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Evaluation of Choroidal Thickness in Diabetic Macular Edema Using Spectral-Domain Optical Coherence Tomography Enhanced Depth Imaging Mode

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ABSTRACT

Purpose: to evaluate the choroidal thickness (CH-T) and the central macular thickness (CMT) in eyes with diabetic macular edema (DME) and to detect if CH-T varies according to the type of DME.

Patients and methods: One hundred forty two eyes of 96 patients were enrolled in the study. Eyes of diabetic patients with non-proliferative diabetic retinopathy (NPDR) with/without DME were evaluated. Eyes of normal subjects with no ocular or systemic diseases were included as a control group. The CMT and the underlying choroidal thickness were estimated using enhanced depth imaging mode of spectral-domain optical coherence tomography (EDI SD-OCT). CH-T thickness was measured at the subfoveal area and at an interval of 500 µm up to 1500 µm from the center of the fovea (nasal, temporal, superior and inferior). In eyes with DME, the type of DME was detected.

Results: DME included cystoid DME (19 eyes), diffuse DME (27 eyes), and DME with serous retinal detachment (SRD) (23 eyes). 33 eyes with NPDR without DME and 40 non diabetic normal eyes were examined. Estimation of the choroidal thickness was performed and the subfoveal CH-T was thickest in the control group and significantly decreased in the diabetic groups especially with DME. The sub-foveal CH-T was 326±25.75 µm in the control group, 256.27±30.5 µm in NPDR without DME group, 210±23.96 µm in Cystoid DME group, 215.5±27.0 µm Diffuse DME group and 195.2±23.9 µm in DME with SRD group. The CMT was 238.75 ± 14.7 µm, 260.85 ± 24 µm, 530± 120.5 µm, 420.8± 101.6 µm and 506.60± 131.87 µm in the control group, NPDR without DME group, Cystoid DME, Diffuse DME and DME with SRD groups respectively. There was a statistically insignificant negative correlation between the subfoveal choroidal thickness and the CMT.

Conclusion; there is an overall decrease in the CH-T in patients with NPDR and this thinning become more pronounced with the presence of diabetic macular edema.

Keywords: diabetic macular edema, choroidal thickness, enhanced depth imaging, spectral-domain optical coherence tomography

INTRODUCTION

There is a growing interest in the role of the choroid in various chorioretinal diseases. Abnormalities of the choroidal integrity have been associated with the pathogenesis of several retinal diseases, such as age-related macular degeneration, central serous chorioretinopathy and diabetic maculopathy [1]. The choroidal vasculature, especially the choriocapillaris, is critical for maintenance of the neurosensory retina because it supplies the outer retina with nutrition and oxygen. It is most important in the foveal avascular zone [2]. The role of the choroid is increasingly gaining attention as a key factor in diabetic eye disease. There is histopathologic evidence that diabetes causes choroidal abnormalities including arteriosclerosis, choriocapillaris degeneration, and neovascularization [3]. Diabetic macular edema (DME) is a leading cause of blindness in patients with diabetic retinopathy worldwide. Although alterations in retinal vasculature resulting in compromise of the blood-retinal barrier have been demonstrated to have a critical role in the pathophysiology of the disease, changes in the choroidal vasculature may also have a contributing role [4]. The choroidal vasculature may play a potential role in modulating disease severity by affecting the hydrostatic or osmotic pressures that determine the absorption rate of intraretinal fluid [5]. Decreased blood flow in the choriocapillaris may cause retinal tissue hypoxia and subsequent increased expression of vascular endothelial growth factor (VEGF), which is one of the mechanisms implicated in the pathogenesis of DME [6].

Prior to the advent of optical coherence tomography (OCT), clinical evaluation of the choroid has involved fundus fluorescein

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angiography (FFA), indocyanine green angiography, and ultrasound. While these methods are useful in detecting vasculature abnormalities, they do not provide cross-sectional anatomical information and poorly identify the depth of vascular pathology [7]. The development of enhanced depth imaging-spectral domain (EDI-SD)-OCT has improved visualization of the choroid with high resolution cross-sectional imaging, enabling reliable and reproducible measurements of full choroidal thickness [8]. The most recent Spectralis software version (Heidelberg Engineering, Heidelberg, Germany) makes EDI even more user friendly by incorporating EDI into the scanning protocols [9]. Spectralis-EDI mode places the retinal pigment epithelium (RPE) near the zero-delay line while producing an upright enhanced choroidal image without the need to manually push the device closer to the eye [10]. Image averaging, eye tracking, high-speed scanning, and low speckle noise produce high-quality choroidal images with the EDI mode in the Spectralis-OCT [9].

