In Vivo Assessment of Choroid in Diabetic Retinopathy by Enhanced Depth Imaging in Spectral Domain Optical Coherence Tomography

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Purpose: The aim of this study was to measure the largest hyporeflective (LHR) lumen in the choroid and subfoveal choroidal thickness (SFCT) in patients with diabetic retinopathy (DR) and in control subjects using enhanced depth imaging (EDI) spectral domain optical coherence tomography (SD-OCT).

Design: This was a prospective, cross-sectional study.

Methods: This was a study of 240 eyes of DR patients (n = 120) and control subjects (n = 120) matched for age, sex, and refractive error. The LHR lumens of the choroidal vessels and SFCT were measured by EDI SD-OCT. Further intergroup classification into nonproliferative and proliferative DR, with or without macular edema, was done.

Results: The mean diameter of the LHR lumen in DR patients (139.24 ± 35.53 μm) was significantly smaller ($P < 0.01$) than in control subjects (186.37 ± 26.43 μm). The mean SFCT was also significantly less ($P < 0.01$) in patients with diabetes (277.15 ± 32.24 μm) as compared with control subjects (313.68 ± 25.13 μm). There was no significant intergroup variation.

Conclusions: Patients with DR showed smaller LHR lumen and SFCT as compared with control eyes. In vivo assessment of the choroid in DR is possible using EDI SD-OCT.

Key Words: EDI SD-OCT, diabetic choroidopathy, diabetic retinopathy, subfoveal choroidal thickness

Diabetes is a multisystem metabolic disorder affecting the ocular tissue as well. It has been demonstrated that in the posterior segment the diabetic retinal and choroidal vessels become blocked. This leads to various choroidal abnormalities, including obstruction of the choriocapillaris, vascular degeneration, choroidal aneurysms, and choroidal neovascularization.[1–3]

In vivo study of the choroid has been attempted in the form of fluorescein angiography and indocyanine green angiography, showing hyperfluorescent and hypofluorescent spots in eyes of patients with diabetes, although the significance is unknown.[3–7] With the advent of enhanced depth imaging spectral domain optical coherence tomography (EDI SD-OCT), several studies have been done to measure the thickness of the choroid and correlate it with the choroidal vascular changes and morphology in diabetes.[8–11] The changes in thickness have been controversial. None of the studies have measured the caliber of the largest choroidal vessels seen distinctly on EDI SD-OCT.

Thus, we decided to study the change of choroidal vessel caliber in nonproliferative and proliferative diabetic retinopathy (DR) and to find its relevance as an in vivo tool of morphological study of the choroid in DR.

MATERIALS AND METHODS

A prospective, cross-sectional study, including 240 eyes of DR patients (n = 120) and control subjects with no diabetes (n = 120), was undertaken. The largest hyporeflective (LHR) lumen of the choroidal vessels and subfoveal choroidal thickness (SFCT) were measured with EDI SD-OCT.

The clinical study included patients with DR who presented between March and June 2014. Ethical approval for this study was provided by the Ethical Committee of the Retina Foundation and Asopalov Eye Hospital, Ahmedabad, Gujarat, in February 2014. Informed consent was obtained from all patients.

The inclusion criteria consisted of all eyes that ophthalmoscopically revealed various grades of DR. Major exclusion criteria were as follows: (1) another ocular disease, (2) previous treatment for DR, or (3) previous pars plana vitrectomy. Patients with uncontrolled hypertension, chronic renal failure requiring dialysis or kidney transplant, or pancreatic transplant were also excluded. Eyes with poor image quality due to media opacification or fundus pigmentation were excluded as well.

A control group (n = 120) was selected from random patients presenting for routine check-up. They were matched for age, sex, and refractive error. Nondiabetic status was confirmed by a thorough history and random blood sugar level measurement.

Detailed evaluation was performed for every patient. This included visual acuity assessment using Snellen chart, refraction, intraocular pressure (IOP) measurement using the auto-noncontact tonometer (NT-3000; Nidek, Japan), anterior segment slit-lamp examination, indirect ophthalmoscopy, and axial length measurement (OTI scan ophthalmic ultrasound; Ophthalmic Technologies Inc, Toronto, Ontario, Canada).

