The thickness and volume of the choroid, outer retinal layers and retinal pigment epithelium layer changes in patients with diabetic retinopathy

Xiang-Ning Wang1, Shu-Ting Li1, Wei Li1, Yan-Jun Hua1, Qiang Wu1,2

1Department of Ophthalmology, Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai 200233, China
2Shanghai Key Laboratory of Diabetes Mellitus, Shanghai 200233, China

Correspondence to: Qiang Wu. Department of Ophthalmology, Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, 600 Yishan Road, Shanghai 200233, China. Qiang.wu@shsmu.edu.cn

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Abstract

AIM: To evaluate the thickness and volume changes of the choroidal, outer retinal layers (ORL) and retinal pigment epithelium (RPE) in patients with diabetic retinopathy (DR) using optical coherence tomography (OCT) and correlate them with visual acuity.

METHODS: We carried out a retrospective observational case series. Consecutive DR patients were recruited for color fundus photography and OCT assessment. The RPE, ORL and choroidal thickness were measured. The correlation with the best-corrected visual acuity (BCVA) was also investigated.

RESULTS: The study included 128 eyes, comprising 45 eyes of 25 diabetic macular edema (DME) patients, 34 eyes of 20 DR without DME (non-DME) patients, and 49 eyes of 25 age-matched normal individuals. The choroidal thickness in DR patients were decreased statistically significantly compared with the control group (P<0.05). The mean macular ORL thickness in DME (73.02±15.34 μm) and non-DME groups (76.35±7.32 μm) were decreased statistically significantly compared with the control group (80.20±5.85 μm; P=0.006, P=0.013, respectively). In both the non-DME and DME groups, the RPE thickness were decreased in the macular and central ring. The BCVA were significant interactions with the total inner retinal volume and macular RPE thickness in the DME group (r=0.115, P<0.001, r=0.013, P=0.017, respectively).

CONCLUSION: The choroid, ORL and RPE thickness are significantly decreased in DR patients compared with controls in different segments.

KEYWORDS: choroid; diabetic macular edema; outer retinal layers; retinal pigment epithelium; diabetic retinopathy

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INTRODUCTION

Diabetic macular edema (DME) is the leading cause of visual impairment in patients with diabetic retinopathy (DR) worldwide[1]. The retina gets nutrients from two discrete circulatory systems, the choroidal blood vessels and the retinal blood vessels. While alterations in retinal vasculature resulting in impairment of the blood-retinal barrier (BRB) have been demonstrated to play a vital role in the pathophysiology of DME, changes in the underlying choroidal vasculature may also play a contributing role[2]. The choroid has been reported to plays an important role in the pathophysiology of DR[3]. Some studies have reported that choroidal thickness is decreased in DME, and the underlying choroidal vasculature changes may also be related to the onset or progression of the disease[4-6]. Karahan et al[7] had reported the correlation between choroidal thickness and the outer retinal layer (ORL) by optical coherence tomography (OCT) scan. The ORL thickness, as defined in this study as the distance between the external limiting membrane (ELM) and the retinal pigment epithelium (RPE), was the sum of the length of the inner and outer segments of photoreceptors. It is known that the outer segments of photoreceptors contain disks filled with opsin, which is responsible for absorbing photons for later signal transduction[8]. Several studies have reported that the photoreceptor layer status and ORL thickness are closely related to visual acuity (VA) in patients with DME[8-10]. The RPE layer, the structure of BRB, is responsible for the mainly retinal oxygen and nutrition supplies. The breakdown of BRB has been demonstrated to play an important role in the processes of diabetes and ischemia[11]. Hence, it is meaningful to study the thickness and volume changes of the choroid, ORLs and the RPE layer in patients with DME.
The purpose of this study was to evaluate the thickness and volume changes of the choroid, RPE and ORL in patients with DME using SD-OCT and correlating with VA.