The current study was conducted to investigate the changes in choroidal thickness within the macular area in eyes with various types of diabetic macular edema, by comparing the measured values with those of healthy normal subjects and of subjects with diabetic retinopathy without diabetic macular edema and to correlate the sub-foveal choroidal thickness measurements with the central macular thickness.

PATIENTS AND METHODS

A prospective, nonrandomized, observational study was conducted to evaluate the central macular thickness (CMT) and the choroidal thickness (CH-T) in eyes with treatment-naïve diabetic macular edema. One hundred forty two eyes of 96 subjects were enrolled in the study. The current study included eyes of patients with type 2 diabetes mellitus and in the stage of non-proliferative diabetic retinopathy (NPDR) with center-involving DME. Eyes of diabetic patients with mild-moderate NPDR without DME and eyes of normal healthy subjects were included. Ethical approval was obtained from the local ethics committee and an informed consent was obtained from recruited subjects.

Exclusion criteria were refractive error more than ±3 diopters, systemic diseases other than diabetes, glaucoma, history of ocular trauma or intraocular surgeries, previous laser therapy or intravitreal injections, uveitis, significant media opacities that precluded fundus examination or imaging, epimacular membrane, vitreomacular traction, ischemic maculopathy, proliferative diabetic retinopathy and other retinal pathologies apart from NPDR as; hypertensive retinopathy, age-related macular degeneration, retinal vein/artery occlusion, etc.

All enrolled subjects had a complete ophthalmic examination, including best-corrected visual acuity, intraocular pressure estimation using Goldmann applanation tonometer, anterior segment examination , dilated fundus examination with indirect ophthalmoscope and slit-lamp biomicroscopic examination with + 90 non-contact lens. FFA was performed to confirm the type of DME and to exclude ischemic maculopathy. OCT was performed using Heidelberg Spectralis SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany). The studied eyes were chosen if the eye meet both the inclusion and exclusion criteria. If both eyes of the same subject were qualified, both were selected.

Central Macular thickness measurement:

The fast macular thickness OCT scan protocol was performed with measurements from 20 x 20-degree raster scans (consisting of 25 scans). The mean thickness of the central 1-mm zone of the 1, 3, 6 mm Early Treatment Diabetic Retinopathy Study (ETDRS) grid thickness map was measured by the program incorporated in the Spectralis OCT software.

Choroidal thickness measurement:

To obtain the choroidal image, Heidelberg Spectralis SD-OCT-EDI button in the Spectralis software was used. The white-on-black image color was used for better contrast between the choroid and the sclera. The choroidal thickness was measured manually, using the caliper tool in the Heidelberg Spectralis OCT software, as perpendicular line, from the outer portion of the hyperreflective line corresponding to the RPE to the choroidoscleral interface. The choroidal thickness was measured from vertical and horizontal scans centered on the fovea. The CH-T measurements were obtained from the subfoveal and parafoveal areas at an interval of 500 μm up to 1500 μm from the center of the fovea (nasal, temporal, superior and inferior). All measurements were performed at the same time of

the day from 1PM-3PM for the diurnal variation of the choroidal thickness.

Detection of Diabetic macular edema type:

DME was classified with OCT into three subtypes: type 1, thickening of the fovea with intraretinal cystoid change (cystoid type); type 2, sponge like diffuse retinal thickening (diffuse type); and type 3, thickening of the fovea with serous retinal detachment (SRD-type) [11]. Only eyes with center-involving DME, as seen on OCT, without prior therapy were included in the study.

Statistical analysis:

Statistical analyses were performed using the Statistical Package for the Social Sciences, (SPSS for Windows version 15.0, Chicago, IL, USA). Data are expressed as means ± standard deviation (Mean ± SD). Comparative analyses of the studied groups were made using one-way analysis of variance (ANOVA), followed by Bonferroni post-hoc tests. The Pearson correlation coefficient was used to evaluate the correlation between the choroidal thickness and the central macular thickness. A 95% confidence interval with a 5% level of significance was adopted; thus, P values of <0.05 were considered to be statistically significant.

