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EFFECT OF OPTIC DISK—FOVEA DISTANCE ON MEASUREMENTS OF INDIVIDUAL MACULAR INTRARETINAL LAYERS IN NORMAL SUBJECTS

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Purpose: To investigate the effect of optic disk—fovea distance (DFD) on measurements of macular intraretinal layers using spectral domain optical coherence tomography in normal subjects.

Methods: One hundred and eighty-two eyes from 182 normal subjects were imaged using spectral domain optical coherence tomography. The average thicknesses of eight macular intraretinal layers were measured using an automatic segmentation algorithm. Partial correlation test and multiple regression analysis were used to determine the effect of DFD on thicknesses of intraretinal layers.

Results: Disk—fovea distance correlated negatively with the overall average thickness in all the intraretinal layers ($r \leq -0.17$, all $P \leq 0.025$) except the ganglion cell layer and photoreceptor. In multiple regression analysis, greater DFD was associated with thinner nerve fiber layer (6.78 μm decrease per each millimeter increase in DFD, $P < 0.001$), thinner ganglion cell—inner plexiform layer (2.16 μm decrease per each millimeter increase in DFD, $P = 0.039$), thinner ganglion cell complex (8.94 μm decrease per each millimeter increase in DFD, $P < 0.001$), thinner central macular thickness (18.16 μm decrease per each millimeter increase in DFD, $P < 0.001$), and thinner total macular thickness (15.94 μm decrease per each millimeter increase in DFD, $P < 0.001$).

Conclusion: Thinner measurements of macular intraretinal layers were significantly associated with greater DFD. A clinical assessment of macular intraretinal layers in the evaluation of various macular diseases should always be interpreted in the context of DFD.

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Evaluation of macular structure is important and useful in diagnosing and evaluating the efficacy of treatment of various ocular diseases involving macular changes, such as macular edema.[1] The introduction of optical coherence tomography (OCT) has facilitated the detection and follow-up of subtle changes in macular structure quantitatively and reliably.[2] Recently, the spectral domain OCT with faster scan speed and higher resolution has been widely used as an important technology for in vivo measurement of macular structure.[3,4] Besides, advances in segmentation algorithms have further allowed detailed separation and demarcation of individual intraretinal layers.[5,6] Previous studies have demonstrated that thickness measurement of intraretinal layers is becoming a powerful and reliable surrogate marker for assessing and monitoring macular changes resulting from retinal diseases, glaucoma, and optic neuropathy.[7–10] Thus, understanding of normal macular structure and its variability is essential for assessing optic neuropathy and maculopathy.

Several factors including axial length, sex, age, and disk area have been reported to be associated with thicknesses of individual retinal layers in normal subjects.[11–14] These findings have been valuable in the clinical assessment of glaucoma and various macular diseases. However, our knowledge about the variation of macular intraretinal structure is far from complete. The distance between the optic disk center and the fovea (DFD) is another biometric variable that may influence the macular thickness. Eyes with large DFD may be associated with a stretching of the posterior fundus, which may cause a change of the retinal thickness. Moreover, DFD has been reported to be

associated with axial length.[15] Thus, it is important to determine the effect of DFD on measurements of individual intraretinal layers. However, to the best of our knowledge, the relationship between DFD and measurements of individual macular intraretinal layers has not been reported.

The purpose of this study was to determine the effect of DFD on measurements of macular intraretinal layers with an automatic retinal layer segmentation algorithm[16] in normal subjects.

Methods

Subjects

In this prospective, cross-sectional observational study, the normal subjects were consecutively recruited from the general clinic of Joint Shantou International Eye Center. All the included subjects received complete ophthalmic examinations including the measurement of best-corrected visual acuity, axial length (IOLMaster; Carl-Zeiss Meditec, Inc, Dublin, CA), refraction, intraocular pressure, fundus examination, and slit-lamp biomicroscopy. Each of the included eyes had no other concurrent ocular disease except a refractive error and mild cataract. One eye was randomly selected if both eyes were eligible. Subjects were excluded if refractive errors over +3.0 or under −6.0 diopters (D), the best-corrected visual acuity was less than 20/40, the intraocular pressure over 21 mmHg, if they had a family history of glaucoma, or if they had a history of intraocular surgery, refractive surgery, macular degeneration, neurological disease, glaucoma, or diabetes. This study followed the tenets of the Declaration of Helsinki and was approved by the local ethical committee with written informed consent obtained from each subject before enrollment.

