

The Change of Visual Acuity Correlated with Choroidal Thickness in Diabetic Retinopathy

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Abstract

Background To probe the change of macular choroidal thickness (MCT) in diabetic retinopathy (DR) by using enhanced depth imaging optical coherence tomography (EDI-OCT). **Methods** A retrospective research was conducted among 136 eyes. Patients' mean age was 57.34 ± 9.42 years. 67 eyes were suffered from diabetic retinopathy (DR) without macular edema (ME), 69 eyes with ME and age matched 64 healthy eyes were as control. The choriocapillaris and the medium vascular layers (Sattler's layer) were defined as the choroidal inner layer, and the large vessel layer (Haller's layer) was defined as the choroidal outer layer. **Results** The whole, inner and out layers of choroid in macular area of the eyes with DR were significantly thinner compared to that of control ($P < 0.001$). The whole and out choroidal layers in DR with ME were significantly thinner than that in DR without ME ($P < 0.001$). The best-corrected visual acuity (BCVA, LogMar) was 0.41 ± 0.37 and 0.70 ± 0.45 for DR without ME and DR with ME, respectively. Univariate linear regression analysis showed a positive correlation between MCT and BCVA in either DR with or without ME groups ($P = 0.023, P = 0.006$). A stepwise multiple linear regression analysis demonstrated that the elucidative variables strong association with MCT were BCVA and central macular thickness (CMT) in DR eyes. **Conclusion** In the eyes with DR, MCT was thinner compared to that of healthy control and this change was more substantial in ME eyes. MCT had a positive correction with BCVA. Our results indicate that the pathological change occurred in choroidal layer of the eyes with DR and this change correlated with impairment of BCVA.

Introduction

Diabetic retinopathy (DR), one of the serious complications of diabetes mellitus (DM), is the leading cause of visual loss in working-age populations [1]. The pathological changes of DR has been presumed as a circulatory dynamic abnormality due to the structural damage of the retinal vascular walls, and subsequent breakdown of the outer blood-retinal barrier [2]. On the other hand, the abnormality of choroidal circulation observed in DM patients plays an important role in the pathogenesis of DR [3]. The choroidal circulation is indispensable to maintain an intact metabolic exchange in the outer retina. Because of the lack of retinal vasculature and a high metabolic demand in photoreceptors, this is particularly important in the macula foveal region. The impairment of choroidal circulation caused severe functional damage to the retinal tissue in fovea [4–6].

A histopathological study showed vascular abnormalities in the choroidal layer of patients, with diabetes, arterio-sclerosis, choriocapillaris degeneration, focal scarring, and neovascularization [7, 8]. In addition, the examination for the patients with diabetes by indocyanine green angiography showed that hyper- and hypofluorescent spots at the level of the choriocapillaris, suggesting that the aneurysms or deficits occurred in the choroidal vasculature [2, 9].

For long period of time, the evaluation of the choroid in vivo was confined by its deep location, behind the retinal pigment epithelium (RPE). Recently, the advent of enhanced depth imaging optical coherence

tomography (EDI-OCT) enables ophthalmologists to measure anatomical changes of the choroid in DM eyes non-invasively and quantitatively.

Several recent studies reported the changes of macular choroidal thickness (MCT) in DR, but the results were contradicting. Most studies reported a thinner MCT in diabetic eyes compared to that in controls [4, 6, 10–14]. Nevertheless, others showed a thicker MCT in patients with diabetes and in the advanced stages of DR [15, 16].

Whereas, to best of our knowledge, there is few research was focused on change of choriocapillaris, Sattler's and Haller's layers in DR eyes. In this research, we intended to observe the change of different sub-layers of choroid for DR either with or without ME.

Patients And Methods

Patient Eligibility:

This study was a retrospective study and was approved by institutional review board of Shandong Provincial Hospital and was conducted in adherence with the tenets of the Declaration of Helsinki. Seventy-one patients with type 2 diabetes and fifty non-diabetic healthy control subjects were enrolled in this study between June 2018 and May 2019. All subjects underwent a complete ophthalmologic examinations, including EDI-OCT, B scan, best-corrected visual acuity (BCVA) and slit-lamp biomicroscopy examination. Exclusive criteria included: patients' age over 85 years old; ocular axial length was more than 25 mm, or less than 22 mm; eyes refractive error over ± 5.0 diopters spherical equivalent; having any other eye diseases and treatments, such as glaucoma, ocular trauma, ocular inflammation, age-related macular degeneration, retinal vein occlusion, panretinal photocoagulation, intravitreal injections, vitrectomy; systemic diseases that might affect MCT, such as systemic lupuserythematosus, anemia, leukemia, and obstructive sleep apnea.