RESULTS

One hundred forty two phakic eyes of 96 age-matched subjects (70 female, 26male) were included in the study, of these, 66 eyes (46.48%) were right eyes. Of the 142 eyes enrolled in the current study; 40 eyes were normal, with no retinal or choroidal pathologies, 33 eyes with NPDR without DME, 19 eyes with cystoid DME, 27 eyes with diffuse DME and 23 eyes with DME and serous retinal detachment (SRD). The basic data for all included subjects are summarized in (Table 1).

CMT measurements

The CMT was significantly increased in eyes with DME. The CMT was 238.75 ± 14.7 µm in the control group, 260.85 ± 24 µm in NPDR without DME group, 530± 120.5 µm in Cystoid DME group, 420.8± 101.6 µm in Diffuse DME group and 506.60± 131.87 µm in DME with SRD group (Figure 1, Table 2). There was a statistically highly significant difference in CMT between the control group and the studied DME groups (P<0.001), while there was non-significant difference between the control group and DR without DME group (P >0.5).

Evaluation of CH-T in different groups:

The subfoveal CH-T was thickest in the control group and significantly decreased in the diabetic groups. The sub-foveal CH-T was 326±25.75 µm in the control group, 256.27±30.5 µm in NPDR without DME group, 210±23.96 µm in Cystoid DME group, 215.5±27.0 µm in Diffuse DME and 195.2±23.9 µm in DME with SRD group (Figures 1, 2 and 3, Table 2).

Accordingly, a statistically highly significant difference was shown between the sub-foveal choroidal thickness in the control group and the NPDR with/without DME groups (P <0.001). The choroidal thickness was highly significantly thinner in DME groups than in NPDR without DME group (P<0.001). Within the DME groups, there was a statistically non-significant difference between CH-T in Cystoid DME group compared with Diffuse DME group (P=1.00); Cystoid DME group compared with DME with SRD group (P=0.74); and Diffuse DME compared with DME with SRD group (P=0.08).

The choroid was noted to be thinner nasally than temporally and inferiorly than superiorly and thickest in the subfoveal region in all studied groups. The thinnest part was nasal followed by inferior, superior then temporal and this order was preserved even with decreased choroidal thickness in NPDR with/ without DME (Figure 4, Tables 2).

The parafoveal CH-T measurements of the nasal, temporal, superior and inferior quadrants at an interval of 500 µm up to 1500 µm from the center of the fovea were statistically significantly thinner in DME groups as compared with that of the control group and NPDR without DME group (P< 0.001).

Correlation between CMT and subfoveal choroidal thickness:

There was a statistically insignificant negative correlation between the CMT and the subfoveal CH-T in NPDR with DME groups (Pearson's correlation coefficients (r) of -0.037,-0.267 and -0.163 and P = 0.88, 0.18 and 0.49 in Cystoid DME, Diffuse DME and DME with SRD groups respectively) (Table 3). Also, there were statistically insignificant correlations between the CMT and the mean CH-T measurements at the nasal, temporal, superior and inferior quadrants in all studied groups (P > 0.1).

Table 1. The basic data for all included subjects

The basic data	Control group	NPDR without DME	Diabetic CME	Diffuse DME	DME with SRD	P
Number of eyes	40	33	19	27	23	----------
Age (years) (Mean ± SD)	49.37±4.6	49.27±4.37	47.7±3.8	48.6±4.7	48.7±3.6	Insignificant
Gender: Male	5	4	5	7	5	----------
Female	18	16	11	13	12	----------

Table 2. Central macular thickness and choroidal thickness measurements in the studied groups

Group of Interest	Eyes No.	CMT (µm)	SFCH-T (µm)	Mean Nasal CH-T(µm)	Mean Temporal CH-T(µm)	Mean Superior CH-T(µm)	Mean Inferior CH-T(µm)
Control group	40	238.75 ± 14.7	326±25.75	301.12±29.6	316.17±28.36	315.7±24.22	305.2±27.34
NPDR without DME	33	260.85 ± 24.0	256.27±30.5	239.5±35.19	251.96±38.076	251.75±29.29	240.57±28.1
Diabetic CME	19	530± 120.5	210±23.96	191.74±24.28	209.68±25.54	207.63±21.74	193.36±23.36
Diffuse DME	27	420.8± 101.6	215.5±27.0	197.5±19.9	215.0±20.0	211.0±20.48	201.2±21.4
DME with SRD	23	506.6± 131.87	195.2±23.9	176.5±22.4	191.04±23.14	187.43±21.49	182.86±22.17

CMT= central macular thickness, SFCH-T= sub-foveal choroidal thickness, NPDR= non proliferative diabetic retinopathy, DME= diabetic macular edema, CME= Cystoid macular edema, SRD= serous retinal detachment.