All eyes underwent SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) with EDI as described by Spaide and colleagues.[12] All OCT measurements were performed by 2 experienced examiners independently of each other. The patients were examined with the OCT device positioned close enough to the eye to produce a clear image. The OCT images were acquired with high-speed mode (768 A-scans). The resultant images were viewed and measured with the Heidelberg Eye Explorer software (version 1.5.12.0; Heidelberg Engineering). The procedure algorithm was as follows:

(1) Three separate line scans, each comprising 100 averaged line scans, were centered on the fovea;
(2) All lumens within 4500 μm were assessed in each line scan, and the larger lumens were localized in each scan;
(3) Among these, the 3 largest lumens were averaged.

The choroid was measured from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium (RPE) to the inner surface of the sclera (Fig. 1). Within the choroid in the outer Haller layer and in the intermediate Sattler
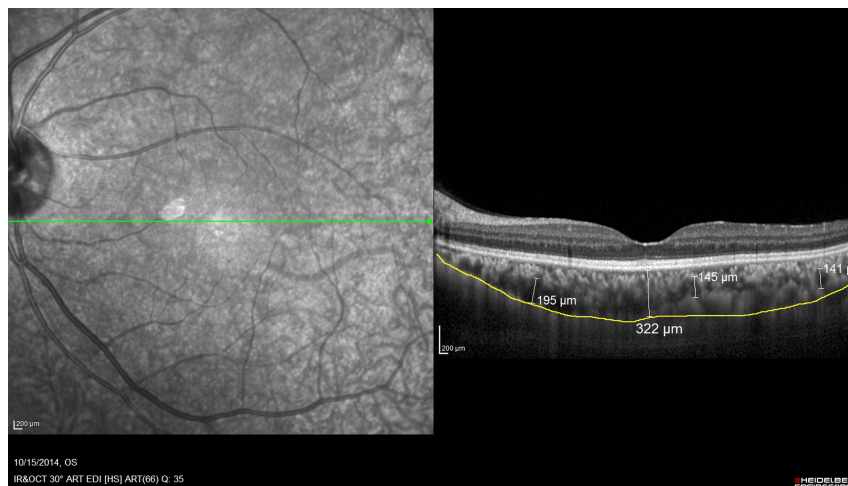
FIGURE 1. Measurement of SFCT and LHR lumen.

layer, we detected hyporeflective lumen in all eyes. The lumens in the choroidal layer were taken as surrogates for choroidal vessels, as an assumption.[13]

All discernible hyporeflective lumens in the choroid, within a zone of 4500 μm centered on the fovea, were assessed, and the larger lumens were localized. Then, the diameters of the larger lumens were measured. Among these, the 3 largest lumens were averaged. The diameter of each hyporeflective lumen was assessed perpendicular to the Bruch membrane. The region of measurement did not differ between the study group and the control group. If the measurements of the 2 examiners differed by more than 15%, the examiners performed the measurement again together. If the difference between both measurements was more than 15%, the mean of the 2 values was used for statistical analysis.

The eyes of patients with diabetes were graded according to the Early Treatment Diabetic Retinopathy Study[14] classification into nonproliferative and proliferative retinopathy. They were then further grouped on the basis of the presence or absence of diabetic macular edema.[15] They were divided into 4 groups: nonproliferative DR with diabetic macular edema (group A), nonproliferative DR without diabetic macular edema (group B), proliferative DR with diabetic macular edema (group C), and proliferative DR without diabetic macular edema (group D).

Statistical analysis was performed using SPSS for Windows version 19.0 (IBM-SPSS, Chicago, Ill). Measurements are presented as mean ± SD. The study group was compared with the control group using Student t test for unpaired samples. Intergroup variations were measured using analysis of variance.

RESULTS

A total of 240 eyes of patients with diabetes (n = 120) and control subjects (n = 120) were included in the study. Among the diabetic patients, 108 were male and 12 were female. The mean age was 60.33 years, ranging from 47 to 69 years. The study population included 48 eyes in group A, 24 in group B, 32 in group C, and 16 in group D. One hundred twenty eyes of patients with no diabetes served as control subjects.