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 15% were included in the study. All the included visual field tests were within normal limits in the glaucoma hemifield test and had a pattern SD P value $>5\%$.

Optical Coherence Tomography

All the included eyes underwent macular and optic disk imaging using the Topcon 3D OCT-2000 (software version 8.11; Topcon). The axial resolution for this spectral domain OCT is 6 μm and the scan speed is 50,000 A-scans per second.[17] Both the macular 3D Scan 512 × 128 protocol and Optic Disc 3D Scan 512 × 128 protocol were performed. Measurements with eye movements during image acquisition were excluded and retaken. Each of the included images had a minimum image quality score of 45, which is recommended by the manual of 3D OCT-2000.[17] The disk area was recorded for subsequent analysis from the analysis printout of the optic disk scan protocol with the built-in OCT software.

The raw data from the macular scan protocol, which consists of a scan area of 6×6 mm^2 and 128 B-scans (512 A-scans per B-scan), was exported for subsequent thickness measurements of individual macular retinal layers. Each 3D-OCT volumetric macula-centered scan was automatically segmented by a graph search algorithm, which is a fast, three-dimension, automatic graph-theoretical segmentation approach.[16,18,19] Using this automatic algorithm, the lowest location of the first surface (internal limiting membrane) in each image was determined and used as a center point of the Early Treatment Diabetic Retinopathy grid. Subsequently, 11 intraretinal surfaces defining 10 retinal layers were segmented and thicknesses of individual layers were then measured on 9 regions according to the Early Treatment Diabetic Retinopathy grid (Figure 1). For analysis, the average thickness of each layer within three concentric rings (Figure 1B) was calculated for the following layers: nerve fiber layer (NFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL),

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X. Chen and M. Zhang contributed equally.

Involved in study design and conduct (M.Z., X.C., and H.C.); data collection, management, and analysis (K.Q., B.C., E.G., and J.Y.), and interpretation (M.Z and K.Q.); and manuscript preparation, review, or approval (M.Z, X.C., H.C., and K.Q.).

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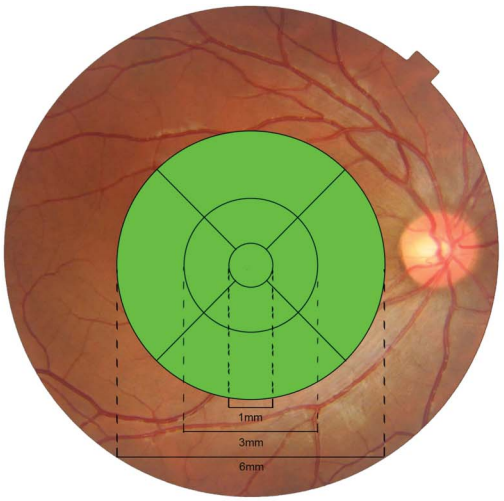

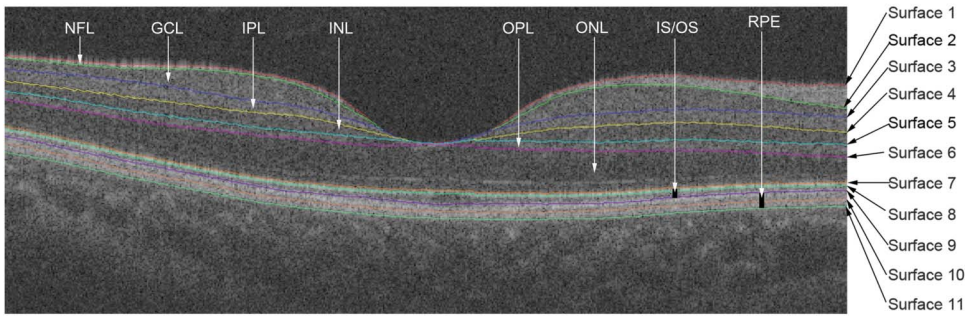

Fig. 1. Segmentation of individual intraretinal layers and thickness measurement in three concentric rings on the Early Treatment Diabetic Retinopathy chart.

photoreceptor inner segment/outer segment (IS/OS), and retinal pigment epithelium (RPE). The central ring was a circle with a diameter of 1 mm, centered on the fovea. The pericentral ring is a concentric ring around the central ring with an inner diameter of 1 mm and an outer diameter of 3 mm. The peripheral ring is another concentric ring extending from the edge of the pericentral ring with an outer diameter of 6 mm centered on the fovea. Because inner retinal layers are almost absent in the fovea, only measurements of outer retinal layers (OPL, ONL, IS/OS, and RPE) were analyzed in the central ring. Thicknesses of ganglion cell—inner plexiform layer (GCIPL, combined measurement of GCL and IPL), ganglion cell complex (GCC, combined measurement of NFL and GCIPL), and total macular thickness (NFL + GCL + IPL + INL + OPL + ONL + IS/OS) were also calculated for analysis.

