Challenges of diagnosing glaucoma in myopic eyes

Qiu, Kunliang

Chapter 9

Effect of optic disc-fovea distance on the glaucoma diagnostic classification of macular inner retinal layers as assessed with OCT in healthy subjects

Kunliang Qiu, Binyao Chen, Jianling Yang, Ce Zheng, Haoyu Chen, Mingzhi Zhang, Nomdo M. Jansonius

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ABSTRACT

Purpose: To determine the influence of the optic disc-fovea distance (DFD) on the glaucoma diagnostic classification based on thickness measurements of macular inner retinal layers with spectral-domain optical coherence tomography (OCT) in healthy subjects.

Methods: A total of 182 eyes from 182 healthy subjects were included (mean [standard deviation] spherical equivalent -0.8 [1.9] D). We performed macula and optic disc imaging with the Topcon 3D-OCT 2000. The thickness of the macular inner retinal layers (macular retinal nerve fiber layer [mRNFL], ganglion cell-inner plexiform layer [GCIPL], and both combined [ganglion cell complex; GCC]) and the corresponding glaucoma diagnostic classifications based on the built-in database were recorded. The occurrence of an abnormal diagnostic classification (occurrence of any thickness variable below the 5th percentile) was related to the DFD and other factors (axial length/refraction, optic disc area, fovea-disc angle, age, gender, image quality, visual field mean deviation, and peripapillary retinal nerve fiber layer thickness), using logistic regression.

Results: Mean (standard deviation) DFD was 4.90 (0.29) mm. A greater DFD was associated with a higher percentage of abnormal diagnostic classification in the OCT parameters describing the thickness of the mRNFL (odds ratio [95% confidence interval] per 0.1 mm increase in DFD: 1.30 [1.13-1.50], P<0.001), GCIPL (1.18 [1.02-1.38], P=0.023), and GCC measurement (1.29 [1.08-1.55], P=0.006).

Conclusions: Eyes with a greater DFD are prone to a false-positive glaucoma classification in the thickness assessment of the macular inner retinal layers. The thicknesses should always be interpreted in the context of DFD.

Introduction

Glaucoma is one of the major causes of irreversible blindness around the world (Weinreb & Khaw 2004; Quigley & Broman 2006). The morphological changes in retinal ganglion cells have been reported to be helpful in the assessment of glaucomatous damage (Desatnik et al., 1996). The spectral-domain optical coherence tomography (SD-OCT) with advances in segmentation algorithm has been emerging as an important technology for in vivo measurements of macular inner retinal layers including the retinal nerve fiber layer (RNFL) and the ganglion cell-inner plexiform layer (GCIPL) (Mwanza et al., 2011). Previous studies have shown that the GCIPL thickness has a similar glaucoma discriminating performance as the peripapillary retinal nerve fiber layer (pRNFL) thickness, both in clinical and in population-based studies (Nouri-Mahdavi et al., 2013; Yang et al., 2015; Springelkamp et al., 2014). However, the discriminative performance of the GCIPL thickness is far from optimal (Nouri-Mahdavi et al., 2013; Yang et al., 2015; Springelkamp et al., 2014; Kim et al., 2015; Leal-Fonseca et al., 2014; Aref et al., 2014).

Several factors including age, gender, axial length, and optic disc area have been shown to be associated with the thicknesses of the macular inner retinal layers (Mwanza et al., 2011; Koh et al., 2012). However, our knowledge concerning the variability of these thicknesses is far from complete. The distance between the optic disc center and the fovea (DFD) is another biometric variable that may influence the macular inner retinal layers. A large DFD may be associated with a stretching of the posterior fundus which may cause a change in the retinal thickness. In our previous study, using a generic segmentation algorithm, we found that the observed thicknesses of the macular inner retinal layers were significantly associated with the DFD (Qiu et al., 2018). The next question is, on how far these associations influence the performance of the built-in software that provides a glaucoma diagnostic classification, which is based on the thicknesses. The diagnostic classification is the primary OCT output used by clinicians.