SUBJECTS AND METHODS

Study Subjects  This study adhered to the tenets of the Declaration of Helsinki and had the approval of the Ethics Committee of Sixth People’s Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China.

A retrospective review was performed on all patients with DR who were examined at the Department of Ophthalmology, Sixth People’s Hospital Affiliated to Shanghai Jiao Tong University, between September 2015 and March 2016. Also, 25 age-matched controls (49 eyes) with normal VA and no retinal or choroidal pathology were included in this study.

At the initial evaluation, all patients received a complete ophthalmologic examination that included the manifest refraction, axial length, best-corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy, a detailed fundus examination, colour fundus photography, SD-OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). The patients with DME were diagnosed by stereoscopic biomicroscopy according to the criteria reported by the ETDRS[12].

Optical Coherence Tomography Scan  In this visit, all patients also underwent SD-OCT. The chosen protocol was a high-resolution volume protocol, composed of 31 horizontal lines, centred to the fovea. An internal fixation light was applied to center the scanning area on the fovea. Each scan was 8.4 mm in length and spaced 240 µm apart from each other. All 31 OCT macular B scans were acquired in a continuous, automated sequence and covered a 30º×25º area centered on the fovea (Figure 1).

Determination of Choroidal, RPE and ORL Thickness and Volume  Only high-quality images were accepted. All images were segmented by the intrinsic software segmentation algorithm (Heidelberg Eye Explorer software ver. 1.9.10.0, Heidelberg Engineering). The RPE thickness was defined as the layers from the RPE to the Bruch’s membrane (BM), the ORL thickness defined as the layers from the RPE to the ELM (Figure 1). After this process, the ORL and RPE thickness were calculated automatically, and presented as a colored topographic map with nine subfields as defined by the ETDRS-style grid through the built-in mapping software. In addition, we moved the automated retinal segmentation line to the choroidal segmentation line, making the dots at the internal limiting membrane line move to the BM line and the dots at the BM line to the chorio-scleral interface line (Figure 1). The choroidal volume in the ETDRS circle 6 mm was also calculated by built-in software. Each reader adjusted the segmentation lines of each image twice for the measurement of test-retest reliability.

Figure 1 The determination of choroidal, RPE and ORL thickness and volume  A: SD-OCT raster scan protocol; B: Standardized grid on the ETDRS circle; C: Manual choroidal segmentation; D: The RPE thickness defined as layers from RPE to BM; E: The ORL thickness defined as layers from RPE to ELM.

Statistical Analysis  Statistical calculations were performed using statistical software (Statistical Package for Social Sciences Version 18.0; SPSS, Inc., Chicago, IL, USA). Comparative analyses of three or more groups were carried out using a one-way analysis of variance (ANOVA) followed by a post-test. Two groups were compared using one- and two-tailed t-tests with Bonferroni’s correction. The correlation analyses were evaluated on the basis of the Pearson correlation coefficient. Multiple linear regression was used to evaluate the explanatory variables with regard to the dependent variable, BCVA, inner retinal volume and macular RPE thickness. Correlation between BCVA and retinal or choroidal thickness in each diabetic group was analyzed using the Pearson’s correlation coefficient. The chosen level of statistical significance was P<0.05.

RESULTS

Baseline Characteristics  A total of 79 eyes from 45 patients with DR meeting inclusion criteria for the study were evaluated. The number of eyes and patients, and the characteristics of the patients [age, gender, laterality, body mass index (BMI), BCVA, HbA1c level, axial length and refractive error] in each group are summarized in Table 1. When comparing the participants and measurements of the three groups, there were no differences in terms of age, gender, laterality, BMI, axial length and refractive error. As expected, BCVA was significantly reduced in eyes from the DR (P<0.001) and DME groups (P<0.001) when compared with control eyes. In addition, DMEs had significantly higher HbA1c levels than non-DMEs (P<0.001).
Inner Retinal Thickness and Choroidal Thickness Between Diabetic and Control Participants

Regarding choroidal thickness, the choroidal thickness in the non-DME and DME groups were decreased statistically significantly compared with the control group ($P<0.05$ for both non-DME and DME groups; Table 2, Figure 2). However, there were no statistically significant differences in terms of any measurement partition between the DME and non-DME groups ($P>0.05$; Table 2, Figure 2).