Measurement of Disk—Fovea Distance

Disk—fovea distance was manually measured on fundus photographs by using ImageJ software (available in the public domain at http://rsbweb.nih.gov/ij/; www.nih.gov, National Institutes of Health, Bethesda, MD). First, 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, based on the coordinates of the fovea and the center of the optic disk. To determine the measurement repeatability, 30 fundus images from 30 subjects were randomly selected. The DFD in each image was measured by the same observer for two times in two separate occasions.

Statistical Analyses

The statistical analyses were performed using the SPSS software (version 22.0; SPSS Inc, Chicago, IL). The coefficient of variation and intraclass correlation coefficient were computed to evaluate the measurement repeatability. Partial correlation test was used to determine the effect of DFD on thicknesses of intraretinal layers after adjusting for other confounders (age, axial length, sex, disk area, and image quality). Stepwise multiple linear regression analysis was performed to evaluate factors associated with the overall measurements of NFL, GCIPL, GCC, and total macular thickness. A P value less than 0.05 was considered statistically significant.

Results

Eleven subjects were excluded because of poor quality of fundus photographs (4 subjects), unreliable visual field tests (5 subjects), and poor OCT scan quality (2 subjects). Finally, 182 eyes from 182 subjects (106 women and 95 right eyes) were included in the analysis. The mean age and DFD were 43.8 ± 15.6 years (range, 20–78 years) and 4.90 ± 0.29 mm (range, 3.98–5.66 mm), respectively. The coefficient of variation and intraclass correlation coefficient of DFD measurement were 0.8% (95% confidence interval: 0.5%–0.9%) and 0.98 (95% confidence interval: 0.94–0.99), respectively. Figure 2 displays the distribution of DFD across all subjects. The mean refraction and axial length were −0.80 ± 1.92 (range, −6.0 to 2.69D) and 23.63 ± 1.11 mm (range, 20.74–26.70 mm), respectively. No significant association was detected between axial length/refraction and DFD (r = −0.12, $P = 0.113$ and r = 0.11, $P = 0.160$, respectively). The mean disk area was 2.24 ± 0.39 mm^2 (range, 1.28–3.28 mm^2). Table 1 summarizes the thickness measurements of the macular intraretinal layers using the automatic segmentation algorithm in the study population.

Table 2 demonstrates the associations between DFD and measurements of individual intraretinal layers/combined retinal layers in three different rings, adjusted for age, axial length, image quality, sex, and disk area. For individual intraretinal layers, DFD correlated significantly and negatively with the overall average thickness in all the retinal layers (all $P \leq 0.025$) except the GCL and IS/OS. In the central ring, there was a significant and negative correlation between DFD and ONL (r = −0.15, $P = 0.041$). In the pericentral ring, DFD correlated negatively with NFL, IPL, INL, and ONL (all $P \leq 0.065$). In the peripheral ring, DFD correlated significantly and negatively with NFL, IPL, OPL, ONL, and RPE (all $P \leq 0.023$). No significant relationship between GCL, IS/OS, and DFD was detected in all three rings. Figure 3 shows the correlation between DFD and the overall average thickness measurements of the individual intraretinal layers. For the combined retinal layers, there were significant and negative correlations between GCIPL, GCC, total macular thickness, and DFD in both regional and overall measurements (all $P \leq 0.045$).

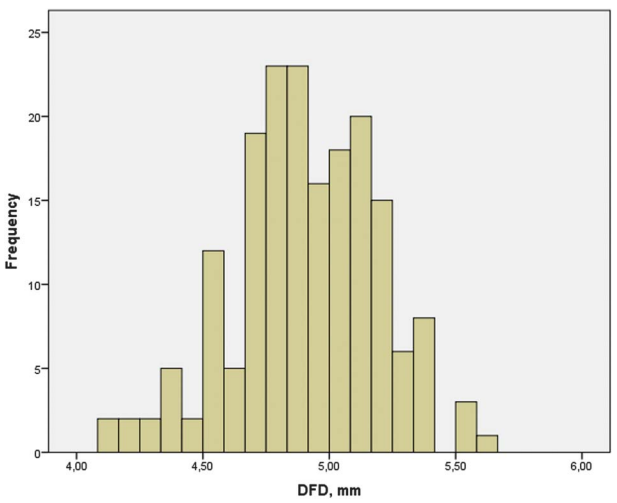

Fig. 2. Histogram of DFD of all included eyes.