The subjects were classified into 3 groups: DR without ME: 49 patients (67 eyes), mean age was 57.34 ± 9.42 years; DR with ME: 44 patients (69 eyes), mean age was 55.52 ± 9.71 years and healthy control: 50 age matched subjects (64 eyes). The DR was diagnosed by two experienced ophthalmologists after pupil dilation. Another senior ophthalmologist would reassure these in case of any doubt. ME was detected by OCT examination.

EDI-OCT:

The MCT of subjects underwent EDI-OCT (RTVue XR; Optovue, Inc., CA, USA) examination. Due to the rhythmic change of MCT during the day, all participants underwent EDI-OCT examination during 8 a.m. to 11 a.m. MCT was measured in macular fovea from the hyperreflective line of Bruch's membrane to the choroid-oscleral junction. The choroid was composed of three layers: Haller's layer (large vessel layer), Sattler's layer (medium vessel layers) and choriocapillaris layer. Due to the limitation of instrument accuracy, in our study, Sattler's and choriocapillaris layers were defined as the choroidal inner layer.

Haller's large vessel layer was defined as the outer layer (Figure. 1). In order to measure thickness of foveal choroidal sub-layers accurately, the EDI-OCT caliper tool was used manually. Two masked examiners measured MCT independently without knowing the subjects' clinical information.

Statistical Analysis

Statistical analyses were performed using SPSS software version 23 (SPSS, Inc., Chicago, IL). All data were expressed as the mean \pm SEM. The whole, inner and outer layers of MCT were compared among DR with ME, DR without ME, and control by using Kruskal–Wallis test and one-way ANOVA. Univariate linear regression analyses were carried out with whole, inner and outer layers of MCT as dependent parameters and with BCVA, age, duration of diabetes and central macular thickness (CMT) as independent parameters. Multivariate linear regression was carried out with MCT as the dependent parameter and the other variables as independent parameters. P value less than 0.05 was considered as statistically significant.

Results

Patient Characteristics:

For the DR without ME sub-group: the mean BCVA was 0.41 ± 0.37 LogMAR, the mean CMT was 282.54 ± 55.78 μm and the mean duration of diabetes mellitus was 12.87 ± 7.65 years. For the DR with ME sub-group: the mean BCVA was 0.70 ± 0.45 LogMAR, the mean CMT was 401.13 ± 136.71 μm and the mean duration of diabetes mellitus was 10.45 ± 6.97 years. For control sub-group: the mean BCVA was 0.06 ± 0.05 LogMAR, the mean CMT was 242.64 ± 27.86 μm . Basic features of studying subjects were showed in Table 1.

The Macular Choroidal Thickness in DR Eyes:

The MCT was 229.50 ± 14.15 μm , 201.11 ± 14.70 μm and 282.31 ± 16.16 μm for DR without ME, DR with ME and control, respectively. The MCT were significantly thinner in either DR without ME or with ME eyes compared to that in control ($P < 0.001$, $P < 0.001$). The MCT were significantly thinner in DR with ME eyes compared to that in DR without ME eyes ($P < 0.001$; Table 2; Figure 2.1). The inner layer of MCT was 84.03 ± 7.89 μm , 81.45 ± 6.86 μm and 90.77 ± 8.67 μm for DR without ME, DR with ME and control, respectively. The inner layer of MCT were significant thinner in either DR without ME or with ME eyes compared to that in control ($P < 0.001$, $P < 0.001$). The MCT showed no statistical difference between DR with ME eyes and DR without ME eyes in inner layer ($P = 0.241$; Table 2; Figure 2.2). The outer layer MCT was 145.47 ± 10.45 μm , 119.66 ± 12.59 μm and 191.55 ± 14.33 μm for DR without ME, DR with ME and control, respectively. The outer layer of MCT were significant thinner in DR either without ME or with ME eyes compared to that in control ($P < 0.001$, $P < 0.001$). The MCT was significant thinner in DR with ME eyes compared to that in DR without ME eyes in the outer layer ($P < 0.001$; Table 2; Figure 2.3).

