• Clinical Research •

Association of choroidal thickness with early stages of diabetic retinopathy in type 2 diabetes

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Abstract

• AIM: To assess the correlation between choroidal thickness (CT) and the early stages of diabetic retinopathy (DR) in type 2 diabetic patients.

• METHODS: We divided 83 diabetic patients (51-80 years of age; 50 females) into non diabetic retinopathy group (NDR) and mild/moderate nonproliferative diabetic retinopathy (NPDR) group, and compared them with 26 non-diabetic control subjects (51-78 years of age; 16 females). Subfoveal choroidal thickness (SFCT) and parafoveal choroidal thickness (PFCT) were measured using enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT). Ocular health status, disease duration, body mass index, and hemoglobin A1c (HbA1c) were recorded.

• RESULTS: The mean ages of the NDR, NPDR, and control groups were 68.0±6.9y, 67.8±6.4y, and 65.1±6.3y, respectively (*P*=0.17). Pearson correlation of the right and left eyes for the control subjects was 0.95 and for the NDR subjects was 0.93. SFCT for the right eyes of the controls was 252.77± 41.10 μm, which was significantly thicker than that of the right eyes in NDR group (221.51±46.56 μm) and the worse eyes of the NPDR group (207.18±61.87 μm; ANOVA, *P*<0.01). In the diabetic patients pooled together, age was the only variable significantly associated with SFCT (multiple linear regression analysis, *P*=0.01).

• CONCLUSION: CT decreased significantly in the NDR and mild/moderate NPDR eyes compared with the control eyes. Age is significantly associated with SFCT in the diabetic patients. Diabetic choroidopathy may be present before clinical retinopathy.

• KEYWORDS: choroidal thickness; diabetic choroidopathy; diabetic retinopathy

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INTRODUCTION

The choroid is highly vascularized tissue that supplies blood to the outer retina, including the retinal pigment epithelium (RPE) cells and photoreceptors[1], especially in the foveal region where there is no retinal vasculature. The choroid plays a crucial part in the physiopathology of many retinal diseases, including diabetic retinopathy (DR). Damage of the choriocapillaris may induce severe harm to the function of the retinal tissue, especially in the macula fovea. Previous histopathologic studies showed vascular abnormalities in the choroid, including obstruction of the choriocapillaris, vascular degeneration, choroidal aneurysms, and choroidal neovascularization in patients with diabetes[2-4]. Doppler flowmetry revealed that choroidal blood flow may fall off at early stages of DR[5]. However, little is known about the changes in the structure of the choroid and their possible effects on retinal tissue *in vivo* because of limitations to effective examinations.

Enhanced depth imaging spectral domain optical coherence tomography (EDI-OCT) is a unique way to visualize and measure the choroid in different diseases, including DR[6-10]. Data on the relationship between choroidal thickness (CT) and DR, however, are sparse and the limited researches show inconsistent results[10-16]. For example, EDI-OCT in diabetic eyes, according to Querques *et al*[13], revealed an overall thinning of the choroid. Xu *et al*[16] reported that the subfoveal choroid in patients with diabetes mellitus were slightly, but statistically significantly, thicker, regardless of the presence or the stage of DR. The results were divergent especially in non-diabetic retinopathy (NDR) and mild/moderate nonproliferative diabetic retinopathy (NPDR). Previous researches revealed that choroidal thickness is associated with age and ocular axial length[17-19]. Some scholars have observed significant diurnal variations in CT[20-22]. Therefore, CT measurements should be done at a similar time of the day. The purpose of this study was to explore changes in CTs and their associations with NDR and mild/moderate NPDR.

SUBJECTS AND METHODS

Patient Eligibility Eighty-three patients with type 2 diabetes and 26 non-diabetic control subjects were recruited from a clinic in the Desheng Community in Beijing, China, from March to December 2014. This study complied with the Declaration of Helsinki and was approved by the Ethics Board of Beijing Tongren Hospital. All subjects gave written informed consent.