The aim of this study was to determine the influence of the DFD on the glaucoma diagnostic classification based on thickness measurements of macular inner retinal layers in healthy subjects. For this purpose, we performed SD-OCT measurements in a large group of healthy subjects and related the occurrence of an abnormal diagnostic classification to the DFD and other ocular factors (axial length/refraction, optic disc area, and fovea-disc angle [FDA]), using logistic regression. Analyses were further adjusted for age, gender, image quality, visual field mean deviation, and pRNFL.

Methods

Subjects

One hundred and ninety three Chinese healthy subjects were consecutively recruited from the general clinic of Joint Shantou International Eye Center. All the included subjects underwent a full ophthalmic examination including the measurement of best corrected visual acuity, intraocular pressure (IOP), refraction, and axial length (IOLmaster; Carl-Zeiss Meditec, Dublin, CA), slit-lamp biomicroscopy, and fundus examination. None of the included eyes had any concurrent ocular disease other than a refractive error. If both eyes were eligible, one eye was randomly selected. Subjects were excluded if the spherical equivalent was less than -6.0 diopters (D), the IOP over 21 mmHg, the best corrected visual acuity was less than 20/40, if they had a family history of glaucoma, or if they had a history of intraocular surgery, refractive surgery, neurological disease, macular degeneration, glaucoma, or diabetes. The study was approved by the local ethical committee with written informed consent obtained from each subject before enrolment. The present study followed the tenets of the declaration of Helsinki.

Visual field testing

Visual field testing was performed with standard automated white-on-white threshold perimetry, using the 24-2 SITA standard strategy (Humphrey Field

Analyzer II; Carl Zeiss Meditec, Inc.). Only reliable visual field tests with fixation loss less than 20% and false positive and negative less than 10% were included in the study (Bengtsson et al., 2000; Junoy Montolio et al., 2012). All the included visual field tests were within normal limits in the glaucoma hemifield test (GHT) and had a pattern standard deviation (PSD) p value > 5%.

Optical Coherence Tomography

Each eye was imaged using the Topcon 3D OCT-2000 (software version 8.11; Topcon). Both the GCC 3D Scan 512×128 protocol and the Optic Disc 3D Scan 512×128 protocol were performed. Images with eye movements during image acquisition were excluded and retaken. All the included images had a minimum image quality score of 45 as recommended by the manual of the device (median value 58) (TOPCON CORPORATION 2009). The GCC scan protocol, which has a scan area of 7×7 mm^2, was used for the thickness measurements of the different inner retinal layers in an area of 6×6 mm^2 centered at the fovea. The built-in software was used to generate thickness maps.

We recorded the superior, inferior, and total (average of the superior and inferior) thickness of the macular RNFL (mRNFL), the GCIPL, and the ganglion cell complex (GCC; combination of mRNFL and GCIPL). We also recorded the corresponding classification (within normal limits [green on printout], below P5 [yellow], and below P1 [red]), which is based on the internal normative database. We further recorded, for each of the three layers (mRNFL, GCIPL, and GCC), the fourth thickness parameter as provided by the device, being the presence of an abnormal diagnostic classification in the thickness deviation map. Each thickness deviation map consists of a 10 × 10 grid. A cell in this grid is color-coded yellow or red if the thickness in the concerning cell is below the lower 95% (“borderline”) or 99% (“outside normal limits”) of the centile ranges, respectively. In the present study, an abnormal diagnostic classification in the thickness deviation map was defined as an area of at least three contiguously color-coded (yellow or red) cells, not including the cells directly adjacent to the fovea. The disc area and the

pRNFL thickness were recorded from the analysis printout of the optic disc scan protocol.

