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Quantification of Diabetic Macular Ischemia Using Optical Coherence Tomography Angiography and Its Relationship with Visual Acuity

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Purpose: To quantify foveal avascular zone (FAZ) area and macular vascular density objectively using optical coherence tomography angiography (OCTA) and to examine correlations with visual acuity in eyes with diabetic retinopathy (DR) in the absence of diabetic macular edema.

Design: Retrospective observational case series.

Participants: Eighty-four eyes from 55 patients with DR and 34 control eyes from 27 age-matched healthy participants.

Methods: All eyes underwent OCTA (RTVue-XR Avanti; Optovue, Inc, Fremont, CA). Integrated automated algorithms were used to quantify FAZ area and macular vascular density.

Main Outcome Measures: FAZ area, vessel area density (VAD), vessel length density (VLD), and visual acuity.

Results: In each study eye, DR was classified as mild nonproliferative DR (NPDR; n = 32 [38%]), moderate-to-severe NPDR (n = 31 [37%]), or proliferative DR (n = 21 [25%]). Mean FAZ area was greater in diabetic eyes compared with control eyes both in the superficial (0.427 mm^2 vs. 0.275 mm^2; $P < 0.001$) and deep (0.616 mm^2 vs. 0.372 mm^2; $P < 0.001$) vascular networks. Mean VAD was lower in diabetic eyes compared with control eyes in both the superficial (49.44% vs. 55.09%; $P < 0.001$) and deep (56.65% vs. 61.32%; $P < 0.001$) networks. Mean VLD was also lower in diabetic eyes compared with control eyes in both the superficial (17.68 mm^{-1} vs. 21.55 mm^{-1}; $P < 0.001$) and deep (21.19 mm^{-1} vs. 24.38 mm^{-1}; $P < 0.001$) networks. In all eyes, there was a statistically significant negative correlation between the logarithm of the minimum angle of resolution (logMAR) visual acuity and the vascular density in both the superficial (VAD, $\rho = -0.52$; VLD, $\rho = -0.54$; $P < 0.001$) and deep (VAD, $\rho = -0.50$; VLD, $\rho = -0.50$; $P < 0.001$) networks. A positive correlation was found between logMAR visual acuity and FAZ area in both the superficial ($\rho = 0.29$; $P < 0.01$) and deep ($\rho = 0.48$; $P < 0.001$) networks.

Conclusions: Automated quantitative algorithms allow for objective assessment of retinal vascular changes in eyes with DR that are correlated to visual acuity. These methods may prove useful in monitoring disease progression and identifying parameters that affect visual function. *Ophthalmology 2016;■:1–10 © 2016 by the American Academy of Ophthalmology*

Diabetic macular ischemia (DMI) is important in the pathogenesis of diabetic retinopathy (DR) and is characterized by narrowing or occlusion of retinal capillaries.[1] Resulting tissue hypoxia leads to an increase in vascular endothelial growth factor levels, resulting in diabetic macular edema (DME).[2] Although DME is the most common cause of vision loss in patients with DR,[3,4] DMI also has been shown to result in vision loss, regardless of the presence or absence of DME.[5]

Diabetic macular ischemia has been well characterized using fluorescein angiography (FA), where there is enlargement of the foveal avascular zone (FAZ) and retinal capillary loss.[6,7] Fluorescein angiography remains an important method for imaging retinal vasculature in DR with the ability to detect microaneurysms, venous beading, capillary nonperfusion, and leakage. Nevertheless, it is an invasive, time-consuming test that requires dye injection, which can lead to several adverse effects that rarely may be life threatening.[8,9] Moreover, because of light scatter by inner retinal layers, FA fails to image the deep capillary network and provides information only about superficial capillary network perfusion.[10]

The recent development of optical coherence tomography angiography (OCTA) has allowed for acquisition of high-resolution depth-resolved images of the retinal vascular layers in a rapid, noninvasive manner.[11] Optical coherence tomography angiography has been used to describe the retinal vasculature in several diseases and in healthy eyes with high reliability and reproducibility.[12–16] More recently, different automated quantification algorithms have

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been used to extract angiographic data, including FAZ area, vascular density, areas of nonflow, and vessel length from OCTA scans.[15,17,18] These algorithms lately have been used to quantify several angiographic parameters in DR eyes as markers for DMI.[12,15] However, these studies have not evaluated the association of these parameters with visual acuity.

In this study, we performed a detailed quantitative analysis of FAZ area and macular vascular density measured by vessel area density (VAD) and vessel length density (VLD). In addition, we investigated the correlation of these parameters with visual acuity in a cohort of patients with DR without DME.