On comparing the characteristics of individuals with diabetes mellitus and control subjects, there was no statistical difference in age, sex, axial length, or IOP (Table 1).

The average duration of diabetes at presentation was 13.64 ± 2.75 years. The group-wise distribution of duration was 11.40 ± 7.81 years for group A, 12.25 ± 5.47 years for group B, 17.60 ± 8.36 years for group C, and 13.33 ± 9.56 years for

group D. The intergroup comparison of duration was not statistically significant (P = 0.43).

The average LHR lumen was tabulated for the various groups. It was 132.48 ± 15.53 μm, 144.42 ± 18.04 μm, 134.08 ± 15.27 μm, and 146 ± 22.90 μm for groups A, B, C, and D, respectively. The average LHR lumen for normal subjects was 186.37 ± 26.43 μm. The mean diameter of the LHR lumen was significantly (P < 0.01) smaller in eyes of patients with diabetes (139.24 μm) as compared with the control group (186.37 μm). The intergroup comparisons among patients with diabetes were not significant (P = 0.19) (Table 2; Figs. 2–5).

The mean SFCT was 277.15 μm in patients with diabetes and 313.69 μm in control subjects. The mean SFCT was also significantly less (P < 0.01) in patients with diabetes. In intergroup measurement, the SFCT was 274.62 ± 43.27 μm in group A, 273.42 ± 18.94 μm in group B, 262.56 ± 41.24 μm in group C, and 298 ± 53.29 μm in group D. The difference among the groups was not statistically significant (P = 0.15) (Table 2; Figs. 2–6).

DISCUSSION

Yang et al[13] conducted a study to measure the hyporeflective lumen in the choroid of patients with central serous chorioretinopathy. They presumed these hyporeflective lumens to be choroidal vessels and showed their engorgement in affected eyes.

A multitude of previous studies have established the metabolic changes produced and growth factors released in the diabetic

TABLE 1. Demographics and Characteristics of Patients With Diabetes and Control Subjects

	Patients With Diabetes	**Control Subjects**	***P***
Age, y	60.33 ± 5	59.99 ± 7	3.05
Sex			—
Male	108 (90%)	0 (91.67%)	
Female	12 (10%)	10 (8.33%)	
Duration at presentation, y	13.64 ± 8.8	—	—
Axial length, mm	23.3 ± 1.15	23.7 ± 1.29	0.12
IOP, mm Hg	16 ± 5	14 ± 5	0.08
LHR lumen, μm	139.24 ± 35.53	186.37 ± 26.43	<0.01
SFCT, μm	277.15 ± 32.24	313.68 ± 25.13	<0.01

TABLE 2. Average LHR Lumen and SFCT Measurements in Groups and Control Subjects

Group	NPDR With DME (Group A)	NPDR Without DME (Group B)	PDR With DME (Group C)	PDR Without DME (Group D)	Control Subjects	P
LHR lumen, μm	132.48 ± 15.53	144.42 ± 18.04	134.08 ± 15.27	146.00 ± 22.90	186.37 ± 26.43	0.19
SFCT, μm	274.62 ± 43.27	273.42 ± 18.94	262.56 ± 41.24	298.00 ± 52.29	313.68 ± 25.13	0.15

NPDR indicates Nonprofilferative Diabetic Retinopathy; PDR, Proliferative Diabetic Retinopathy; DME, Diabetic Macular Oedema.

choroid to be similar to those of the retina. The choroidal vascular system has further been implicated in the pathogenesis of DR.[16–20] Recently, the emergence of EDI SD-OCT has allowed for the in vivo assessment of choroidal thickness and possibly its vasculature. With this in mind, this study was conducted to delineate the choroidal changes in DR.

