retinal thickness ratios

The two original RTVue-100 parameters for the GCC scan are GLV and focal loss volume (FLV). Detailed analysis methods have been reported elsewhere.<sup>2,3</sup> In brief, GLV measures the average amount of GCC loss over the entire GCC map and is based on the fractional deviation (FD) map. The FLV measures the average focal loss over the entire GCC map and is based on both the FD and pattern deviation maps. Ratio parameters were calculated using the following published formula:<sup>8,9</sup>

 $G/O \text{ ratio } (\%) = (GCC \text{ thickness}/OR \text{ thickness}) \times 100$ (1)

Table 1. Subject demographic parameters

G/T ratio (%) = (GCC thickness/macular (2) total retinal thickness)×100

#### **Statistical analysis**

Differences between groups were assessed using a Mann-Whitney U-test. Multiple regression analysis was used to evaluate the relationships between GCC thickness and OR thickness, age and axial length. The ROC curves were used to assess the ability of each variable to differentiate between highly myopic eyes and normal eyes. The ROC curve also shows the trade-off between sensitivity and specificity. An AUROC of 1.0 represents perfect discrimination, whereas an AUROC of 0.5 represents chance discrimination. The MedCalc software (version 12.3.0; MedCalc Software, Mariakerke, Belgium) was used to draw and compare ROC curves. All other statistical analyses were performed using SPSS statistical software (version 17.0; SPSS Inc., Chicago, IL). A *P* value of <0.05 was considered statistically significant.

#### RESULTS

#### **Participants**

One hundred eyes initially qualified for study inclusion, but 10 eyes were excluded because of poor OCT image quality. Four of these 10 eyes had an SSI of <45 and the remaining six eyes had segmentation errors. Therefore, the final analyses included 90 eyes. The normal group was made up of 60 eyes (60 subjects) and the highly myopic group was made up of 30 eyes (30 subjects). The characteristics of these groups are summarized in Table 1. Significant

	Normal eyes ( $n = 60$ )		Highly myopic eyes ( $n = 30$ )		Р
Gender					0.119 <sup>:</sup>
Male	42	2	16		
Female	18		14		
	Mean	Median (Interquartile range)	Mean	Median (Interquartile range)	
Age (years)	35.83 ± 7.13	36.50 (12.75)	33.63 ± 6.66	32.00 (12.25)	0.174
Spherical Equivalent (D)	$-2.4 \pm 2.0$	-2.3 (3.2)	-8.3 ± 1.4	-8.3 (2.7)	< 0.001
Axial length (mm)	24.71 ± 1.21	24.63 (2.04)	26.83 ± 0.97	26.72 (1.71)	< 0.001
IOP (mmHg)	13.86 ± 2.45	14.00 (4.00)	15.13 ± 2.37	16.00 (2.50)	0.024
MD in HFA (dB)	-0.55 ± 1.01	-0.50 (1.65)	$-0.89 \pm 0.98$	-0.94 (1.09)	0.099
PSD in HFA (dB)	$1.45 \pm 0.27$	1.45 (0.39)	$1.49 \pm 0.27$	1.46 (0.32)	0.705

Data are presented as mean  $\pm$  standard deviation, where applicable. <sup>†</sup>Indicates statistical significance (P < 0.05). <sup>‡</sup>Indicates  $\chi^2$  test. D, dioptre; HFA, Humphrey Field Analyzer; IOP, intraocular pressure; MD, mean deviation; OR, macular outer retinal thickness; PSD, pattern standard deviation.

differences were found between the groups in SE, axial length and IOP.

#### Optical coherence tomography measurements

No significant difference between the two groups was found in either the G/O or G/T ratio, but significant differences were observed in GCC, FLV, GLV and cpRNFL (Table 2). The effects of OR thickness, axial length and age on GCC thickness for each group are summarized in Table 3. In highly myopic eyes, a significant positive relationship between GCC and OR thickness was found in the superior (P = 0.001) and inferior (P = 0.004) retinal hemispheres, as well as over the entire macula (P = 0.001). In normal eyes, average GCC and superior GCC thicknesses were also significantly associated with OR thickness (P = 0.037 and P = 0.024, respectively). The standardized partial regression coefficient for OR thickness was bigger in the highly myopic group (0.753) than in the normal group (0.285). No significant relationship was found between subject age or axial length and GCC thickness in either study group.