Regarding inner retinal thickness, there were no statistically significant differences in terms of any measurement between the non-DME and control group ($P>0.05$; Table 2, Figure 2). However, there were no statistically significant differences in terms of any measurement partition between the DME and non-DME groups ($P>0.05$; Table 2, Figure 2).

RPE and ORL Thickness Between Diabetic and Control Participants

In all three groups, the RPE and ORL thickness were thickest in the macular or central ring among the all the assessed quadrants. Comparing among each group, there were no statistically significant differences in terms of any measurement partition between the DME and non-DME groups ($P>0.05$; Table 3, Figures 3 and 4). Regarding the ORL thickness, there were no statistically significant differences among each group, except in the macular and central ring ($P=0.04$, $P=0.006$, respectively; Table 2). However, the inner retinal thickness in the DME groups was increased statistically significantly in terms of any measurement compared with the non-DME and control groups ($P<0.001$ for both DR and control groups; Table 2).

Table 1 Characteristics of patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control group</th>
<th>Non-DME group</th>
<th>DME group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ($n$)</td>
<td>25</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Eyes ($n$)</td>
<td>49</td>
<td>34</td>
<td>45</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.2±8.4</td>
<td>61.9±7.9</td>
<td>61.3±9.3</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>15/10</td>
<td>12/8</td>
<td>15/10</td>
</tr>
<tr>
<td>Laterality (right/left)</td>
<td>25/24</td>
<td>18/16</td>
<td>25/20</td>
</tr>
<tr>
<td>BMI</td>
<td>24.4±3.2</td>
<td>24.6±3.1</td>
<td>24.7±3.4</td>
</tr>
<tr>
<td>BCVA$^a$, logMAR</td>
<td>0.1±0.1</td>
<td>0.2±0.1</td>
<td>0.4±0.2</td>
</tr>
<tr>
<td>HbA1c$^b$, %</td>
<td>-</td>
<td>7.3±1.6</td>
<td>9.1±2.3</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>23.2±1.2</td>
<td>23.8±1.0</td>
<td>23.6±1.3</td>
</tr>
<tr>
<td>Refractive error</td>
<td>0.7±1.7</td>
<td>0.2±1.8</td>
<td>0±1.4</td>
</tr>
</tbody>
</table>

DME: Diabetic macular edema; BMI: Body mass index; BCVA: Best-corrected visual acuity; HbA1c: Hemoglobin A1c. $^a$Significant difference among groups by one-way ANOVA ($P<0.001$). $^b$Significant difference by $t$-test ($P<0.001$).

In both the non-DME and DME groups, the RPE thickness was decreased statistically significantly compared with the control group ($P<0.05$; Table 3, Figure 4), except in the macular and central ring.

BCVA According to Different Factors

We investigated the interaction between the variables that were found to be
and DME groups. It has been demonstrated that decreased normal healthy subjects, and no significant central choroidal evaluated by OCT is reduced in DR patients compared with onset and/or progression of the DR.

In the present study, we found that central choroidal thickness significantly compared with the control group and with a worse VA. The ELM is known to correspond to the adherens junctions between the inner and outer segments of the photoreceptors (IS/OS) on OCT images. These layers on the OCT images be significantly associated with worse VA. We found that there were significant interactions with the total inner retinal volume and macular RPE thickness in the DME group ($r=0.115$, $P<0.013$, $r=0.017$, respectively).