All participants had a comprehensive ophthalmological examination, which included best-corrected visual acuity (BCVA) measurements, slit-lamp biomicroscopy, and detailed fundus examination. BCVA was determined with Early Treatment Diabetic Retinopathy Study (ETDRS) protocol charts. We recorded the glycosylated hemoglobin A1c (HbA1c) of all the diabetic patients if the measurement was not older than one month; otherwise it was tested immediately after the patients were recruited. We also documented such information as the weight and height of the subjects and the duration of their diabetes. Exclusion criteria consisted of refractive error of over ±3.0 diopters, severe NPDR, proliferative DR, DR with diabetic macular edema (DME), or retinal disease other than DR, such as age-related macular degeneration (AMD) or retinal vein occlusion. Patients with blood pressure (≥140/90 mm Hg, or ≤90/60 mm Hg) were excluded. Also excluded were patients with a history of glaucoma, ocular trauma, ocular inflammation, or a history of any type of intraocular surgery, or a history of retinal photocoagulation.

Diabetic Retinopathy Grading Retinal status was recorded with a fundus photograph with seven 30° fields (Canon, Lake Success, NY, USA) with pupil dilated. The photographs were evaluated by an experienced ophthalmologist (Wei WW). Another ophthalmologist (Zhu WL) would reassess the photos in case of any doubt. The retinopathy severity was graded according to the ETDRS standard classification[23]. Retinopathy was considered present if there was at least one microaneurysm. The eyes were divided into 2 groups: no DR (NDR, level 10) or any DR (level 20 and above). The DR group was further graded into mild NPDR (20≤ETDRS level<43) and moderate NPDR (43≤ ETDRS level<53).

DME was diagnosed and excluded through stereoscopic biomicroscopy in accordance with the criteria reported by ETDRS, and was confirmed on spectral-domain optical coherence tomography (SD-OCT).

Enhanced Depth Imaging Spectral-domain Optical Coherence Tomography All Participants underwent SD-OCT examinations including EDI after pupil dilation (Cirrus-HD; Carl Zeiss Meditec, Inc., Dublin, CA, USA). The subfoveal choroidal thickness (SFCT) was measured at macular fovea from the outer portion of the hyperreflective line corresponding to the RPE to the hyporeflective line or margin corresponding to the sclerochoroidal interface. The OCT examinations were performed during the day between 9 a.m. and 10 a.m. The CT was measured by two other retinal ophthalmologists (Shen ZJ and She CY), who were blinded to the DR grading. Parafoveal choroidal thickness (PFCT) was measured at the nasal, superior, temporal, and inferior choroid quadrants (at a manually measured distance of 1500 μm from the foveal center) using the same method. We compared the values of each observer and then averaged them for analysis. Central macular retinal thickness (CMT) was determined automatically in all eyes.

Statistical Analysis We carried out statistical analysis by using SPSS statistical software (SPSS for Windows, version 17.0; SPSS Inc., Chicago, IL, USA). All data are presented as the mean±SD. The difference in SFCT between the control, NDR, and NPDR groups was generated by conducting one-way ANOVA followed by Bonferroni's post-hoc test for multiple comparisons. CTs of both eyes of the same subject were compared using paired *t*-test. The concordance correlation coefficient (Pearson correlation) was calculated for inter-observer correlations. Univariate linear regression analyses were carried out with SFCT as a dependent parameter and with age, CMT, BCVA, duration of diabetes, body mass index (BMI), and HbA1c as independent parameters in the diabetic groups. Multivariate linear regression was carried out with SFCT as the dependent parameter and the other variables as independent parameters. A value of $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics Eighty-three diabetic patients were enlisted in the study, including 50 females (60.2%) and 33 males (39.8%); the mean age was 67.9±6.7y (range 51-80y). All of the participants self-identified as Han Chinese. Of the 83 subjects, 49 were enrolled in the NDR group with an average age of 68.0±6.9y, while 34 patients with at least one eye having mild/moderate NPDR were enrolled in the NPDR group, with an average age of 67.8±6.4y. Of the 34 mild/moderate NPDR subjects, 15 had mild/moderate NPDR in one eye and NDR in the other eye, and 19 had NPDR in both eyes. Twenty-six non-diabetic control subjects with an average age of 65.1±6.3y (range 51-78y) were also recruited for the study, including 16 females (61.5%) and 10 males (38.5%). There was no significant difference in age and sex between the subjects with diabetes and the non-diabetic controls. Table 1 shows the basic characteristics of the subjects.