In our study, the average duration of diabetes at presentation was 13.64 years. This strongly emphasizes the fact that the frequency of retinopathy has an association with the duration of diabetes. As the duration increases, the prevalence of the retinopathy changes also increases. This correlation has been well documented in several other studies.[21,22]

Regarding the sex ratio, we selected patients as they came to the outpatient department and fit our criteria. Most of the females in the clinic had more advanced systemic involvement on presentation, and they were excluded for accompanying morbidities. It was just a matter of chance that most females did not meet our inclusion criteria.

The measured diameter of the LHR lumen in the choroidal layer was 186.37 ± 26.43 μm in the control group. Yang et al[13] also evaluated choroidal vessel caliber in their study. It was measured to be 140 ± 40 μm. Correspondingly, the mean SFCT in the control group of 313.68 ± 25.13 μm compared well with the mean SFCT reported in a pilot study by Margolis and Spaide (287 ± 71 μm)[23] and that recently measured in a larger group of healthy Chinese subjects (262 ± 88 μm).[24] These comparisons may serve to validate the data obtained in our study.

Diabetic retinopathy has been known to create a condition of choroidal compromise suggested by luminal narrowing of the capillaries, capillary dropout, and focal scarring. Various choroidal abnormalities, including obstruction of the choriocapillaris, vascular degeneration, choroidal aneurysms, and choroidal neovascularization, have been reported in previous studies on eyes of patients with diabetes.[1–3] The changes in the choroidal arteries partially resemble the arteriosclerotic arteries of diabetic glomerulosclerosis, namely,

Kimmelstiel-Wilson disease.[1] Small choroidal blood vessels have thickened basement membranes.

We assessed the SFCT. It was 277.15 ± 32.24 μm in patients with diabetes and 313.68 ± 25.13 μm in control subjects. We saw a significant thickness reduction ($P < 0.01$) in patients with diabetes. This might be a consequence of the thinning and dropout of the choroidal vessels as seen by the luminal narrowing, leading to an overall decrease in choroidal thickness.

The LHR lumen noted in the patients with diabetes in our study was 139.24 ± 35.53 μm. This was significantly smaller ($P < 0.01$) than that in the control subjects (186.37 ± 26.43 μm). This supports the luminal narrowing and dropout of the choroidal vessels seen by electron microscope.[1]

As hypothesized by Querques et al[25] in their study of EDI OCT in type 2 diabetes, decreased choroidal thickness at the fovea may be a reason for the development of macular edema. The reduced SFCT, probably due to the dropout of the choriocapillaris (and determining increased vascular resistance), may cause retinal hypoxia. In fact, it is the role of the choroidal vasculature, especially the choriocapillaris, to provide nutrients to the RPE and outer retinal layers in the foveal region. Because of tissue hypoxia, vascular endothelial growth factor expression increases in the RPE, pericytes, and microvascular endothelial cells and may induce the breakdown of the blood-retinal barrier, which is the basis of diabetic macular edema.

We also noted that cases with and without diabetic macular edema showed a difference of lumen thickness that was not statistically significant ($P = 0.10$), but on close observation, the subjects with macular edema had smaller lumens. This could be similar to DR, where there is a decrease in the vascular caliber of the veins, and these changes are all related to progressive capillary nonperfusion and retinal ischemia. They are also markers of an increased risk of progressing to proliferative disease. The choroidal changes may be inferred as a duplication of retinopathy.