The BCVA Correlated with Choroidal Thickness:

BCVA (LogMar) was 0.41 ± 0.37 , 0.70 ± 0.45 and 0.06 ± 0.05 for DR without ME, DR with ME and control, respectively. In DR without ME group, there was a significant positive correlation between the whole/inner/outer layer of MCT and BCVA, respectively ($P=0.006$, $P=0.034$, $P=0.037$). In DR with ME group, there was a significant positive correlation between the whole/inner layers of MCT and BCVA, respectively ($P=0.023$, $P=0.025$). No correlation was found between outer layer of MCT and BCVA ($P=0.149$). In control group, no correlation was found between whole/inner/outer layer of MCT and BCVA ($P=0.075$, $P=0.787$, $P=0.065$; Table 3.1).

The Association of other Potential Factors with MCT:

The impact of each potential factor of age, duration of diabetes, and CMT on MCT was analyzed by using a univariate linear regression. In control group, ages were negatively associated with whole and outer layers of MCT, respectively ($P=0.029$, $P=0.045$) and inner layer of MCT was positively associated with CMT ($P=0.014$; Table 3.2). A stepwise multiple linear regression analysis demonstrated that in DR group, BCVA (LogMar) was negatively associated with whole, inner and outer layer of MCT ($P<0.001$, $P=0.002$, $P=0.001$) and CMT was a significant predictor of whole and outer layers of MCT ($P<0.001$, $P<0.001$; Table 4.1). Similarly to the result of univariate linear regression analysis, CMT was positively associated with inner layer of MCT in control group ($P=0.015$; Table 4.2).

Taken together, in the eyes with DR, the whole, inner and outer layers of MCT significantly decreased compared to that of healthy control. Moreover, the whole and outer layers of MCT significantly decreased in DR with ME group compared to that in DR without ME group. MCT had a positive correlation with BCVA. A stepwise multiple linear regression analysis demonstrated that in DR eyes the elucidative variables strong association with MCT were BCVA and CMT. Our results indicate that the pathological change occurred in choroidal layer of DR eyes and then induced the impairment of BCVA.

Discussion

Although EDI-OCT has confirmed morphological choroidal changes in DM eyes, there are few research to investigate the change of choriocapillaris, Sattler's and Haller's layers in DR eyes, especially in DR with ME eyes. In this study, EDI-OCT was employed to evaluate the change of MCT in inner and outer layers. Our study indicated that the whole, outer and inner layers of MCT in DR eyes were significantly thinner than that in control. Compared with DR without ME eyes, the whole and outer layers of MCT in DR with ME eyes were significantly decreased. These data indicate that in DR eyes, MCT was thinner than that of healthy subjects, and this reduction was due to decrease of choroidal thickness in both inner and outer layers. Moreover, in DR with ME eyes, the MCT was even thinner than that in without ME eyes and this decrease mainly occurred in the outer layer of choroid.

The changes in choroidal thickness of DR eyes have been conducted by several researchers. Whereas, the reports of relationship between DR and MCT are still controversial. In this research, it was found a significant reduction of MCT in DR eyes as compared to that in health subjects. This is in agreement with reports that MCT was significantly thinner in middle NPDR, PDR eyes [6, 10]. Ours and others results

corroborate with previous reports that reduction of choroidal blood flow velocity is associated with severe DR [9, 17]. On the contrary, Kim et al. reported the increase of subfoveal choroidal thickness in DR eyes compared to that in the normal subjects. The subfoveal choroid was even thicker in the eyes with DME than that in the eyes without DME and thickest choroid was observed in eyes with subretinal detachment-type of DME [16]. On the other hand, Xu et al. did not find any significant association between MCT and DR changes [15]. The discrepancy may be due to the different enrolled criteria of patients. The MCT of DR is influenced by a variety of factors. Several researches have certified that panretinal photocoagulation, intravitreal anti-VEGF therapy, and intravitreal triamcinolone acetonide injection could affect MCT [18–20]. To eliminate these factors, only DR eyes without any history of ocular treatment were enrolled in this research.