Table 3. Correlation between the central macular thickness and the subfoveal choroidal thickness

Group of Interest	CMT (µm)	SFCH-T (µm)	The correlation coefficients (r)*	P
Control group	238.75 ± 14.7	326±25.75	-0.072	0.66
NPDR without DME	260.85 ± 24.0	256.27±30.5	0.083	0.65
Diabetic CME	530± 120.5	210±23.96	-0.037	0.88
Diffuse DME	420.8± 101.6	215.5±27.0	-0.267	0.18
DME with SRD	506.6± 131.87	195.2±23.9	-0.163	0.49

*Correlation is significant at the 0.05 level (2-tailed).

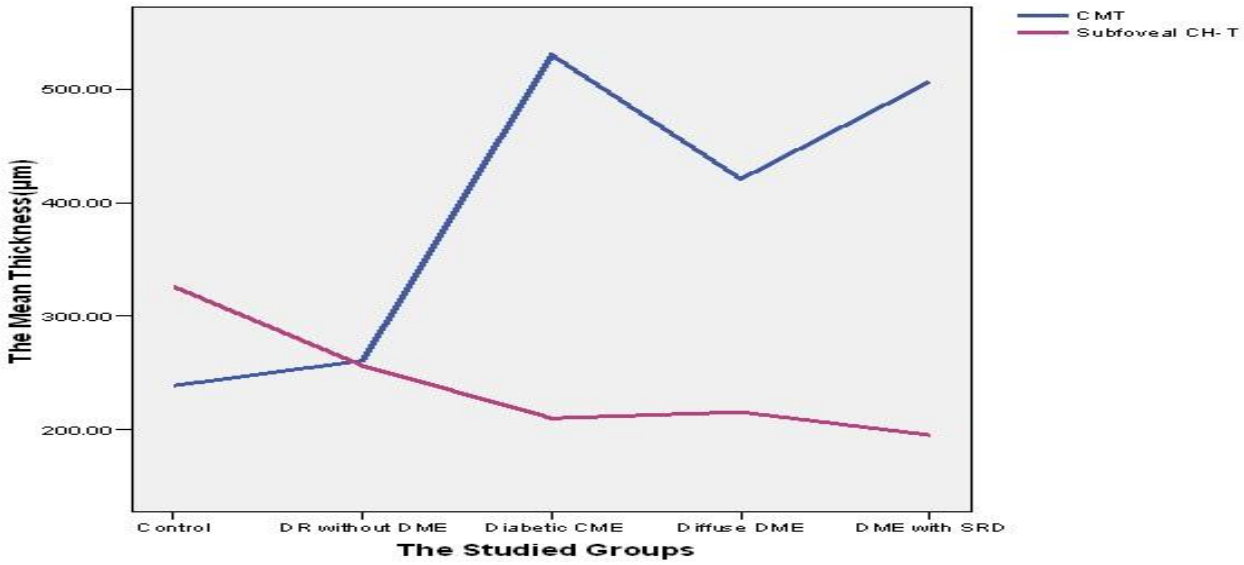

Figure 1. The mean central macular thickness (CMT) and the mean subfoveal choroidal thickness (CH-T) in the studied groups