Table 3 presents the multiple linear regression analysis regarding the associations between various factors and the overall average thickness of NFL, GCIPL, GCC, central macular thickness, and total macular thickness. Greater DFD was independently and significantly associated with thinner NFL (6.78 μm decrease per each millimeter increase in DFD, $P < 0.001$), thinner GCIPL (2.16 μm decrease per each millimeter increase in DFD, $P = 0.039$), thinner GCC (8.94 μm decrease per each millimeter increase in DFD, $P < 0.001$), thinner central macular thickness (18.16 μm decrease per each millimeter increase in DFD, $P < 0.001$), and thinner total macular thickness (15.94 μm decrease per each millimeter increase in DFD, $P < 0.001$).

Discussion

This study was performed to determine the effect of DFD on measurements of macular intraretinal layers in normal subjects. We demonstrated that thickness measurements of several individual retinal layers varied significantly with DFD. Thinner measurements of NFL, IPL, INL, OPL, ONL, RPE, GCIPL, GCC, and total macular thickness were significantly associated with greater DFD, independent of other covariates. Such findings are of potential significance in clinical evaluation of macular structural measurements obtained using OCT.

Variations about the thicknesses of individual intraretinal layers have been described previously.[11–14,20,21] Factors including age, axial length, sex, and disk area have been reported to be associated with thickness measurements of individual macular retinal layers.[11–14,20,21] To the best of our knowledge, however, the effect of DFD on thicknesses of macular intraretinal layers has not been studied. In the current study, negative relationships between DFD and the overall average thickness measurements of NFL, IPL, INL, OPL, ONL, and RPE were detected after adjusting for age, axial length, sex, and disk area. Our

Table 1. Thickness Measurements of the Individual Macular Intraretinal Layers/Combined Retinal Layers (n = 182)

	Mean ± SD	Range
NFL		
Overall	37.7 ± 4.3	28.6–52.3
Pericentral ring	22.8 ± 1.9	16.8–27.8
Peripheral ring	36.7 ± 3.7	29.3–48.7
GCL		
Overall	34.6 ± 2.7	27.3–41.3
Pericentral ring	55.0 ± 5.7	26.8–68.3
Peripheral ring	33.8 ± 3.0	25.9–41.9
IPL		
Overall	37.0 ± 2.8	28.3–48.4
Pericentral ring	39.1 ± 3.4	30.5–47.5
Peripheral ring	40.1 ± 3.2	29.5–53.2
INL		
Overall	35.0 ± 2.2	28.1–40.6
Pericentral ring	43.0 ± 3.2	34.9–53.1
Peripheral ring	36.1 ± 2.4	28.1–42.6
OPL		
Overall	26.0 ± 2.1	22.1–35.4
Center	21.4 ± 7.0	11.4–48.1
Pericentral ring	28.8 ± 4.7	21.8–48.0
Peripheral ring	26.4 ± 1.9	22.8–33.2
ONL		
Overall	77.9 ± 7.0	46.8–96.5
Center	114.4 ± 11.8	82.9–143.8
Pericentral ring	92.8 ± 9.4	67.3–116.5
Peripheral ring	76.1 ± 7.3	39.7–95.7
IS/OS		
Overall	29.5 ± 2.9	20.5–40.6
Center	32.8 ± 3.2	16.4–41.1
Pericentral ring	27.9 ± 2.9	17.2–41.7
Peripheral ring	29.1 ± 3.4	20.5–41.6
RPE		
Overall	36.7 ± 2.5	31.2–43.4
Center	41.1 ± 3.9	28.1–41.1
Pericentral ring	40.5 ± 3.4	32.0–47.7
Peripheral ring	36.6 ± 3.1	30.0–36.6
GCIPL		
Overall	71.6 ± 4.5	59.0–83.5
Pericentral ring	94.1 ± 6.9	65.2–108.0
Peripheral ring	73.9 ± 5.2	59.3–86.9
GCC		
Overall	109.3 ± 7.1	92.3–128.7
Pericentral ring	116.9 ± 8.0	84.0–132.9
Peripheral ring	110.5 ± 7.1	93.2–126.9
Total macular thickness		
Overall	262.2 ± 13.5	216.1–290.7
Center	216.8 ± 17.1	166.4–272.7
Pericentral ring	293.8 ± 15.5	245.6–330.7
Peripheral ring	262.7 ± 14.0	212.9–291.4