Measurement of DFD and FDA

DFD was manually measured on fundus photographs (taken with the fundus camera of the OCT system at an angle of 45° centered at the fovea) with ImageJ software (available in the public domain at http://rsbweb.nih.gov/ij/; www.nih.gov, National Institutes of Health, Bethesda, MD, USA), based on the coordinates of the fovea and the center of the optic disc. Firstly, a rectangle was fitted to the height and width of the ONH manually. Two diagonal lines were drawn, and their crossing was considered as the ONH center. Subsequently, DFD was determined. We also measured the FDA. The FDA was defined as the angle between the disc-fovea line and a horizontal line through the fovea. A positive FDA value indicates that the fovea is located inferiorly with respect to the optic disc center.

Statistical Analysis

Partial correlation tests were performed to determine the effect of DFD on the thickness of the mRNFL, GCIPL, and GCC. These tests were adjusted for axial length, optic disc area, FDA, age, gender, image quality, visual field mean deviation, and average pRNFL thickness. Factors associated with an abnormal diagnostic classification (superior, inferior, or total thickness borderline or outside normal limits, or the presence of an abnormal diagnostic classification based on the thickness deviation map) of the mRNFL, GCIPL, and GCC were evaluated with logistic regression analysis. We used backward stepwise regression by including initially all variables (DFD, axial length, optic disc area, FDA, age, gender, image quality, visual field mean deviation, and average pRNFL thickness) and subsequently removing, one at a time, those variables with $P>0.05$, starting with the variable with the highest P value. A P value less than 0.05 was

considered statistically significant. The statistical analyses were performed by using the SPSS software (ver. 22.0; SPSS Inc, Chicago, IL).

Results

Eleven subjects were excluded because of an unreliable visual field test (5 subjects), poor quality of the fundus photographs (4 subjects), or poor OCT scan quality (2 subjects). As a result, we included 182 eyes from 182 subjects (106 females and 95 right eyes). Table 1 shows the demographics of the study population. The mean (standard deviation [SD]; range) DFD was 4.90 (0.29; 3.98 to 5.66) mm. Table 2 demonstrates the associations between DFD and mRNFL, GCIPL, and GCC thickness. DFD, adjusted for other covariates, correlated negatively with all the thickness measurements of the macular inner retinal layers (all $P \leq 0.001$).

Table 1. Characteristics of the study population (n=182)

	Mean ± SD	Range
Age, y	43.8 ± 15.6	20 to 78
Refractive error, D	-0.80 ± 1.92	-6.00 to 2.75
Axial length, mm	23.63 ± 1.11	20.74 to 26.70
Visual field mean deviation, dB	-1.15 ± 1.23	-6.67 to 1.78
DFD, mm	4.90 ± 0.29	3.98 to 5.66
FDA, deg	9.60 ± 3.48	-2.56 to 21.10
Disc area, mm^2	2.24 ± 0.39	1.28 to 3.28
Average pRNFL, μm	107.6 ± 8.8	79 to 131
GCC scan image quality	57.8 ± 4.3	45 to 66
Average mRNFL, μm	36.7 ± 4.0	27 to 48
Average GCIPL, μm	69.7 ± 4.6	57 to 82
Average GCC, μm	106.5 ± 7.0	89 to 121

Table 2. Associations between DFD and the average thickness of the macular inner retinal layers, adjusted for axial length, optic disc area, FDA, age, gender, image quality, visual field mean deviation, and average pRNFL thickness (n=182; partial correlation analysis)

	r	P
Total mRNFL	-0.49	<0.001
Superior mRNFL	-0.39	<0.001
Inferior mRNFL	-0.50	<0.001
Total GCIPL	-0.28	<0.001
Superior GCIPL	-0.25	0.001
Inferior GCIPL	-0.28	<0.001
Total GCC	-0.46	<0.001
Superior GCC	-0.39	<0.001
Inferior GCC	-0.49	<0.001