Enhanced Depth Imaging Spectral-domain Optical Coherence Tomography All participants underwent EDI-OCT examination of both eyes; five left eyes (three in the control group and two in the NDR group) could not be assessed because of severe lens opacities or vitreous clouding. The concordance correlation coefficient was found to correlate significantly between the two observers ($P=0.01$).

Table 1 Baseline characteristics of subjects $\bar{x} \pm s$

Parameters	Control subjects	NDR	Mild or moderate NPDR
No. of participants	26	49	34
Age (a)	65.1±6.3	68.0±6.9	67.8±6.4
DM duration (a)	-	10.43±6.65	13.68±7.60
HbA1c (%)	-	6.48±0.81	6.99±1.25
BMI	24.97±2.60	24.16±2.95	24.94±3.32
BCVA, EDTRS	62.31±4.61	62.45±7.08	60.18±6.74
CMT (μm)	236.92±21.77	239.39±20.84	248.44±24.14

NDR: Non-diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; DM: Diabetes mellitus; HbA1c: Glycosylated hemoglobin A1c; BMI: Body mass index; BCVA: Best-corrected visual acuity; CMT: Central macular retinal thickness. BCVA and CMT: Data of the right eyes of controls and NDR subjects, and the worse eyes of NPDR subjects.

Table 2 SFCT and PFCT in the control, NDR, and NPDR groups

Parameters	Control	NDR	Mild/moderate NPDR	*P*
SFCT	252.77±41.10	221.51±46.56[a]	207.18±61.87[a]	0.00
Nasal (1.5 mm)	207.85±55.36	185.69±48.34	182.50±59.05	0.15
Temporal (1.5 mm)	218.62±36.52	197.53±38.90	200.62±43.03	0.08
Inferior (1.5 mm)	220.77±53.08	202.43±43.19	194.97±48.95	0.11
Superior (1.5 mm)	225.54±39.65	201.35±39.51	206.26±47.98	0.06

SFCT: Subfoveal choroidal thickness; PFCT: Parafoveal choroidal thickness; NDR: Non-diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; *P*: Statistical difference with control group; [a]Statistically significant compared with controls.

Intra-group comparisons were done for CT of both the two eyes. SFCT values for the 23 subjects in the control group were 252.46±42.85 μm in the right eyes and 255.83±45.61 μm in the left eyes. Pearson correlation of the right and left eyes was 0.95 (P<0.01). The paired t-test revealed no significant difference in SFCT between the right and left eyes in the control group (t=1.55, P=0.14).

The SFCT values for the 47 subjects in the NDR group were 221.28±46.87 μm in the right eyes and 225.82±45.37 μm in the left eyes. Pearson correlation of the right and left eyes was 0.93 (P<0.01). Neither did the paired t-test find any significant difference in SFCT between the right and left eyes in NDR group (t=1.81, P=0.08).

Of the 19 mild/moderate NPDR subjects having NPDR in both eyes, SFCT was 210.40±56.59 μm in the right eyes and 206.24±58.63 μm in the left eyes. Pearson correlation of the right and left eyes was 0.89 (P<0.01). No significant difference was found in SFCT of the right and left eyes in these subjects (t=0.68, P=0.51). Of the 15 mild/moderate NPDR subjects having NPDR in only one eye, SFCT was 234.73±71.41 μm in the NDR eyes and 213.20±67.04 μm in the NPDR eyes. SFCT in the NDR eyes was significantly thicker than that in the NPDR eyes using the paired t-test (t=4.24, P<0.01).

The right eyes of the controls, the right eyes of the NDR subjects, and the worse eyes of the NPDR subjects were chosen for the following analysis among groups: SFCT was 252.77±41.10 μm in the right eyes of the control group (26 eyes); 221.51±46.56 μm in the right eyes of the NDR group (49 eyes); and 207.18±61.87 μm in the worse eyes of the NPDR group (34 eyes). There was a statistical difference in SFCT among the three groups (F=6.06, P<0.01). SFCT in the control group was significantly thicker than in the NDR and NPDR groups (P=0.04 and P<0.01, respectively). No significant difference of SFCT was found between NDR and NPDR groups (P=0.54).