Table 2. Associations Between DFD and Individual Intraretinal Layers/Combined Retinal Layers, Adjusting for Axial Length, Sex, Age, Disc Area, and Image Quality (Partial Correlation Test, n = 182)

	r	*P*
NFL		
Overall	−0.51	<0.001
Pericentral ring	−0.31	<0.001
Peripheral ring	−0.47	<0.001
GCL		
Overall	−0.02	0.774
Pericentral ring	−0.11	0.131
Peripheral ring	0.05	0.493
IPL		
Overall	−0.22	0.003
Pericentral ring	−0.27	<0.001
Peripheral ring	−0.27	<0.001
INL		
Overall	−0.26	<0.001
Pericentral ring	−0.26	<0.001
Peripheral ring	−0.23	0.002
OPL		
Overall	−0.24	0.002
Center	−0.08	0.306
Pericentral ring	−0.11	0.140
Peripheral ring	−0.28	<0.001
ONL		
Overall	−0.17	0.025
Center	−0.15	0.041
Pericentral ring	−0.14	0.065
Peripheral ring	−0.17	0.023
IS/OS		
Overall	−0.06	0.426
Center	−0.09	0.241
Pericentral ring	−0.11	0.138
Peripheral ring	0.10	0.169
RPE		
Overall	−0.24	0.001
Center	−0.08	0.307
Pericentral ring	−0.06	0.431
Peripheral ring	−0.24	0.001
GCIPL		
Overall	−0.16	0.039
Pericentral ring	−0.23	0.002
Peripheral ring	−0.15	0.045
GCC		
Overall	−0.38	<0.001
Pericentral ring	−0.27	<0.001
Peripheral ring	−0.34	<0.001
Total macular thickness		
Overall	−0.38	<0.001
Center	−0.31	<0.001
Pericentral ring	−0.34	<0.001
Peripheral ring	−0.32	<0.001

results suggest that DFD is one of the important factors determining the thickness measurements of macular intraretinal layers.

Why is DFD associated with measurements of macular intraretinal layers? Regarding macular NFL thickness, one possible explanation is the different scan area for the NFL measurement. Because the fovea is farther away from the optic disk in eyes with a greater DFD, the OCT scan area (centered at the fovea) is farther away from the optic disk. Previous studies have demonstrated that the RNFL is thinner