The overall frequency of ≥1 abnormal diagnostic classification (abnormally low average thickness superior, inferior, or total, or an abnormal diagnostic classification based on the thickness deviation map; for definitions see Methods section) was 73.1% (134 eyes) for the mRNFL, 23.1% (42 eyes) for the GCIPL, and 19.2% (35 eyes) for the GCC, respectively. Figure 1 shows the number of eyes classified as abnormal according to the four employed parameters (superior, inferior, or total thickness, cluster in the thickness deviation map) for the different macular inner retinal layers. As can be seen in this figure, an abnormal classification in the thickness deviation map most often occurred in the mRNFL (abnormal classification 73.1, 23.1, and 19.2% for the mRNFL, GCIPL, and GCC, respectively; P<0.001 [two-way ANOVA]).

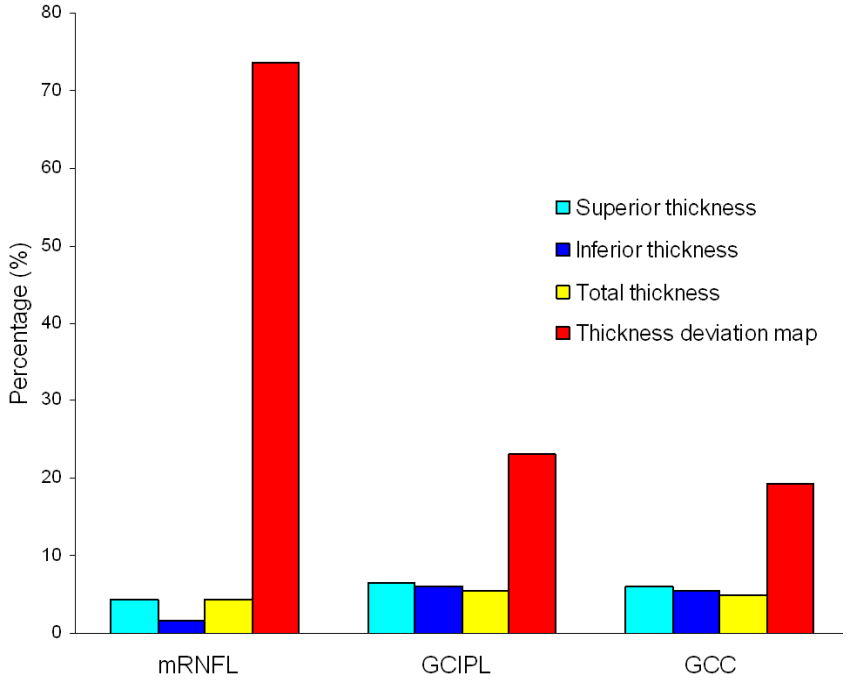

Figure 1. Percentages of eyes classified as abnormal according to the four OCT parameters (superior thickness, inferior thickness, total thickness, and cluster in thickness deviation map) for the mRNFL, GCIPL, and GCC.

Eyes that classified as abnormal according to at least one of the four employed parameters, had a significantly greater DFD (4.95 versus 4.78 mm, P<0.001 for mRNFL; 4.95 versus 4.88 mm, P<0.001 for GCIPL; 5.00 versus 4.88 mm, P=0.027 for GCC) than that of eyes classified as normal. Table 3 presents the logistic analysis. After adjusting for the effects of other covariates, a greater DFD was associated with an increased occurrence of an abnormal diagnostic classifications for the mRNFL (odds ratio [95% confidence interval] per 0.1 mm increase in DFD: 1.30 [1.13-1.50], P<0.001), GCIPL (1.29 [1.08-1.55], P=0.005), and GCC measurement (1.18 [1.02-1.38], P=0.006).

Figure 2 demonstrates the effect of the DFD on the diagnostic classifications for the mRNFL, GCIPL, and GCC, in four healthy eyes. With increasing DFD, an

increasing number of parameters were reported to be borderline or outside normal limits.