The studies with laser doppler flowmetry and histopathological suggest that the early diabetic choroidal changes most likely occur in the choriocapillaris [17, 21], a vascular layer with a minimal thickness. Histological studies also revealed basement membrane thickening of the choroidal vasculature, and loss of choriocapillaris in donor eyes with DR [7]. Accordingly, our results suggest that the reduction of thickness in both inner and outer layers occurred in DR eyes.

The correlation analysis of the mean changes of MCT and mean change of BCVA showed a significant positive correlation. Our study suggest the reduction of MCT may be one of the major causes of impairing BCVA by disturbing the metabolism of outer layer retina in the macular area. In diabetic patients, the reduction of MCT might induce retinal hypoxia because of the degeneration of choriocapillaris [8]. Hypoxia could then increase the expression of vascular endothelial growth factor in RPE cells, pericytes, and microvascular endothelial cells, that induces dysfunction of the blood-retinal barrier and causes the basic pathological change of DR [22]. Thus, choriocapillaris degeneration, should be one of the important factors causing the impairment of visual function in diabetes patients [8].

In our study, we demonstrated that increasing age was significantly associated with decreasing MCT in whole and outer layers in control group. This is in consistent with a study that described a decrease of macular choroidal thickness, of approximately 3 microns per year of age [23]. Besides, our multivariate regression analyses showed a negative correlation between CMT and the whole and outer layers of MCT in DR eyes. Because the choroidal circulation makes an indispensable part of metabolic exchange in the outer retina, especially in macula avascular region, the impairment of choroidal circulation may be an important factor caused impairment of central macular retina.

Our research indicate that choroidal thickness in whole, inner and outer layers was significantly reduced in DR eyes compared to that in control. Nevertheless, the underlying mechanism of choroidal thinning remains to be fully elucidated. The choroid is vascular structure with innervation by abundant neurons, mainly under control by autonomic nervous system. There were a few studies investigating the relationship between choroidal blood flow and choroidal thickness. Zengin et al. found a significant reduction in choroidal thickness after ingestion of nicotine, which was caused by decreasing choroidal blood flow due to the vasoconstrictor action [24]. Similarly, sildenafil citrate and coffee were found to

cause the change of MCT due to their vasodilatory or vasoconstrictive effects on choroidal circulation [25] [26]. Thus, the activation of the autonomic nervous system might conduce decreasing in choroidal thickness through vasoconstriction of the choroidal vessels [27]. Therefore, it is necessary to illustrate the mechanisms of autonomic nervous system in decreasing choroidal layers of DR eyes in future.

There are several limitations in our study. Firstly, in this research only the central macular choroidal thickness was measured, while parafoveal choroidal thickness varied in each patients [28], further studies are needed to figure out layer thickness in broad spectrum. Secondly, the number of participants was limited, which may affect the correlation analysis outcome. Thirdly, previous researches have shown that hypertension and dyslipidemia, may affect the choroidal thickness [29, 30]. While, in this research these factors were not included as variable factors. Fourthly, there was lack of histopathological results to corroborate our results.

In conclusion, our study demonstrated the whole, inner and outer layer of MCT had significantly decreased in DR eyes, especially in DR with ME eyes. This research suggests that the change of MCT is closely correlated with DR and the thinning of choroidal layer, at least from one aspect, may reflect progression of diabetic choroidopathy. Our results indicate that the pathological change of MCT caused impairment of BCVA. DEI-OCT as a novel non-invasive instrument, is vital to investigate choroidal change in DR. We should pay attention to the pathological change of DR not only in retina but also in choroid in our clinical practices and research. Further better understanding of the pathological change in diabetes, would be essential for the development of novel therapeutic method to combat this leading blindness disease.

Abbreviations

MCT: macular choroidal thickness; DR: diabetic retinopathy; DEI-OCT: enhanced depth imaging optical coherence tomography; ME: macular edema; BCVA: best-corrected visual acuity; CMT: central macular thickness; DM: diabetes mellitus; RPE: retinal pigment epithelium.

Declarations

Ethics approval and consent to participate

This study was approved by institutional review board of Shandong Provincial Hospital and was conducted in adherence with the tenets of the Declaration of Helsinki. There were no potential risks that may cause any harm in any form on the study subjects. Coding and aggregate reporting were used to eliminate respondents' identification and ensure anonymity and the data will not transfer to the third body and was used only for the research purpose to ensure confidentiality.

Consent for publication

Not applicable.

Availability of data and materials

We have sent all the available data and we do not want to share the raw data as we are doing related study.