## Diagnostic performance of optical coherence tomography parameters

The AUROC for the average G/O and G/T ratios was significantly lower than the AUROC for the average GCC thickness (P < 0.05). The parameter with the lowest sensitivity at a specificity of >70% was the average G/O and G/T ratios (Table 4). The ROC curves for the average G/O ratio and average GCC thickness are shown in Figure 1.

#### DISCUSSION

In this study, we compared novel SD-OCT glaucoma diagnostic parameters between normal and nonglaucomatous highly myopic eyes. The ratio parameters did not significantly differ between the two groups, but the conventional OCT parameters (i.e. GCC thickness, GLV, FLV, cpRNFL thickness) did.

Highly myopic eyes had significantly longer axial lengths than normal eyes, and IOP in the highly myopic group averaged 1.3 mmHg higher than in the normal group. This observed difference in IOP is in agreement with findings of previous studies.<sup>1,11</sup>

Previous studies have found that both GCC and cpRNFL thicknesses are related to axial length,

**Table 2.** Spectral-domain optical coherence tomography measurements

Mean ± SD     Median     Mean ± SD     Median       (Inter quartile range)     (Inter quartile range)     (Inter quartile range)	0.001
GCC thickness (μm)	0.001
	0.001
Average 94.02 ± 3.73 93.32 (9.00) 09.47 ± 4.23 09.33 (3.30)	0.001
Superior         94.12 ± 6.24         93.27 (9.44)         89.88 ± 4.28         89.74 (5.00)	0.003
Inferior 93.92 ± 5.82 93.92 (8.37) 89.06 ± 4.77 88.94 (6.14)	<0.001 <sup>+</sup>
TR thickness (µm)	
Average         262.85 ± 10.49         261.51 (15.44)         253.80 ± 12.02         253.61 (11.42)	<0.001 <sup>+</sup>
Superior         265.22 ± 11.16         264.74 (16.06)         255.98 ± 11.93         256.20 (14.72)	<0.001 <sup>+</sup>
Inferior 260.40 ± 10.33 258.07 (12.38) 251.47 ± 12.75 252.14 (12.53)	0.001
OR thickness (µm)	
Average 168.83 ± 7.02 167.57 (9.76) 164.33 ± 8.69 164.41 (8.47)	0.007
Superior 171.11 ± 7.28 170.05 (9.29) 166.10 ± 8.63 166.36 (10.47)	0.005
Inferior 166.48 ± 7.06 165.38 (10.87) 162.41 ± 9.21 162.22 (7.78)	0.010 <sup>†</sup>
FLV (%) $0.62 \pm 0.74$ $0.28 (0.86)$ $1.31 \pm 1.58$ $0.86 (1.35)$	0.041 <sup>†</sup>
GLV (%) 6.52 ± 0.53 6.03 (6.92) 9.99 ± 4.12 10.13 (5.22)	0.001
RNFL thickness ( $\mu$ m) 104.06 ± 8.57 103.80 (10.96) 95.84 ± 7.65 94.43 (10.39)	<0.001 <sup>+</sup>
G/O ratio (%)	
Average         55.74 ± 3.43         55.43 (4.50)         54.50 ± 2.15         54.42 (2.63)	0.176
Superior         55.05 ± 3.60         54.68 (3.85)         54.16 ± 2.22         54.01 (3.80)	0.402
Inferior 56.48 ± 3.69 56.16 (5.60) 54.90 ± 2.53 55.32 (3.07)	0.068
G/T ratio (%)	
Average 35.76 ± 1.39 35.69 (1.87) 35.26 ± 0.90 35.24 (1.10)	0.176
Superior 35.47 ± 1.47 35.35 (1.62) 35.12 ± 0.94 35.07 (1.59)	0.402
Inferior 36.06 ± 1.50 35.96 (2.29) 35.42 ± 1.07 35.62 (1.27)	0.068

<sup>†</sup>Indicates statistical significance (P < 0.05). FLV, focal loss volume; GCC, macular ganglion cell complex; GLV, global loss volume; G/O ratio, ganglion cell complex thickness to outer retinal thickness ratio; G/T ratio, ganglion cell complex thickness to total retinal thickness ratio; OR, macular outer retina; RNFL, circumpapillary retinal nerve fibre layer; TR, macular total retina.