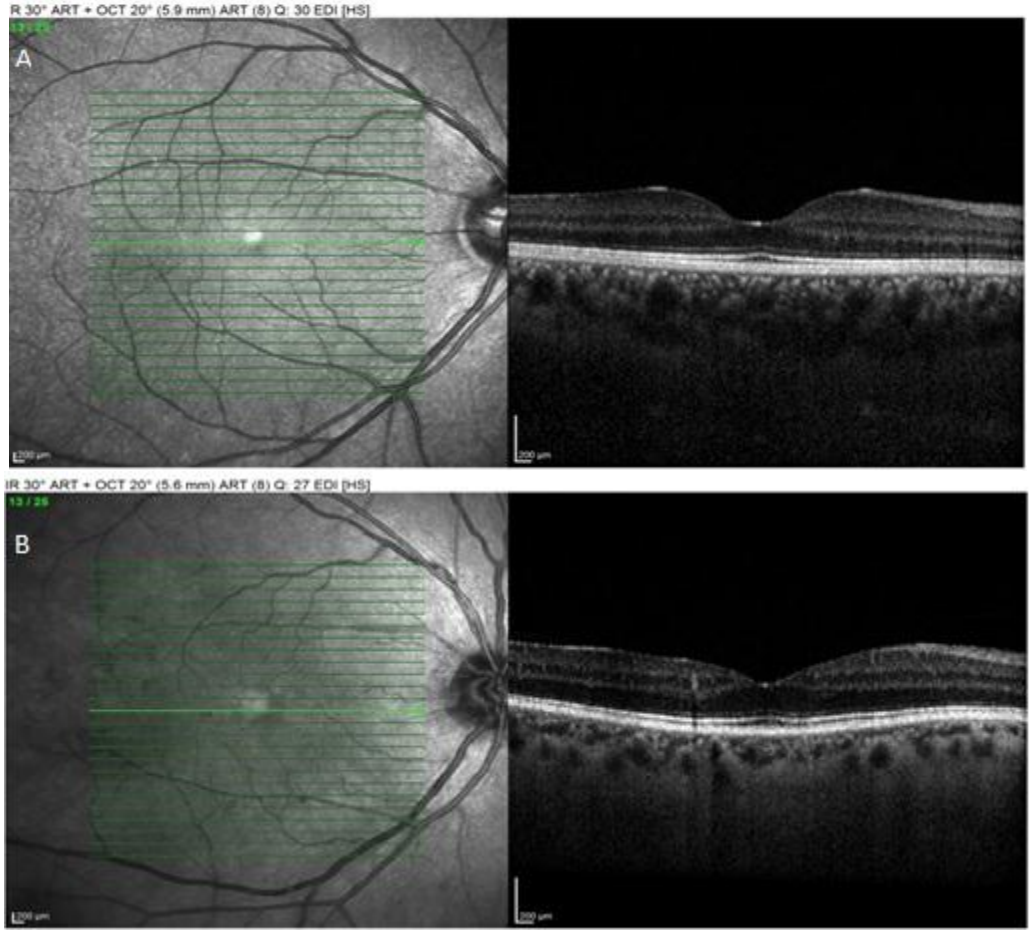

Figure 2 (A, B). Choroidal imaging with Enhanced depth image mode SD-OCT in (A) the right eye of a normal subject and (B) the right eye of a patient with diabetic retinopathy without diabetic macular edema.

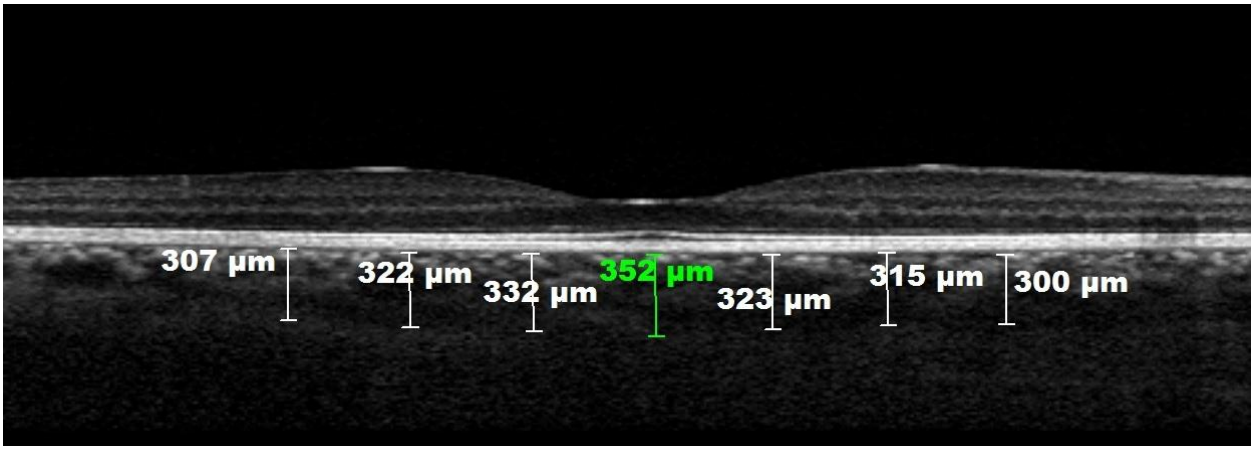

Figure 3. Manual estimation of the Choroidal thickness in the right eye of a normal subject using the caliper tool (1:1 µm ratio image).