The choroid was thinnest nasally and thickest in the subfoveal region in the NDR, NPDR, and control groups. The PFCT in the NDR and NPDR groups at the nasal, superior, temporal, and inferior choroid quadrants (at 1500 μm intervals from the center of the fovea) was not statistically significantly different as compared with that of the control group (Table 2).

Table 3 demonstrates the outcome of univariate linear regression analyses using SFCT as a dependent parameter and age, CMT, BCVA, duration of diabetes, BMI, and HbA1c as independent parameters. No variation associated with SFCT was found in either NDR or NPDR groups. Age showed a relative association with SFCT in the NPDR group (P=0.05). CMT was associated with SFCT in the control group.

A stepwise multivariate linear regression analysis was performed using SFCT as the dependent parameter and all of the others in the univariate analysis as independent parameters. There were no variations associated with SFCT in the NDR and NPDR groups. CMT was again associated with SFCT in the control group. If all diabetic cases including the NDR and NPDR subjects were pooled as a group, age (P=0.01) was a significant predictor of SFCT after the stepwise multiple linear regression analysis (Table 4).

Table 3 Univariate linear regression analysis of various factors for the SFCT

Parameters	Unstandardized coefficients estimate (standard error)	Correlation coefficients	*P*
NDR			
Age	-1.10 (1.22)	-0.16	0.37
BCVA	1.13 (1.17)	0.17	0.34
CMT	-0.03 (0.34)	-0.01	0.94
Duration of diabetes	-0.24 (1.10)	-0.03	0.83
HbA1c	-9.29 (8.67)	8.67	0.29
BMI	2.21 (2.38)	2.38	0.36
NPDR			
Age	-3.90 (1.87)	-0.42	0.05
BCVA	0.90 (1.67)	0.10	0.59
CMT	0.81 (0.44)	0.32	0.07
Duration of diabetes	-0.34 (1.36)	-0.04	0.80
HbA1c	1.03 (8.48)	0.02	0.90
BMI	4.19 (3.38)	0.23	0.23
Controls			
Age	-2.13 (1.26)	-0.31	0.11
BCVA	0.05 (1.73)	0.01	0.98
CMT	1.03 (0.36)	0.52	0.02[a]
BMI	-4.47 (3.01)	-0.27	0.15

SFCT: Subfoveal choroidal thickness; NDR: Non-diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; BCVA: Best-corrected visual acuity; CMT: Central macular retinal thickness; HbA1c: Glycosylated hemoglobin A1c; BMI: Body mass index; [a]Statistically significant.

Table 4 Multivariate linear regression analysis of various factors for SFCT in 83 diabetic patients

Parameters	Correlation coefficients	*P*
Age	-0.28	0.01[a]
BCVA	0.14	0.79
CMT	0.15	0.19
Duration of diabetes	-0.07	0.53
HbA1c	0.15	0.83
BMI	0.17	0.12

SFCT: Subfoveal choroidal thickness; BCVA: Best-corrected visual acuity; CMT: Central macular retinal thickness; HbA1c: Glycosylated hemoglobin A1c; BMI: Body mass index; [a]Statistically significant.

DISCUSSION

We assessed the changes of CT in NDR and mild/moderate NPDR in patients with type 2 diabete using EDI-OCT. A significant reduction of SFCT was found in patients with NDR or mild/moderate NPDR in comparison with the non-diabetic control group. Although a trend of reduction was observed, the difference of PFCT in both NDR and NPDR groups was not statistically significant. These data indicate that choroidal thinning is diffusely present in NDR and mild/moderate NPDR. Moreover, the choroid was thinnest nasally and thickest in the subfoveal region in the NDR, NPDR, and control groups. This confirms recently published data on the CT in the macular area in normal and diabetic subjects[14-15,24]. Previous studies by Tan *et al*[20] and Usui *et al*[21] have shown a circadian rhythm pattern of approximately a 20- to 30-μm change in CT measurements by OCT. The OCT examinations in our study were all performed at a similar time of day to avoid bias. In the present study, we did not include the stages of PDR and DME because most of previous studies came to similar conclusions for these stages of DR in which the SFCT was thinner than in normal eyes[11-15,25]. Subjects with refractive error of over ±3.0 diopters were excluded to decrease the effect of refractive error[8].