Independent variable	Partial Regression coefficient	95% CI		Standardized partial regression coefficient	Р
Normal Eyes					
Average GCC thickness					
Average OR thickness ( $\mu$ m)	0.233	0.015	0.451	0.285	0.037 <sup>+</sup>
Age (years)	-0.029	-0.231	0.173	-0.036	0.776
Axial length (mm)	-0.756	-2.017	0.505	-0.159	0.235
Superior GCC thickness					
Superior OR thickness (µm)	0.269	0.036	0.502	0.314	0.024 <sup>+</sup>
Age (years)	-0.024	-0.247	0.198	-0.028	0.828
Axial length (mm)	-0.537	-1.921	0.848	-0.104	0.441
Inferior GCC thickness					
Inferior OR thickness (µm)	0.171	-0.049	0.391	0.207	0.125
Age (years)	-0.034	-0.241	0.173	-0.042	0.743
Axial length (mm)	-1.005	-2.297	0.286	-0.209	0.125
Highly myopic eyes					
Average GCC thickness					
Average OR thickness ( $\mu$ m)	0.368	0.001	0.563	0.753	0.001+
Age (years)	-0.019	-0.256	0.219	-0.029	0.873
Axial length (mm)	0.565	-0.994	2.125	0.129	0.463
Superior GCC thickness					
Superior OR thickness (µm)	0.396	0.186	0.605	0.798	0.001 <sup>+</sup>
Age (years)	-0.092	-0.337	0.154	-0.143	0.450
Axial length (mm)	0.598	-1.093	2.289	0.136	0.474
Inferior GCC thickness					
Inferior OR thickness (µm)	0.309	0.105	0.514	0.597	0.004 <sup>+</sup>
Age (years)	0.083	-0.191	0.356	0.115	0.539
Axial length (mm)	0.416	-1.326	2.158	0.085	0.628

**Table 3.** Multiple linear regression analysis examining the relationship between ganglion cell complex thickness (dependent variable), and macular outer retinal thickness, age and axial length (independent variables)

<sup>†</sup>Indicates P < 0.05. CI, confidence interval; GCC, macular ganglion cell complex; OR, macular outer retina.

refractive error and age.<sup>6,7,12-15</sup> However, multiple regression analysis in the current study indicated that GCC thickness is not influenced by axial length or age in either normal or highly myopic eyes. This difference may result from the smaller range of refractive errors and age in our study compared with that of Kim and colleagues,6 and Zhao and colleagues.<sup>7</sup> Interestingly, a significant positive relation between GCC thickness and OR thickness was seen in both study groups. We previously found that GCC thickness was significantly correlated with OR thickness in middle-aged participants.8 When the standardized partial regression coefficient between GCC thickness and OR thickness was evaluated in each group, the highly myopic group was highly related, but the normal eve group was only weakly related. We cannot explain this difference between the two study groups.

Diagnosis of glaucoma using imaging instruments is commonly made by referencing normative data with the diagnostic classification (within normal limits, borderline, abnormal) provided in the automated analysis printout. However, cpRNFL and GCC thickness measurements are frequently classified as abnormal in healthy myopic eyes when compared with the normative database.<sup>16-19</sup> This may be explained by the fact that the RTVue-100 normative data was obtained from a group of healthy patients where only 2.8% of myopes had a refractive error of -5.0 D or more.<sup>20</sup> According to the description in the user's manual (User's Manual, Optovue Inc.), the normative database is adjusted for age and race, but not for axial length or refractive error. Thus, normal high myopic databases are required for glaucoma to be accurately diagnosed with OCT measurements. Adjusting normative GCC thickness data for axial length or refractive error would provide better OCT specificity for glaucoma detection.

In our study, highly myopic eyes (SE < -6 D) and normal eyes were compared because there are no ratio parameters in the manufacturer's normative database. The ROC curves were used to assess whether highly myopic eyes were classified as normal or abnormal, compared with normal eyes. As a result, GCC thickness, GLV, FLV and cpRNFL thickness could be used to classify high myopes as abnormal. Therefore, these parameters are effective in classifying both highly myopic and glaucomatous eyes.<sup>2–4</sup> The preperimetric glaucoma discriminating ability using average GCC thickness has been **Table 4.** Comparison of parameters using the area underreceiver operating characteristics curve and sensitivities at fixedspecificities

