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Original article

# Comparison of glaucoma diagnostic accuracy of macular ganglion cell complex thickness based on nonhighly myopic and highly myopic normative database

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ABSTRACT

*Background/Purpose:* To evaluate and compare the diagnostic discriminative ability for detecting glaucoma in highly myopic eyes from a normative database of macular ganglion cell complex (mGCC) thickness based on nonhighly myopic and highly myopic normal eyes.
*Methods:* Forty-nine eyes of 49 participants with high myopia (axial length $\geq$ 26.0 mm) were enrolled. Spectral-domain optical coherence tomography scans were done using RS-3000, and the mGCC thickness/significance maps within a 9-mm diameter circle were generated using built-in software. We compared the difference of sensitivity, specificity, and diagnostic accuracy between the nonhighly myopic database and the highly myopic database for differentiating the early glaucomatous eyes from the nonglaucomatous eyes.
*Results:* This study enrolled 15 normal eyes and 34 eyes with glaucoma. The mean mGCC thickness of the glaucoma group was significantly less than that of the normal group ($p < 0.001$). Sensitivity was 96.3%, and the specificity was 50.0% when using the nonhighly myopic normative database. When the highly myopic normative database was used, the sensitivity was 88.9%, and the specificity was 90.0%. The false positive rate was significantly lower when using the highly myopic normative database ($p < 0.05$).
*Conclusion:* The evaluations of glaucoma in eyes with high myopia using a nonhighly myopic normative database may lead to a frequent misdiagnosis. When evaluating glaucoma in high myopic eyes, the mGCC thickness determined by the long axial length high myopic normative database should be applied.


## 1. Introduction

Glaucoma is a multifactorial optic neuropathy characterized by a progressive loss of retinal ganglion cells, retinal nerve fiber layer (RNFL) thinning, and leading to irreversible visual impairment. Myopia is a refractive error and affects a significant proportion of the population, especially in East Asian countries. Most of the population-based studies and clinical trials have showed that moderate to high myopia is associated with increased risk of primary open-angle glaucoma, normal tension glaucoma, and ocular hypertension.[1,2] However, a myopic optic nerve can pose significant challenges with regard to making the correct diagnosis of glaucoma. They may have considerable morphological variations, e.g., larger disc sizes, tilted disc, shallower optic cups, and peripapillary atrophy.[3] The opportunity and risk of falsely diagnosing a glaucomatous individual as normal or a normal individual as glaucomatous may be high, especially in early glaucomatous damage.

Myopic eyes have longer axial lengths (ALs) and vitreous chamber depths.[4,5] Von Graefe[6], in an anatomical and ophthalmoscopic investigation, first postulated the relationship between long axial length and high myopia. Elongated axial length of the globe leads to various changes in the topography of the posterior pole, with concomitant decreased thickness of the retina, and development of macular pathologic features,[7] which usually affects specificity and sensitivity on glaucoma evaluation.[8,9]

Spectral-domain optical coherence tomography (SD-OCT) is currently the most advanced commercially available application of imaging technology, and it can offer more accurate and reproducible results.[10,11] Glaucoma damage affects retinal ganglion cells, which are

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densely present in the macular region. Several researchers have suggested that macular thickness measurement could be a valuable parameter of glaucomatous structural change, and SD-OCT has enabled automatic assessments of macular ganglion cell complex (mGCC) thickness.[12] This combined inner retinal layers includes retinal nerve fiber layer, ganglion cell layer, and inner plexiform layer.

The thickness of mGCC can be used for early detection of glaucoma,[10] and the study conducted by Kim and colleagues[13] suggested that mGCC thickness measurements may be a good alternative or a complementary measurement to RNFL thickness assessment in the clinical evaluation of glaucoma in patients with high myopia. However, we need to know the mGCC thickness of the normative database in normal eyes, and this database should be obtained from an effective number of normal eyes and include the mGCC thicknesses of various areas around the fovea. Although the normative database is based on statistics, high myopes are usually not included, and therefore the normative database might not represent all patient populations. Thus, myopia can be a confounding factor in the assessment of RNFL thickness attributed to its influence on the RNFL thickness and leads to misdiagnoses.[14]

As AL increases, average mGCC thickness of both high myopic and glaucomatous eyes is relatively less than that in healthy emmetropic eyes. This suggests that axial length should be taken into account when assessing the reliability of OCT data.[14] It is also difficult to differentiate whether lower mGCC thickness is due to myopic changes or because of glaucomatous damage in eyes with both myopia and glaucoma. Even with these new imaging modalities with improved accuracy and precision for detecting glaucoma, OCT technology presents some challenges when evaluating myopic eyes.[15] Development and assessment of other diagnostic parameters of highly myopic globes is necessary to detect glaucoma.