Table 3. Factors associated with an abnormal diagnostic classification of macular inner retinal layers according to the built-in normative database (n=182; logistic regression analysis)

	Odds ratios (95%CI)	P
mRNFL		
DFD (per 0.1mm)	1.30 (1.13-1.50)	<0.001
Disc area (per mm^2)	0.18 (0.07-0.49)	<0.001
GCIPL		
DFD (per 0.1mm)	1.18 (1.02-1.38)	0.023
Age (per year)	1.05 (1.03-1.09)	0.001
pRNFL (per um)	0.90 (0.85-0.95)	0.02
Gender (female)	2.39 (1.01-5.62)	0.037
Axial length (per mm)	2.10 (1.32-3.31)	<0.001
GCC		
DFD (per 0.1mm)	1.29 (1.08-1.55)	0.006
pRNFL (per um)	0.87 (0.82-0.92)	<0.001
Age (per year)	1.04 (1.01-1.07)	0.008

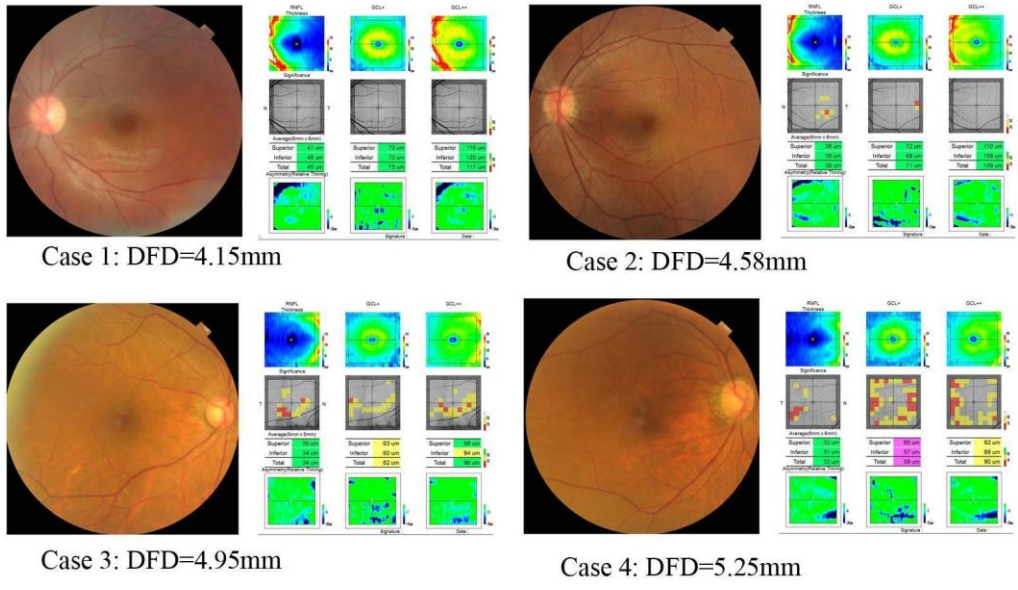

Figure 2. Four cases demonstrating the association between the DFD and the occurrence of abnormal diagnostic classifications in the OCT printout.

Discussion

A greater DFD is associated with a higher percentage of abnormal diagnostic classification for the OCT parameters describing the thickness of the mRNFL, GCIPL, and GCC in healthy subjects.

In a previous study, we found that the DFD was significantly associated with the thickness of individual macular intraretinal layers as measured with a generic segmentation algorithm (Qiu et al., 2018). In the current study, we confirmed our previous finding by using the built-in software of the OCT device and we showed that the DFD has a clinically relevant impact on the glaucoma diagnostic classification and is an important, independent factor determining the thickness of the macular inner retinal layers. To the best of our knowledge, no other reports regarding DFD and OCT glaucoma diagnostics have been published thus far. A longer axial length has been found to be associated with a higher percentage of abnormal diagnostic classification for the GCIPL (Leal-Fonseca et al., 2014; Aref