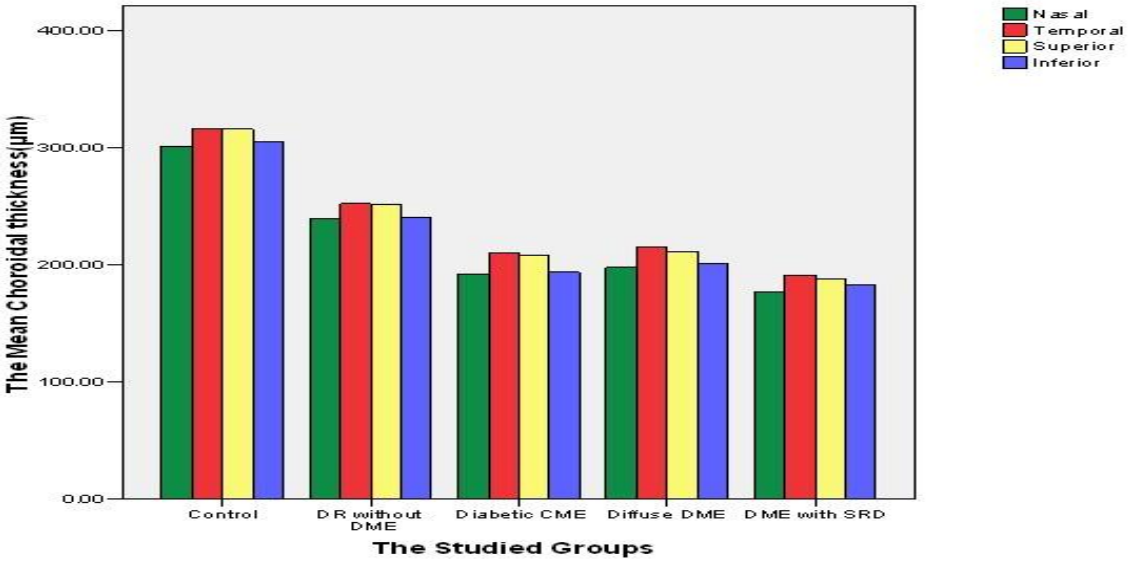

Figure 4. The Mean choroidal thickness (µm) at nasal, temporal, superior and inferior quadrants in the studied groups

DISCUSSION

The choroidal circulation forms an integral part of metabolic exchange in the outer retina. This is of particular significance in the macula, due to the lack of retinal vasculature (the foveal avascular zone) and a high metabolic demand from an increased photoreceptor density [12]. CH-T varies topographically within the posterior pole. The choroid is thickest under the fovea. The CH-T is thinner nasally than temporally, and thinner inferiorly than superiorly [13]. Dysfunction of the choroidal circulation has been long implicated in diabetic retinopathy and maculopathy [12]. There are several contradictory reports on the choroidal thickness in eyes with diabetic retinopathy [14] . **Regatieri *et al*.** [15] reported that choroidal thickness was altered in diabetes and may be related to the severity of retinopathy. Presence of DME was associated with a significant decrease in the choroidal thickness. However, **Kim *et al.*** [16] reported that choroidal thickness increased significantly as the severity worsened from mild-moderate NPDR to PDR. The subfoveal choroid was thicker in eyes with DME than in those without, and was thickest in eyes with SRD-type DME.

There are two types of pathologic changes in the diabetic choroid; the changes that decrease the choroidal thickness, such as the narrowing of the capillary lumens, capillary dropout; and the changes that increase the choroidal thickness, such as inflammation, dilatation of vessels, and interstitial edema. The choroidal thickness evaluated by OCT

represents the overall results of these changes and the inconsistent balance of these opposite changes in each study may have caused the discrepancy of the previous reports [14].