**DISCUSSION**

The purpose of this study was to evaluate the thickness changes of the choroid, RPE and ORL in patients with DME, and to investigate the correlation with VA. A structurally and functionally normal choroidal vasculature is necessary for retinal functioning; while abnormal choroidal blood volume and/or compromised blood flow can lead to photoreceptor dysfunction and death. The pathologic findings in diabetic people included focal vascular dilatation and narrowing, hypercellularity, increased tortuosity of the blood vessels, vascular loops and microaneurysm formation, areas of nonperfusion and sinus-like structure formation between the choroidal lobules. These changes may be involved in the onset and/or progression of the DR.

In the present study, we found that central choroidal thickness evaluated by OCT is reduced in DR patients compared with normal healthy subjects, and no significant central choroidal thickness changes were observed between the non-DME and DME groups. It has been demonstrated that decreased choroidal thickness might be associated with retinal tissue hypoxia, because the major source of nutrition for the RPE and ORL come from the choroid. Furthermore, choroidal thinning could explain the increased susceptibility to retinal hypoxia and ischemia in diabetics. Finally, choroidal thinning may be related to the destruction of the BRB, leading to the onset or progression of DME.

In this study, the macular/english ORL thickness in the DME groups and non-DME groups were decreased significantly compared with the control group and with a worse VA. The ELM is known to correspond to the adherens junctions between the photoreceptor cells and Müller cells, which is also prevents passage of macromolecules. The light perception represent the photoreceptor function, which is the junction between the inner and outer segments of the photoreceptors (IS/OS) on OCT images. These layers on the OCT images be regarded indicate significant implication about pathologies of the photoreceptors. According to research findings, there was a relationship between damage to the foveal photoreceptors and the VA in retinal vascular diseases. Wong et al investigated the correlation between ORL thickness and VA in 78 patients with DME. They found that central ORL thickness correlates better with vision than the total retinal thickness.
In our study, the macular/central ring ORL thickness in DR patients was significantly decreased compared to that of the control group. However, the BCVA was not only associated with the ORL thickness. These may indicate that the BCVA is more closely related to the internal structure and function of ORL rather than the thickness changes. Uji et al\textsuperscript{[21]} reported that eyes with an intact inner segment ellipsoid line or ELM line had significantly better VA and higher parallelism than eyes with a discontinuous or absent inner segment ellipsoid line or ELM line in DME patients. Parallelism correlated well with VA. It was also been reported that hyperreflective foci in DME are related to foveal photoreceptor damage and concomitant visual disturbance\textsuperscript{[22-24]}.

In this study, the macular/central ring RPE thickness in the DME and non-DME groups were decreased significantly compared with the control group and with a worse VA. Boynton et al\textsuperscript{[25]} found that untreated patients with proliferative diabetic retinopathy (PDR) also had diffusely thinned RPE layers compared with controls. The RPE exerts a enormous function on supporting photoreceptor function by transporting the vitamin A derivative retinal and supplying essential metabolites. The RPE is also responsible for light absorption and phagocytosis of shed photoreceptor of outer segments\textsuperscript{[26]}. Furthermore, the RPE is of great important for photoreceptor renewal and for the phagocytosis of membranes shed by the photoreceptors\textsuperscript{[25]}. In patients with PDR, the thinned RPE layer in both groups revealed the disruption of normal RPE-photoreceptor complex anatomic features, structural findings that correlate well with the compromised RPE and photoreceptor function in these patients\textsuperscript{[20]}.

This study has several limitations. The first is the small sample size of the study. Selection bias could occur as a result of choosing a small group. There were measurement errors in the analysis of choroidal, ORL and RPE thickness. Also, the structure and function of each layers were not included in this study. With the development of analysis techniques and software, further studies should be performed on a large number of subjects.

In conclusion, the choroidal, ORL and RPE thickness were significantly decreased in DR patients compared with controls in different segments, while no significantly changes were found between non-DME and DME groups. The total inner retinal volume and macular RPE thickness were associated with BCVA in DME.

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REFERENCES

Outer retina in diabetic retinopathy