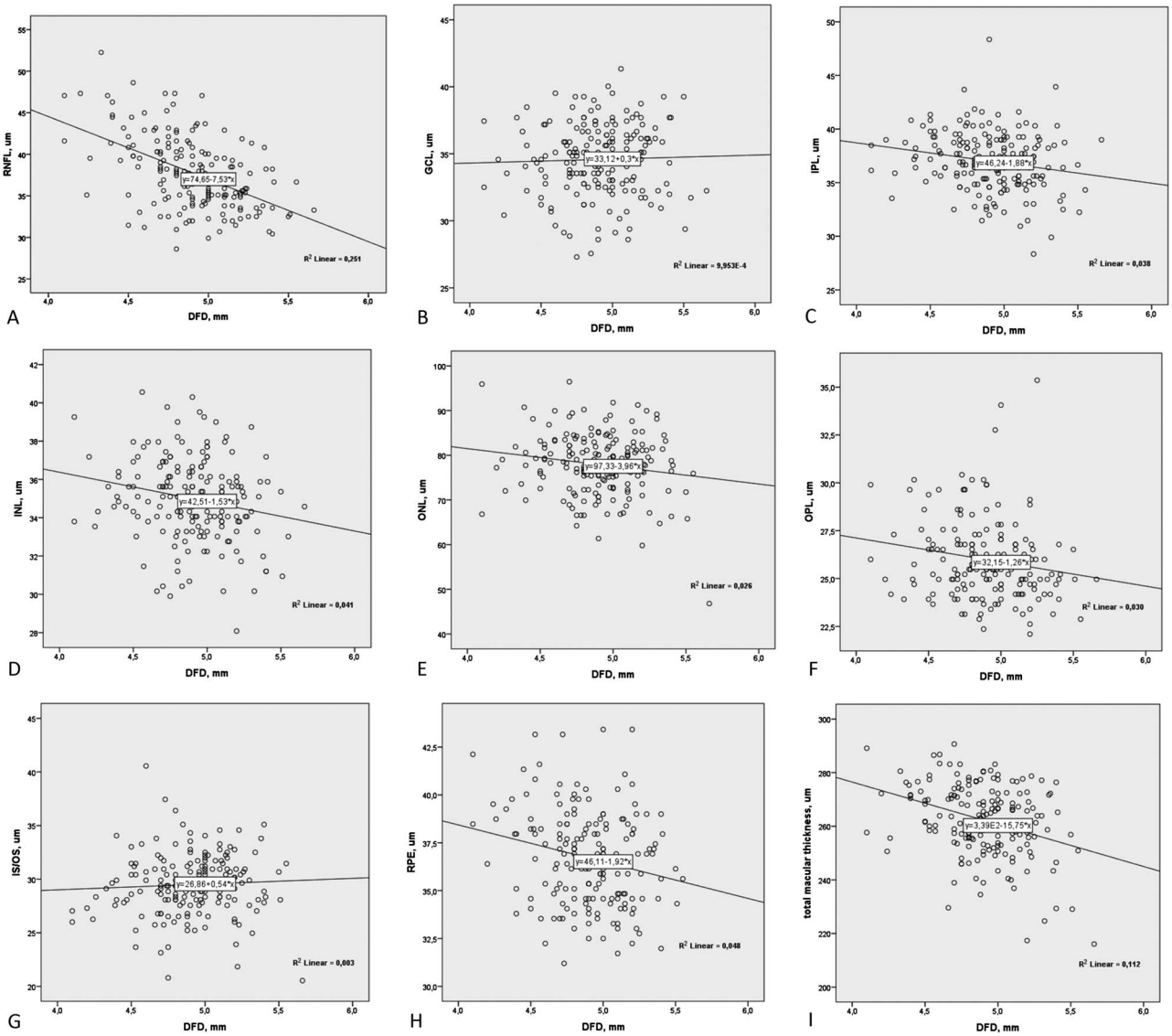

Fig. 3. Scatter plots of DFD versus overall average thickness of individual intraretinal layers/combined retinal layers. DFD and NFL overall average thickness (**A**); DFD and GCL overall average thickness (**B**); DFD and IPL overall average thickness (**C**); DFD and INL overall average thickness (**D**); DFD and OPL overall average thickness (**E**); DFD and ONL overall average thickness (**F**); DFD and IS/OS overall average thickness (**G**); DFD and RPE overall average thickness (**H**); DFD and total macular thickness (**I**).

farther from the optic disk than it is closer to the optic disk margin.[22] Therefore, one would expect to find thinner NFL measurement in eyes with greater DFD. About thicknesses of IPL, INL, OPL, ONL, and RPE, a possible explanation is the stretching of the posterior fundus in eyes with a greater DFD. The DFD has been found to be associated with the parapapillary zones[15] and the peripapillary retinal nerve fiber distribution in healthy eyes.[23] In the current study, we found that measurements of several intraretinal layers significantly decreased in eyes with greater DFD. On the basis of these findings, we speculate that the posterior fundus in eyes with greater DFD are stretched, which may cause the decrease of thicknesses of the macular intraretinal layers. The relationship between DFD and the intraretinal layers may be established during the development of the retina.

The current results have potential clinical significance in the evaluation of glaucoma, optic neuropathy, and retina disease involving macular changes. For example, evaluation of NFL, GCIPL, GCC, central macular thickness (central subfield thickness), and total retinal thickness in macular region has been reported to be useful in clinical evaluation of glaucoma, multiple sclerosis, Alzheimer disease, and

Table 3. Factors Associated With Overall Average Thickness of NFL, GCIPL, GCC, Central Macular, and Total Macular (Stepwise Multiple Linear Regression Analysis, n = 182)