Thus, in our study, we have tried to establish a simple, noninvasive, and less time-consuming method for simultaneous in vivo morphological assessment of the choroid in cases of DR and its correlation with the retinopathy.
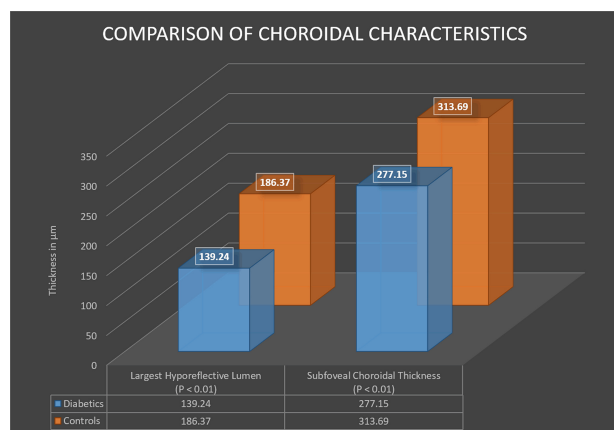
FIGURE 2. Comparison of choroidal characteristics.
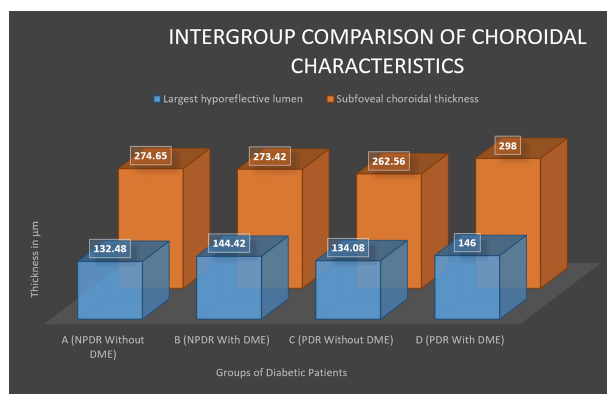
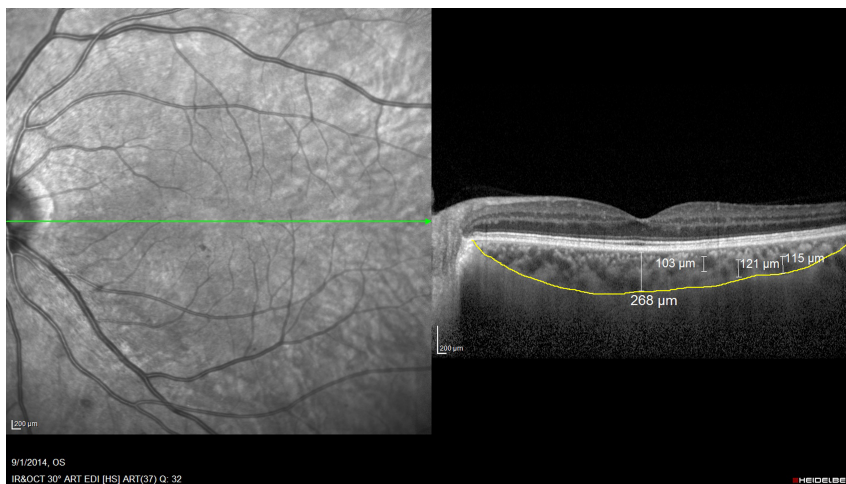**FIGURE 3.** Intergroup comparison of choroidal characteristics.

FIGURE 4. Largest hyporeflective lumen and SFCT in Nonproliferative Diabetic Retinopathy.

FIGURE 5. Largest hyporeflective lumen and SFCT in Nonprofilferative Diabetic Retinopathy with Diabetic Macular Oedema.
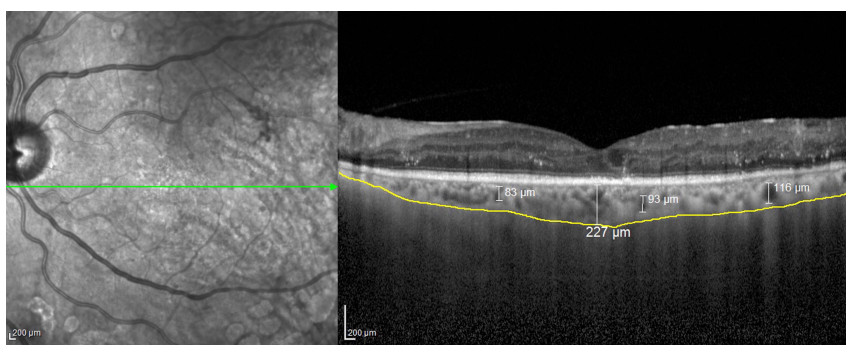

FIGURE 6. Largest hyporeflective lumen and SFCT in Proliferative Diabetic Retinopathy.

Further study is necessary to determine if the changes in the choroid appear before the retinopathy and if they can act as an early marker for impending retinopathy.

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