	Normal vs. highly myopic eyes				
	AUROC (SE)	Р	Sn/Sp (Sp >70%)		
GCC thickness					
Average	0.721 (0.05)	<0.0001	60.00/73.33		
Superior	0.694 (0.06)	0.0005	60.00/70.00		
Inferior	0.735 (0.05)	<0.0001	63.33/70.00		
FLV	0.632 (0.07)¶	0.046	63.33/70.00		
GLV	0.726 (0.05)	<0.0001	63.33/71.67		
RNFL thickness	0.775 (0.05)	<0.0001	73.33/76.67		
G/O ratio					
Average	0.588 (0.06) <sup>†§</sup>	0.147 <sup>++</sup>	23.33/71.67		
Superior	0.554 (0.06) <sup>†§</sup>	0.386 <sup>††</sup>	40.00/70.00		
Inferior	0.618 (0.06) <sup>‡¶</sup>	0.045	33.33/70.00		
G/T ratio					
Average	0.588 (0.06) <sup>†§</sup>	0.147 <sup>++</sup>	23.33/71.67		
Superior	0.554 (0.06) <sup>†§</sup>	0.386 <sup>++</sup>	40.00/70.00		
Inferior	0.618 (0.06) <sup>‡¶</sup>	0.045	33.33/70.00		

<sup>†</sup>Indicates statistical significance (P < 0.05) for comparison of GCC thickness and GLV. <sup>‡</sup>Indicates statistical significance (P < 0.05) for comparison of GCC thickness. <sup>§</sup>P < 0.01 for comparison of RNFL thickness. <sup>¶</sup>P < 0.05 for comparison of RNFL. <sup>††</sup>Indicates that the AUROC was not significantly better than 0.5. AUROC, Area under receiver operating characteristic curve; FLV, focal loss volume; GCC, macular ganglion cell complex; GLV, global loss volume; G/O ratio, ganglion cell complex thickness to outer retinal thickness ratio; G/T ratio, ganglion cell complex thickness to total retinal thickness ratio; RNFL, circumpapillary retinal nerve fibre layer; SE, standard error; Sn, sensitivity; Sp, specificity.



**Figure 1.** Receiver operating characteristics curve of average macular ganglion cell complex (GCC) thickness and ganglion cell complex thickness to outer retinal thickness ratio (G/O ratio).

reported to be 0.74–0.823.<sup>21,22</sup> Our discriminating ability in highly myopic eyes was similar (AUROC range, 0.694–0.735).

No significant differences were observed in either the G/O ratio (normal group = 56%, highly myopic group = 55%) or the G/T ratio (normal group = 36%, highly myopic group = 35%) between highly myopic and healthy eyes in this study. If axial length becomes

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longer, both GCC and OR thickness become thinner and the ratio parameter does not change. Ratio parameters were not useful to classify highly myopic eyes. Further, ratio parameter AUROCs were significantly lower than those of GCC and cpRNFL thickness. Therefore, ratio parameters seem unaffected by high myopia.

An insensitivity to high myopia is a requirement for glaucoma diagnostic parameters. Ratio parameters meet this requirement and appear effective to diagnose glaucoma.<sup>8,9</sup> This is not the case for GCC thickness, which is affected by both glaucoma and high myopia. Therefore, ratio parameters provide better specificity for glaucoma detection; a normative database for healthy highly myopic eyes may not be necessary if ratio parameters are used.

Limitations of our study include its homogeneous (all Japanese subjects) and relatively small sample size. OCT measurements vary between people of different cultures. Africans have a thinner GCC than normal Japanese subjects,23 and a positive relationship between GCC thickness and OR thickness was observed in healthy eyes of Japanese, but not Hungarian, subjects.<sup>24</sup> Further investigations are necessary in other ethnic groups to understand these ethnic differences better. Because the RTVue-100 does not correct for the magnification effects of myopia, there is a chance that our results might have been different with this correction applied. The GCC thickness can be measured using a different OCT, such as 3D-OCT 2000 (Topcon) or RS3000 (Nidek); however, the measurement algorithm may slightly vary with the use of RTVue-100. Therefore, a further investigation is necessary regarding the possibility whether this study could be applied to other OCT devices.

In conclusion, GCC thickness and cpRNFL thickness measurements should be used with caution when analysing eyes with high myopia. The new ratio parameters may not be influenced by high myopia and their use could improve our understanding of retinal thickness analysis using OCT as well as question the need for a separate normative database for healthy highly myopic eyes.

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