The results of the present study were consistent with those of previous studies[11-13]. The study by Querques *et al*[13] involved 63 consecutive diabetic patients and 21 healthy subjects. They found that the mean SFCT remarkably decreased in diabetic groups including NDR in comparison with the control group. Esmaeelpour *et al*[11-12] mapped CT in both type 1 and type 2 diabetic patients and found that the choroid was thinner regardless of disease stage compared to healthy controls matched for axial length and age. However, there were different results with regard to the changes of CT in diabetic eyes. For example, the study by Xu *et al*[16] based on population showed that the subfoveal choroid in diabetic patients were slightly, but statistically significantly, thicker, while the presence and stage of DR were not related to an abnormal SFCT. However, of the 246 patients with diabetes mellitus in that population-based study, only 23 had DR. Vujosevic *et al*[15] investigated 102 type 1 or type 2 diabetic patients as well as 48 normal subjects and found that the mean SFCT progressively and significantly decreased with increasing levels of DR; there was no significant difference in SFCT between the controls and the diabetic eyes with no detectable DR. A study by Regatieri *et al*[14] showed that no significant difference in CT between normal subjects and the NPDR group was observed. One of the reasons for the divergent results from the various studies might be the relatively small sample sizes for the different stages of DR, especially in NDR and the mild/moderate NPDR stages. Another possible reason is the measurement of CT was done at different times of the day[20-21]. In this current study, we paid special attention to the time of CT measurements. This finding of choroidal thinning in eyes with NDR and mild/moderate NPDR showed a novel way to detect early changes in diabetic eyes, even without detectable DR.

The concept of diabetic choroidopathy was first introduced by Hidayat and Fine[2], who observed capillary dropout and choroidal neovascularization (CNV) in enucleated eyes of diabetic patients using light and electron microscopy. However, few studies about diabetic choroidopathy were performed because high-resolution visual image of the choroid was difficult. A laser Doppler flowmetry study found decreasing

blood flow of the choroid in patients with type 2 diabetes before diabetic retinopathy manifested itself[5]. Indocyanine green angiographic findings disclosed that vascular changes might also affect the choroid in patients with NPDR[26]. Until the development of EDI-OCT, the CT could be visualized and measured and then choroidopathy could be clinically studied. Several studies using EDI-OCT, including ours, showed that the CT was thinned in the NDR and mild/moderate NPDR stages[11-13,15]. However, the mechanism of choroidal thinning in eyes with NDR and mild/moderate NPDR remains unknown. Histologic findings have proved atrophy and extensive dropout of the choriocapillaris in eyes with diabetic retinopathy[3,27].

In diabetic subjects, the decreased CT might cause retinal hypoxia because of the degeneration of choriocapillaris[4]. Hypoxia could increase the expression of vascular endothelial growth factor (VEGF) in RPE cells, pericytes, and microvascular endothelial cells[28], and could induce dysfunction of the blood-retinal barrier, which is the basis of DR in patients with diabetes[29]. In addition, compromised choriocapillaris could result in insufficient removal of waste generated by the RPE cells, causing an accumulation of such waste in the Bruch membrane[4,30-31]. Diabetic choroidopathy might play an important role in the pathogenesis of DR since the outer retinal layers are largely dependent on the choroid for their nutrition and oxygenation[2]. Choroidopathy, such as choriocapillaris degeneration, may be responsible for the reduced visual function in subjects with diabetes before the onset of retinopathy[4].

In conclusion, we showed that in NDR and the mild/moderate NPDR stages of diabetic eyes, there was an overall thinning of the CT on EDI-OCT. Age was significantly associated with SFCT in the diabetic patients. The findings indicate that in diabetic eyes, choroidopathy might be present before the clinical retinopathy. EDI-OCT is a noninvasive technology for assessing diabetic choroidopathy even without DR.

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