It is known that ocular magnification of retinal images is affected by AL, refractive error, corneal curvature, and anterior chamber depth.[16,17] We should also consider AL-associated ocular magnification when evaluating mGCC thickness in high myopic eyes, as the difference in scanned area can lead to a misdiagnosis.[14]

The RS-3000 SD-OCT (Nidek, Gamagori, Aichi, Japan) may solve these two problems. There are two kinds of normative databases for this SD-OCT device: the original installed age-adjusted reference regular database for eyes with ALs < 26 mm, and an optional database for eyes with ALs between 26 mm and 29 mm for highly myopic eyes.[18,19] This normative database was developed based with data from normal eyes with long AL. Data were collected from Asian individuals by measuring the macular area in three dimensions to obtain retinal thickness.

High or pathologic myopia is typically defined as a refractive correction of −6.00 D or more and an AL > 26.0 mm.[20,21] The purpose of this research was to evaluate the various measurements of diagnostic ability of these two different databases in the RS-3000 SD-OCT device to diagnose glaucoma in Taiwanese eyes with high myopia.

## 2. Methods

### 2.1. Participants

This is an observational cross-sectional study and the participants were informed of the purpose and procedures of the measurements. Medical records of patients with high myopia (AL ≥ 26.0 mm) who were examined at the Glaucoma Clinic of the Department of Ophthalmology, Chang Gung Memorial Hospital, Taoyuan, Taiwan, were reviewed. All of the procedures conformed to the tenets of the Declaration of Helsinki.

All participants had comprehensive ophthalmic evaluation including slit-lamp biomicroscopy, intraocular pressure measurements by Goldmann applanation tonometry, central corneal thickness, gonioscopic examination by a Goldmann three-mirror lens, optic nerve head evaluation and fundus examination, digital color fundus photography (Digital Non-Mydriatic Retinal Camera, Canon, Tokyo, Japan), AL measurements by Optical Biometer AL-Scan (Nidek), central 30-2 Swedish Interactive Threshold Algorithm standard automated perimetry using a Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA), measurements of the best-corrected visual acuity, automatic objective determination of the refractive errors, and SD-OCT examinations (RS-3000; Nidek).

The inclusion criteria were AL ≥ 26.0 mm, best-corrected visual acuity ≥ 20/20 in Snellen equivalents, normal anterior segment, normal and open angle by gonioscopy, presence of RNFL defects on color fundus photographs consistent with the glaucomatous appearances of the optic disc, and the presence of normal or glaucomatous visual field (VF) defects by automated perimetric test.

The exclusion criteria were: previous intraocular or refractive surgery; patients with diabetes mellitus; poorly controlled hypertension; other systemic disease; neurological diseases that might cause VF defects or RNFL damage; and other vitreous retinal disorders that can influence the retinal thickness, such as an epiretinal membrane, degenerative myopia with patchy chorioretinal atrophy or choroidal neovascularization, and low quality SD-OCT images were also excluded. When both of a patient's eyes were eligible, one eye was randomly selected for analysis.

### 2.2. Glaucoma diagnosis

Glaucomatous optic neuropathy was diagnosed when the optic disc had a glaucomatous appearance, for example, localized or diffuse neuro-rim thinning of the optic nerve head and/or RNFL defects corresponding to the glaucomatous VF defects. Glaucomatous visual filed defects were defined as those with one or more of the following criteria with reliable standard automated perimetry results: (1) a cluster of three points with probabilities of < 5% on the pattern deviation map in at least one hemifield, including one point or more with a probability of < 1%, or a cluster of two points with a probability of < 1%; (2) glaucomatous hemifield test results outside the normal limits; and (3) a pattern standard deviation (PSD) beyond 95% of normal limits as confirmed by at least two reliable examinations (false positive/negatives < 15%, fixation losses < 15%).[22]

Eyes were in the normal group if they did not have glaucomatous optic neuropathy appearance, visible RNFL defects, or glaucomatous VF defect on two reliable SAP tests. Participants with preperimetric glaucoma were excluded from this study.

### 2.3. SD-OCT measurement

All participants were imaged with the high-resolution scan procedure of the RS-3000 SD-OCT (Nidek) to obtain images of the mGCC. For wide-area three-dimensional imaging of the posterior pole, we performed OCT raster scanning over a 30 × 30 degree square area with a scan density of 512 A-scans vertically × 128 B-scans horizontally. Image quality was checked carefully and only good-quality scans, defined as scans with signal strength index < 6/10, and without any artifact were used for analysis. The mGCC thickness was calculated with the default software, Navis-EX version 1.4.1 (Nidek). Navis-EX is a viewing combines with image filing software that enables data from various Nidek diagnostic imaging devices to be stored and processed in a centralized database. This program can also correct the effect of the AL-related ocular magnification using a modified formula.[16]After correcting the ocular magnification, the mGCC thickness and significance maps were determined for a 9-mm diameter circle, which centered on the fovea. The mGCC thickness was measured from the internal