Competing interests

All the authors declare that they have no competing interests.

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Authors' contributions

ZBJ was responsible for the project design. ZBJ, MAH and ZXY have been involved in revising the manuscript critically for important intellectual contents. ZXY, LFJ and JWZ have involved in collection and interpretation of data. All authors have involved in drafting and editing the manuscript. All authors have participated in the final approval of the version to be published. All authors agreed to be accountable for all aspects of the work including integrity or accuracy of any part of the work.

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Tables

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Figures

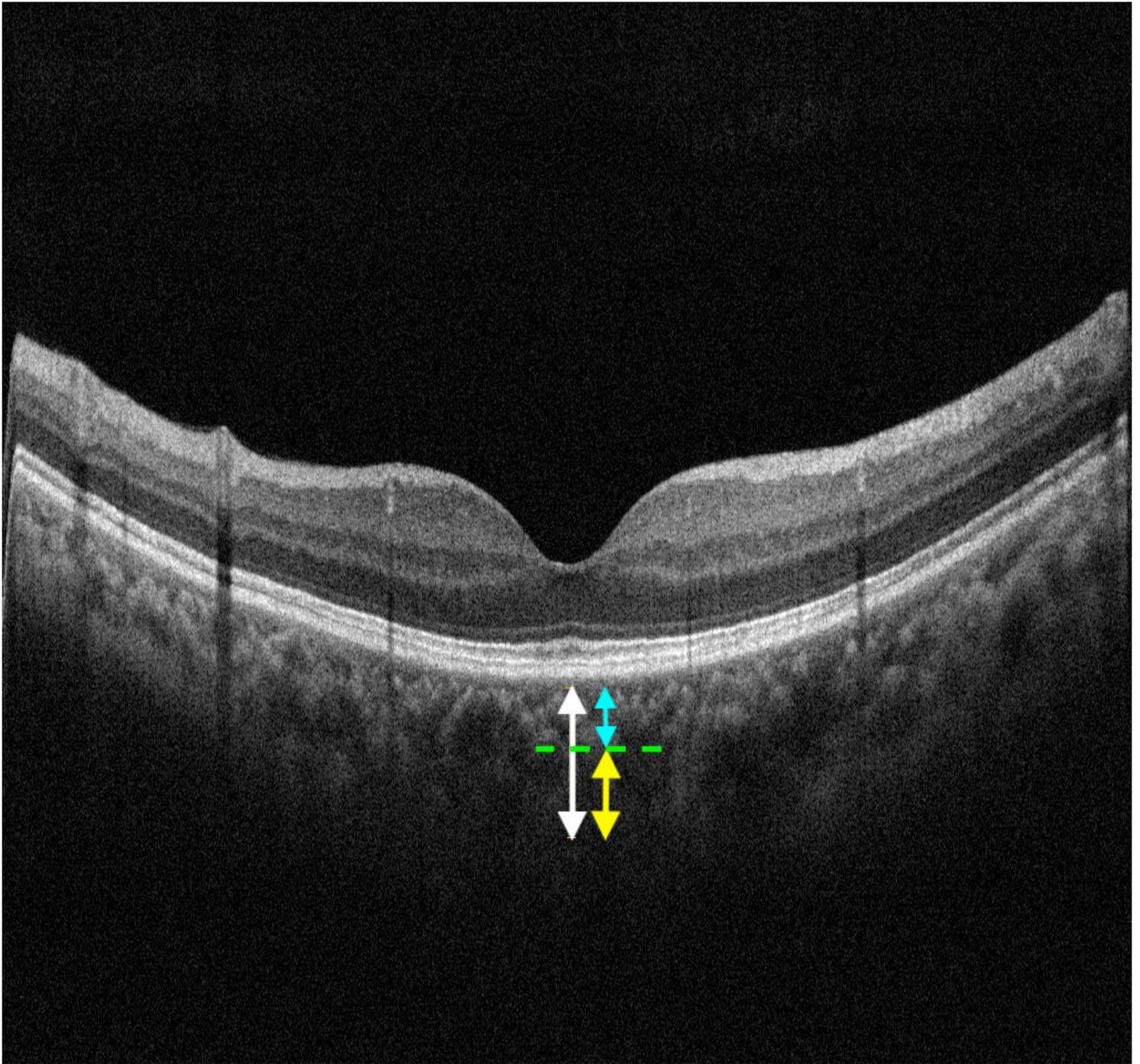


Figure 1

Identification of choroidal thicknesses by EDI-OCT in a healthy control. White line: the choroidal whole layer thickness was measured from the hyperreflective line of Bruch's membrane to the choroid-scleral junction in macular fovea; Blue line: the choroidal inner layer thickness was measured from the Bruch's membrane to the innermost layer of the choroidal large blood vessel (green line); Yellow line: the choroidal outer layer thickness was obtained by subtracting the choroidal inner layer thickness (blue line) from the choroidal whole layer thickness (white line).