Methods

Participants

This retrospective observational cases series was approved by the Institutional Review Board of Wills Eye Hospital and complied with the Health Insurance Portability and Accountability Act. Patients with a diagnosis of diabetes mellitus with DR who underwent OCTA of one or both eyes at the Retina Service of Wills Eye Hospital between January 1, 2015, and August 30, 2015, were evaluated. All diabetic participants underwent standard ophthalmic examination and spectral-domain optical coherence tomography (SD OCT; Spectralis; Heidelberg Engineering, Heidelberg, Germany), and the stage of retinopathy was determined with fundus examination based on the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Severity scale before the acquisition of the OCTA scans.[19] Patients with DME on SD OCT, concomitant retinal disease (age-related macular degeneration or retinal vascular occlusion), or both were excluded. Age-matched healthy controls with no history of systemic disorders were selected from a normative database collected by our service. The healthy participants underwent dilated ophthalmic examination before obtaining OCTA scans to ensure a healthy macular status. Best-corrected visual acuity was measured based on current spectacle correction with pinhole.

Optical Coherence Tomography Angiography Image Acquisition

Optical coherence tomography angiography images were obtained with the AngioVue OCTA system on the commercially available Avanti SD OCT device (Optovue, Inc, Fremont, CA). This system uses split-spectrum amplitude decorrelation angiography algorithm (version 2015.100.0.35) and operates at 70 000 A-scans per second to acquire OCTA volumes consisting of 304×304 A-scans. Orthogonal registration and merging of 2 consecutive scans were used to obtain OCTA volume scans over a central 3×3-mm area. Optical coherence tomography angiography images of the superficial and deep capillary networks were generated separately using the automated software algorithm. Based on these default settings, the boundaries of superficial network extended from 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer. The deep capillary network extended from 15 to 70 μm below the inner plexiform layer.

Two experienced independent graders (W.A.S., A.S.) reviewed the OCTA images. Patients with poor image quality were excluded based on the presence of one or more of the following criteria: low signal strength index (SSI; <50), presence of 1 or more blink artifacts, poor fixation leading to motion or doubling artifacts, media opacity obscuring view of the vasculature, and presence of cystoid macular changes causing disrupted retinal anatomic features and segmentation errors. Of 108 eyes with DR without DME, 24 eyes (22%) were excluded based on the aforementioned image quality criteria.

Vascular Density and Foveal Avascular Zone Measurement

Using the acquired images, measurements of the FAZ area were calculated using the nonflow function on the OCTA software at the level of the superficial and deep vascular networks (Fig 1). Vascular density values were calculated for the entire en face scan for superficial and deep networks excluding the FAZ area. To allow quantification of vascular density, the OCTA software converts the obtained scans into 2 forms of binary images using an automated thresholding algorithm. One form represents binarization of the original scan obtained, allowing for measurement of VAD (Fig 1C). Vessel area density is calculated as the percentage area occupied by blood vessels, with the blood vessels being defined as pixels having decorrelation values above the threshold level. Vessel area density is calculated using the following formula:

$$\text{VAD} = \text{area occupied by vasculature (pixels)} / (\text{total scan area} - \text{FAZ area})(\text{pixels}).$$

The second binary form is obtained by skeletonizing the acquired scan into 1-pixel−wide vessels allowing for measurement of VLD (Fig 1D). Vessel length density is calculated by measuring the total vessel length in the obtained scan using the following formula:

$$\text{VLD} = \text{length of skeletonized vasculature (mm)} / (\text{total scan area} - \text{FAZ area})(\text{mm}^2).$$

Statistical Analysis

Statistical analyses were performed with SPSS software version 20 (SPSS, Inc, Chicago, IL). Best-corrected visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR). Variable normality was inspected using histograms and the Shapiro−Wilk test. The FAZ area, superficial VAD, and visual acuity data were skewed negatively with no simple transformation to redress the skewed data, and accordingly, the Mann−Whitney *U* test or unpaired *t* test was used to compare FAZ area and vascular density between diabetics and controls based on variable normality. Analysis of variance with the post hoc Tukey (parametric) or Kruskal-Wallis (nonparametric) test was used to compare age, central macular thickness, FAZ area, and vascular density between different stages of DR and controls. Statistical test application was dependent on the normality of data for each variable. Spearman's correlation was used to assess the relationship between logMAR visual acuity and vascular density as well as FAZ area. A *P* value of less than 0.05 was considered statistically significant.

Results

Eighty-four eyes from 55 patients with DR and 34 control eyes from 27 age-matched healthy participants were included in this study. Baseline characteristics are listed in Table 1. Diabetic retinopathy was classified as mild nonproliferative diabetic retinopathy (NPDR) in 32 eyes (38%), moderate-to-severe NPDR in 31 eyes (37%), and proliferative DR (PDR) in 21 eyes (25%). Thirty-two diabetic eyes (38%) had been treated previously. Prior treatments are listed in Table 2. There was no significant difference in age across all groups ($P = 0.17$). Mean visual acuity was 0.19±0.136 logMAR in diabetic eyes (Snellen equivalent, 20/31; range, 20/20−20/80) and 0.03±0.047 logMAR in control eyes