In the current study, the choroidal thickness changes at the sub-foveal and within 1500µm from the center of the fovea within the macular area were evaluated using Spectralis SD-OCT-EDI mode in eyes with different types of DME and these changes were compared with measured values from age-matched normal healthy subjects and patients with NPDR without DME. There was a highly significant thickness reduction of the subfoveal choroidal thickness in eyes with NPDR ($P < 0.001$). Within the NPDR groups, there was a highly significant difference in the subfoveal choroidal thickness measurements with the presence of DME compared to those without DME.

In their study **de Freytas *et al.*** [17] reported a significantly lower subfoveal choroidal thickness in eyes with DME when compared to healthy eyes. **Nagaoka *et al.*** [18] evaluated the changes in choroidal blood flow at the foveal region in patients with type 2 diabetes using laser Doppler flowmetry. Subfoveal blood flow was significantly reduced in all diabetic patients, especially those with NPDR and DME.

The present study demonstrates a reduction in the total choroidal thickness in eyes with NPDR and DME and in eyes with less advanced disease (NPDR only) compared with controls. The reduction in the total choroidal thickness in eyes with NPDR and DME is consistent with a previous study by **Regatieri *et al.*** [15] on choroidal thickness in patients with diabetic retinopathy. Also, **Totan *et al.*** [4] reported that the CH-T was significantly decreased in DME treatment-naive patients.

In the present study, the choroid was noted to be thinner nasally than temporally and inferiorly than superiorly and thickest in the subfoveal region. The thinnest part was nasal followed by inferior, superior then temporal and this order was preserved even with decreased choroidal thickness in NPDR with/ without DME.

The current results are consistent with those of **Gerendas *et al.*** [3] who also studied the choroidal thickness measurements on SD-OCT images and found that choroidal thickness maps revealed the typical choroidal thickness distribution (nasal versus temporal, superior versus inferior). This pattern was the same for healthy control and in eyes with DME. In eyes with choroidal thinning, a similar reduction was seen over the entire posterior pole**.**

In their study of EDI-OCT in type 2 diabetes, **Querques *et al*.** [19] hypothesized that the decreased choroidal thickness at the fovea may be a reason for the development of macular edema. The reduced subfoveal CH-T, probably due to the dropout of the choriocapillaris may cause retinal hypoxia. Because of tissue hypoxia, VEGF 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.

In the present study, there was statistically insignificant negative correlation between the CMT and the subfoveal CH-T in the studied groups. This result is consistent with that of **Lee *et al.*** [20] who also investigated the relationship between the choroidal and foveal thicknesses in diabetic group and among eyes exhibiting macular edema and found no evident correlation. Also, **Querques *et al*.** [19] reported no correlation between the CMT and choroidal thickness in the fovea in diabetic eyes without diabetic retinopathy; diabetic eyes with NPDR and no clinically significant macular edema; and diabetic eyes with NPDR and clinically significant macular edema.

In the current study, considerations regarding age, diurnal variation and the effects of previous treatment of DME on CH-T were taken into account. The study included eyes of age-matched groups to avoid the effect of age on the choroidal thickness. Furthermore, to avoid the diurnal fluctuations in the choroidal thickness, all the OCT CH-T measurements were performed at the same time of the day and only treatment naïve eyes were included to avoid the effect of various treatment options on the choroidal thickness.

Choroidal thickness has been shown to vary with age, refractive error, and even time of day [5]. Age is a variable that needs to be taken into account when comparing choroidal thickness. In normal eyes, progressive choroidal thinning occurs over time at a rate of 1.56 µm per year in the subfoveal area [9]. Diurnal variation in the choroidal thickness has been reported [21] and the choroid thickness shows a diurnal variation of about 30 µm [20].

The limitations of the current study included the small number of enrolled eyes within each group, both eyes of the same person were included in some subjects, which may introduce a sampling bias and that the choroidal thickness measurements were

performed manually. Hence, further studies could be performed on a larger number of patients and to include evaluation of choroidal thickness in diabetic patients before the development of diabetic retinopathy to detect if choroidal changes precede diabetic retinopathy.

Conclusion:

Spectral-domain OCT-EDI mode is a useful noninvasive method to evaluate the choroidal thickness. The current study demonstrates an overall decrease in the choroidal thickness in patients with NPDR and this thinning becomes more pronounced with the presence of diabetic macular edema.

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Conflicts of interest

There are no conflicts of interest.

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