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Original article

Thickness of the retinal photoreceptor outer segment layer in healthy volunteers and in patients with diabetes mellitus without retinopathy, diabetic retinopathy, or diabetic macular edema☆

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Abstract

Purpose: The purpose of this study was to investigate whether the severity of diabetic disease in the retina is paralleled by changes in the photoreceptor layer.
Methods: This cross-sectional study included healthy volunteers (30 volunteers, 60 eyes) and patients with diabetes (48 patients, 96 eyes). Each patient underwent a single session of spectral domain optical coherence tomography (OCT) in which each retina was imaged twice. On each OCT image, the thickness of the PROS layer was measured at the foveal center and at points 750 μm temporal to and nasal to the center. For statistical analyses, OCT images were assigned to one of the following groups: healthy, diabetes without retinopathy (DM), diabetic retinopathy (DR), or diabetic retinopathy with macular edema (DME).
Results: The mean PROS thickness at the foveal center in the first and second-obtained OCT images was as follows: healthy, 38.5 μm and 38.6 μm; DM, 38.2 μm and 38.2 μm; DR, 35.6 μm and 36.1 μm; DME, 32.6 μm and 32.6 μm. In the first and second-obtained images, significant differences were found between the healthy group and DR and DME ($p < 0.05$ for all), between the DM group and the DME ($p < 0.05$ for all), and between the DR group and the DME group ($p < 0.05$ for all). No significant differences between groups were found at the nasal and temporal locations.
Conclusion: The PROS layer at the foveal center was thinner in patients who had diabetic retinopathy or diabetic macular edema than both the healthy volunteers and diabetic patients without retinopathy.

Keywords: Diabetes mellitus, Diabetic retinopathy, Fovea centralis, Macular edema, Photoreceptor cells

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Introduction

Retinal abnormalities in patients with diabetes mellitus have been a focus of research since the late 1800s and have comprised an increasingly diverse range of phenomena.[1–7] Recent findings have extended this range to include abnormalities in the structure of the retina's layers, particularly the photoreceptor layer.[8–10]

One finding that suggests photoreceptor dysfunction in diabetes is the abnormally weak Stiles-Crawford effect – the

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sensitivity of the retina to the angle of light falling on it – that has been reported for patients with diabetes.[11,12] Further evidence comes from retinal abnormalities detected on optical coherence tomography (OCT). The line taken as representing the junction between the photoreceptor inner and outer segments (the IS/OS line) has been found to be disrupted in patients with diabetic macular edema.[13–15] The external limiting membrane has similarly appeared disrupted.[14,16] More recently, an adaptive optics method has been used to measure the population density of cone cells in the retina, and in patients with diabetes the method appears to show a reduction in this density.[17]

Photoreceptor structure in patients with diabetes has also been investigated in terms of OCT-based measurements of retinal layer thickness.[8–10,19] In patients with diabetes but no retinopathy, the layer representing photoreceptors at the fovea was reported to be thinner than the corresponding layer in healthy volunteers.[8] In patients with diabetic macular edema, visual acuity was found to vary according to thickness of the photoreceptor outer segment layer (PROS).[9,10] particularly when this thickness was measured at or near the center of the fovea.[9] Therefore, the purpose of the present study was to use OCT to measure the PROS layer thickness and total length of the photoreceptors in 4 groups of eyes: healthy group, diabetics without retinopathy (DM), diabetics with diabetic retinopathy but no diabetic macular edema (DR), and diabetics with diabetic macular edema (DME).

Methods

Participants

In this cross-sectional study, demographic and clinical data were collected prospectively from healthy group (30 volunteers, 60 eyes) and from patients with DM (48 patients, 96 eyes), with retinal findings in the latter group ranging from normal to diabetic retinopathy plus macular edema. For the purpose of this study, the diagnosis of diabetes mellitus was based on the medical records available at the time of each patient's referral for ophthalmologic evaluation. Diabetic retinopathy was diagnosed according to ETDRS criteria and patients with a CRT of >300 μm were considered to have DME.[20]

Patients were not included in the study if they had macular ischemia on fluorescein angiography, or signs of other retinal diseases such as age related macular degeneration, and retinal vein occlusion. Data collected from each participant included visual acuities measured via the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 meters, and retinal layer thicknesses measured via OCT. Details of OCT procedures and retinal layer thickness measurements are described below.

OCT procedure

Pupils were not dilated before retinas were imaged. Each participant underwent a single imaging session during which two successive images were obtained from the left eye and two successive images from the right eye, with the use of a spectral domain OCT device (Spectralis, Heidelberg Engineering, Germany). The acquisition of two images from each eye provided two sets of data by which groups of eyes could be compared, and also provided data for repeatability analysis. Throughout the two imaging procedures for a given eye, the participant's chin remained in place on the frame of the device, and the participant was instructed to move as little as possible. According to the manufacturer, the device has a transverse resolution of 14 μm and an axial resolution of 3.9 μm. Another feature of the device is an automatic real-time eye tracking system. During our participants' imaging sessions, this system was set at its maximum value of 100 to provide for the highest image quality attainable with the device.

The images were horizontal cross sections through the foveolar depression, with the width of the image corresponding to a length of 6 mm along the surface of the retina. Central retinal thickness, although not investigated specifically in this study, was determined from the images with the semi-automated procedure routinely used with this device, in which the software detects the inner and outer boundaries of the retina and then the measurement line intersecting the retina perpendicularly can be moved sideways if necessary so as to pass through the lowest point of the fovea.

Photoreceptor outer segment layer measurements

The manual measurement of the PROS layer was performed as previously described.[18] The OCT images were digitally enlarged to 4 times their original size and the OCT device's calipers application was used to mark the boundaries of the layer and measure the distance between them. We defined this layer by marking its boundaries at the inner border of the inner segment – outer segment junction and at the inner border of the retinal pigment epithelium layer. We also defined a thicker layer that was assumed to include the total length of the photoreceptors and we measured it similarly, with boundaries at the outer border of the external limiting membrane layer and at the inner border of the retinal pigment epithelium layer.

For each eye in the study, in each of the 2 OCT images, measurements with the manual calipers were made at 3 different locations: at the lowest point of the fovea, at 750 μm nasal to this point, and at 750 μm temporal to this point (Fig. 1). The fovea is known to have 1500 μm diameter; therefore, the locations that were 750 μm away from the fovea were chosen for making the measurements from the edges of the fovea. All of the measurements were made by the same physician (YK) who was blinded to the clinical data of the patients (see Fig. 2).

Data analysis

For statistical analyses, eyes were assigned to one of 4 groups: healthy group, DM, DR, and DME. First one-way ANOVA test was used to evaluate intergroup difference among the four groups; then, if there was a significant difference, between-groups differences were then evaluated pairwise with the use of Student's unpaired t test. In each set of pairwise tests, in which each group was compared in turn with each other group, the resulting six p values were then corrected with the Bonferroni method, i.e. by multiplying each p value by the total number of times the test was performed[21] - in this case six - so as to take into account the effect of performing multiple tests. Pearson's test was used for correlation analysis. A p value of less than 0.05 was

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