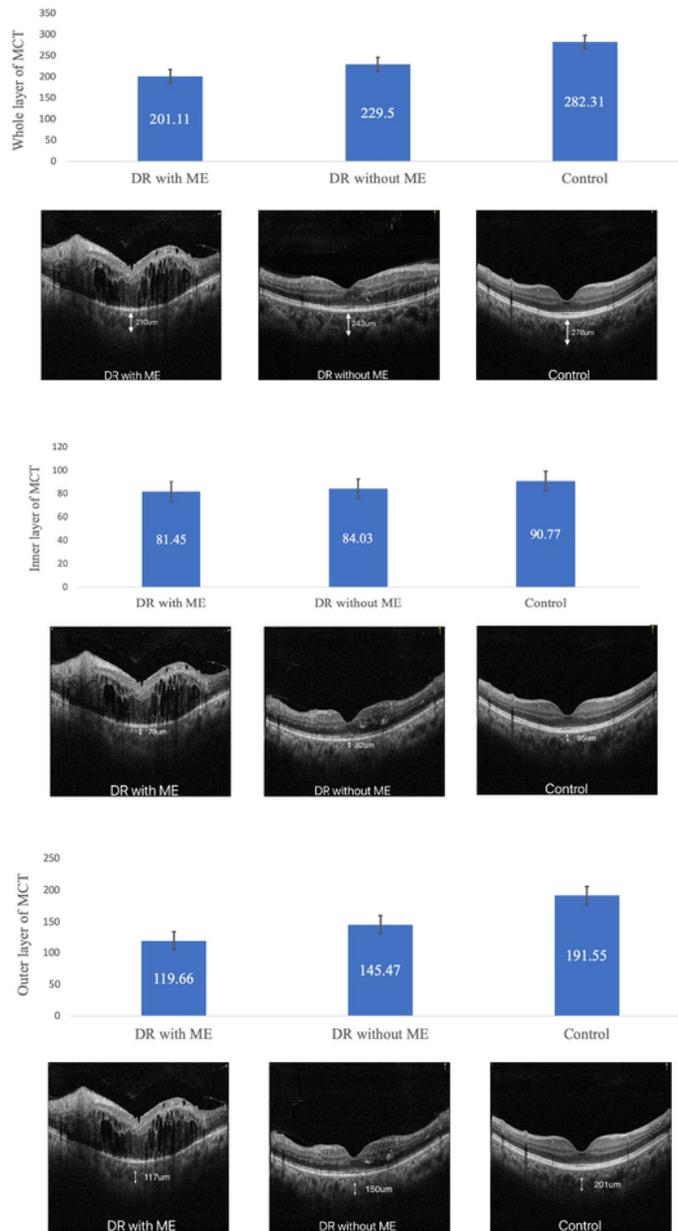


Figure 2

2.1. The whole layer of MCT in diabetic patients compared to that of control The whole layer of MCT was significantly thinner in DR eyes with or without ME compared to that in control ($P < 0.001$, $P < 0.001$). The MCT was significantly thinner in DR with ME eyes compared to that in DR without ME eyes ($P < 0.001$).

2.2. The inner layer of MCT in diabetic patients compared to that of control The inner layer of MCT was significantly thinner in DR eyes with or without ME compared to that in control ($P < 0.001$, $P < 0.001$). The

MCT had no statistical difference between DR with ME eyes and DR without ME eyes in inner layer (P=0.241). 2.3. The outer layer of MCT in diabetic patients compared to that of control The outer layer of MCT was significantly thinner in either DR eyes with or without ME compared to that in control (P<0.001, P<0.001). The outer layer of MCT was significantly thinner in DR with ME eyes compared to that in DR without ME eyes (P<0.001).

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