et al., 2014; Kim et al., 2015). This is in agreement with our findings. Previous studies reported that the disc area was associated with false positive results regarding the pRNFL but not GCIPL (Leal-Fonseca et al., 2014; Kim et al., 2015). In agreement with this, we found that disc area was significantly associated with an abnormal diagnostic classification for the mRNFL but not for the GCIPL or GCC. It has been reported that the FDA was significantly associated with the distribution of the pRNFL (Choi et al., 2014), and Kim et al. reported that the FDA was significantly associated with an abnormal diagnostic classification for the GCIPL (Kim et al., 2015). In the current study, we did not detect a significant association between the FDA and an abnormal diagnostic classification for the macular inner retinal layers. Differences in study design could have contributed to these conflicting results, such as different measurement area of the GCIPL, different study populations, and adjustment for other covariates. In agreement with our findings, Mwanza et al. reported that the glaucoma diagnostic performance of RNFL parameters did not improve by correcting the RNFL profiles for the FDA (Mwanza et al., 2016).

It is worth to note that a high percentage (73%) of abnormal diagnostic classification was observed for the mRNFL in the present study. Assessment of the mRNFL has been reported to be useful in glaucoma diagnosis (Akashi et al., 2013a; Akashi et al., 2013b), but the reported areas under the receiver operating characteristic curves (AUCs) ranged from 0.589 to 0.940 for detecting early glaucoma patients with high myopia,20 and similar values (0.486 to 0.859) were found in another study (Lee et al., 2016). These AUC values show that improvement in diagnostic performances is needed, and reducing noise by adjusting for factors that contribute to the observed variability is a logical approach. The DFD is one of these factors that can easily be determined from data available in the scans.

Several limitations exist in the current study. First, only Chinese subjects were included. As racial differences in macular thickness have been reported (Girkin et al., 2011), the current findings may not apply to other populations. A second

limitation is the cross-sectional nature of the present study. Some eyes with subclinical glaucomatous damage may have been included accidentally. Although strict inclusion and exclusion criteria were applied, future longitudinal follow-up is necessary to confirm our results. On the other hand, if such a longitudinal study would reveal the spurious inclusion of early glaucoma cases, the DFD would be a risk factor for glaucoma rather than for a false-positive classification. Finally, some of the current results may not apply to other OCT devices, as there are differences in scan protocol, segmentation algorithm, and normative database between different devices. Strength of the present study are the strict in- and exclusion criteria and the large sample size.

Why is the DFD associated with the thickness of the mRNFL, GCIPL, and GCC? Regarding the mRNFL thickness, a possible explanation is the difference in scan area for the mRNFL assessment between eyes with different DFD. In eyes with a greater DFD, the OCT scan area (centered at the fovea) is farther away from the optic disc. The RNFL is thinner farther away from the optic disc than it is closer to the disc (Gabriele et al., 2007). Thus, one would expect to find that the mRNFL is thinner in eyes with a greater DFD. With respect to the GCIPL thickness, one possible explanation is the stretching of the posterior fundus. In a previous study, the DFD has been reported to be associated with the peripapillary retinal nerve fiber distribution in healthy eyes (Hong et al., 2010). We speculate that the posterior fundus in eyes with a greater DFD is stretched, which may cause a decrease in GCIPL thickness in the macular region. Importantly, stretching of the posterior pole could also be caused by an increase in axial length, but our multivariable analysis showed that the DFD is an independent factor. In the present study, the mRNFL and GCIPL thickness were both significantly and negatively associated with the DFD. The observed significant and negative correlation between the DFD and the GCC thickness is a logical consequence, as the mRNFL and GCIPL form together the GCC.

In conclusion, eyes with a greater DFD are prone to a false-positive glaucoma classification in the thickness assessment of the macular inner retinal layers. The

thicknesses should always be interpreted in the context of DFD. DFD-adjusted normative databases should be developed, and future research should evaluate such normative databases in terms of improvement in diagnostic performance.

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