	Overall NFL		Overall GCIPL		Overall GCC		Central Macular Thickness		Overall Total Macular Thickness	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
DFD (mm)	−6.78	<0.001	−2.16	0.041	−8.97	<0.001	−18.16	<0.001	−15.94	<0.001
Axial length (mm)	1.40	<0.001	−1.56	<0.001	—	—	2.88	0.007	−3.65	<0.001
Age (per year)	—	—	−0.13	<0.001	−0.16	<0.001	—	—	−0.42	<0.001
Sex	2.45	<0.001	—	—	—	—	−6.57	0.006	−3.66	0.034
Disk area (mm^2)	—	—	2.17	0.010	3.06	0.015	—	—	—	—
Image quality	0.18	0.005	—	—	—	—	—	—	—	—

various maculopathies.[9,10,24,25] However, individual variability of thicknesses of intraretinal layers may limit their use in clinical practice. In a systematic review, it is reported that central retinal thickness (with cutoffs ranging between 230 and 300 μm) measured using OCT is not sensitive enough (0.81) nor specific enough (0.85) to detect the central type of clinically significant macular edema.[26] Therefore, it is important to understand the variability of normal macular structure. Consistent with previous studies,[15,23] significant interindividual variation of DFD was observed in the current study population. More importantly, we found that DFD was significantly associated with thickness measurements of several macular intraretinal layers. Extrapolation from the regression analyze indicated that average NFL thickness decreases by 18.0% (6.78 μm) per millimeter of greater DFD; average GCC thickness decreases by 8.2% (8.94 μm) per millimeter of greater DFD; central macular thickness decreases by 8.4% (18.16 μm) per millimeter of greater DFD; and average macular thickness decreases by 6.1% (15.94 μm) per millimeter of greater DFD. The data and results were adjusted for other confounders including axial length, age, sex, image quality, and disk area. Our current findings indicate that a clinical assessment of thickness measurements of macular retinal layers should take into consideration of DFD. Moreover, by using the OCT built-in manual measurement tool, it would not be difficult for a clinician to obtain DFD measurements on the OCT fundus image.[27]

In this study, segmentation and measurements of macular intraretinal layers were performed using an automatic graph search algorithm, which has been validated in previous studies.[16,18] Associations between GCIPL thickness, GCC thickness, total macular thickness, and axial length have been reported previously.[14,28–33] Consistent with most of the previous studies, we found that thinner GCIPL was associated with longer axial length.[14,29] In line with previous studies,[33] regional variations of association between macular thickness and axial length were observed in the current study. Conflicting data regarding the relationship between axial length and GCC thickness has been reported.[29–32] Kim et al[29] reported that GCC thickness did not correlate with axial length. However, others reported that GCC thickness varied significantly with axial length.[30–32] In this study, no significant relationship between axial length and GCC thickness was detected. Several differences in study design could have contributed to these conflicting results, such as adjustment for different covariates and different study populations (inclusion of high myopic eyes or not).

The effect of ocular magnification has been reported previously.[12,34] According to previous reports, OCT measurements, OCT scan area, and measurements on fundus photographs could be different due to ocular magnification.[34] Because only the uncorrected measurements are available in a clinical setting with commercial devices and software, we decided to perform the analysis with and without correction for ocular magnification. Using Bennett formula,[35] the actual measurements of DFD and disk area were calculated for analysis. We found significant but minor difference between corrected and uncorrected DFD measurements (4.90 vs. 4.73 mm, $P < 0.001$). We then repeated the analyses using the magnification corrected measurements. In the partial correlation analysis, we found similar pattern of associations regarding the relationship between DFD and measurements of individual macular intraretinal layers (Table 4). For the macular scan area, unfortunately, the actual scan area is not possible to obtain in this study. However, to reduce this effect, analyses were repeated in a subgroup of eyes with a narrow range of axial length (25–75 percentiles, 22.88–24.33 mm). Similar and stronger correlations were observed between DFD and thickness measurements of macular intraretinal layers (Table 5). On the basis of these findings, we believe

Table 4. Associations Between Magnification Corrected DFD and Individual Intraretinal Layers/Combined Retinal Layers, Adjusting for Axial Length, Sex, Age, Magnification Corrected Disk Area, and Image Quality (Partial Correlation Test, n = 182)

	r	*P*
NFL		
Overall	−0.50	<0.001
Pericentral ring	−0.31	<0.001
Peripheral ring	−0.47	<0.001
GCL		
Overall	−0.02	0.806
Pericentral ring	−0.11	0.138
Peripheral ring	0.06	0.464
IPL		
Overall	−0.21	0.005
Pericentral ring	−0.26	<0.001
Peripheral ring	−0.26	<0.001
INL		
Overall	−0.25	<0.001
Pericentral ring	−0.26	<0.001
Peripheral ring	−0.22	0.003
OPL		
Overall	−0.23	0.002
Center	−0.08	0.325
Pericentral ring	−0.11	0.163
Peripheral ring	−0.28	<0.001
ONL		
Overall	−0.17	0.028
Center	−0.16	0.040
Pericentral ring	−0.14	0.063
Peripheral ring	−0.17	0.028
IS/OS		
Overall	−0.06	0.419
Center	−0.09	0.262
Pericentral ring	−0.11	0.148
Peripheral ring	0.10	0.170
RPE		
Overall	−0.24	0.001
Center	−0.08	0.308
Pericentral ring	−0.06	0.437
Peripheral ring	−0.24	0.001
GCIPL		
Overall	−0.15	0.048
Pericentral ring	−0.18	0.019
Peripheral ring	−0.28	<0.001
GCC		
Overall	−0.38	<0.001
Pericentral ring	−0.27	<0.001
Peripheral ring	−0.34	<0.001
Total macular thickness		
Overall	−0.37	<0.001
Center	−0.30	<0.001
Pericentral ring	−0.33	<0.001
Peripheral ring	−0.31	<0.001

Table 5. Associations Between DFD and Individual Intraretinal Layers/Combined Retinal Layers, Adjusting for Axial Length, Sex, Age, Disk Area, and Image Quality (Partial Correlation Test in a Subgroup of Eyes With Axial Length Ranging From 22.88 to 24.33 mm, n = 93)

	r	*P*
NFL		
Overall	−0.58	<0.001
Pericentral ring	−0.36	<0.001
Peripheral ring	−0.53	<0.001
GCL		
Overall	−0.17	0.104
Pericentral ring	−0.20	0.059
Peripheral ring	−0.13	0.230
IPL		
Overall	−0.29	0.005
Pericentral ring	−0.28	0.009
Peripheral ring	−0.31	0.003
INL		
Overall	−0.40	<0.001
Pericentral ring	−0.39	<0.001
Peripheral ring	−0.38	0.003
OPL		
Overall	−0.26	0.016
Center	−0.08	0.465
Pericentral ring	−0.09	0.407
Peripheral ring	−0.32	0.003
ONL		
Overall	−0.23	0.033
Center	−0.25	0.020
Pericentral ring	−0.22	0.036
Peripheral ring	−0.23	0.031
IS/OS		
Overall	0.06	0.585
Center	−0.20	0.057
Pericentral ring	−0.16	0.137
Peripheral ring	0.15	0.179
RPE		
Overall	−0.35	0.001
Center	−0.06	0.572
Pericentral ring	−0.13	0.247
Peripheral ring	−0.37	<0.001
GCIPL		
Overall	−0.29	0.006
Pericentral ring	−0.27	0.011
Peripheral ring	−0.42	<0.001
GCC		
Overall	−0.51	<0.001
Pericentral ring	−0.36	<0.001
Peripheral ring	−0.46	<0.001
Total macular thickness		
Overall	−0.49	<0.001
Center	−0.41	<0.001
Pericentral ring	−0.46	<0.001
Peripheral ring	−0.43	<0.001

that greater DFD is indeed associated with thinner thickness measurements of macular intraretinal layers.

The current study had some limitations. First, only ethnic Chinese were evaluated in this study and the findings may vary in other ethnic groups. Second, the measurement of DFD which was based on the two-dimensional images may be underestimated because some of the eyes may have a steeper posterior retinal

curvature than emmetropic eyes. To minimize this effect, we excluded high myopic (refraction ≤ -6D) eyes in this study (mean refraction: 0.80 ± 1.93D). All the included eyes were reviewed carefully and eyes with myopic macular degeneration including a posterior staphyloma were excluded from the study. Moreover, a similar and stronger pattern of correlations was detected regarding the relationship between DFD and macular intraretinal layers in a subgroup of eyes with a narrow range of axial length (Table 5, axial length range: 22.88–24.33 mm).

In conclusion, thinner measurements of NFL, IPL, INL, OPL, ONL, RPE, GCIPL, GCC, and total macular thickness were significantly associated with greater DFD, independent of other covariates. A clinical assessment of thickness measurements of macular intraretinal layers in the evaluation of glaucoma, optic neuropathy, and retinal disease involving macular changes should always be interpreted in the context of DFD.

Key words: macular intraretinal layers, maculopathy, optic disk—fovea distance, optic neuropathy, spectral domain OCT.

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