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Correlation Analysis between Foveal Avascular Zone and Peripheral Ischemic Index in Diabetic Retinopathy: A Pilot Study

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Purpose: To investigate the foveal avascular zone (FAZ) by OCT angiography (OCT-A) in patients affected by diabetic retinopathy and its correlation with peripheral retinal ischemic index.

Design: Observational, cross-sectional study, prospectively designed.

Participants: Consecutive patients with treatment-naïve diabetic retinopathy were prospectively recruited between October 2015 and January 2017.

Methods: All patients underwent a comprehensive ocular examination including OCT, OCT-A, ultra-widefield (UWF) color fundus images, and UWF fluorescein angiography.

Main Outcome Measures: Variables analyzed included best-corrected visual acuity (BCVA) expressed in logarithm of the minimal angle of resolution (logMAR); diabetic retinopathy grading; FAZ area at full-thickness (internal limiting membrane to Bruch's membrane) OCT-A angiogram; superficial capillary plexus; deep capillary plexus; ischemic index; and central macular thickness (CMT).

Results: Twenty-two eyes of 22 patients (11 male, mean age 54.9±15.8 years) were included. Mean FAZ areas at full thickness, superficial plexus, and deep plexus were 0.331±0.137 mm^2, 0.340±0.140 mm^2, and 1.028±0.447 mm^2, respectively. Mean ischemic index was 13.6% (range, 0%−50.2%). A significant correlation was found between ischemic index and FAZ area at both full-thickness ($r = 0.60$, $P = 0.0035$) and superficial ($r = 0.68$, $P = 0.0005$) layers. Disease severity correlated to ischemic index ($r = 0.49$, $P = 0.0204$), and FAZ area at full-thickness ($r = 0.53$, $P = 0.0108$) and superficial ($r = 0.47$, $P = 0.0292$) plexuses. No significant correlation between ischemic index and FAZ at deep plexus was found. BCVA correlated only to CMT ($r = 0.66$, $P = 0.0008$).

Conclusions: The association between peripheral and macular perfusion found in this study supports the hypothesis that both conditions share a common pathogenic mechanism that leads to capillary nonperfusion. *Ophthalmology Retina 2017;■:1−7 © 2017 by the American Academy of Ophthalmology*

Diabetic retinopathy is one of the leading causes of blindness in developed countries.[1] Reasons for vision loss are diabetic macular edema, macular ischemia, and complications of proliferative diabetic retinopathy, including vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma.[2]

Fluorescein angiography (FA) is a helpful test in the evaluation of diabetic retinopathy. Traditional angiograms explore 30° to 50° of the retina at once; however, visualization of peripheral retina is helpful to assess nonperfused areas, vascular leakage, microvascular abnormalities, and neovascularizations.[3] To overcome these pitfalls, widefield and ultra-widefield (UWF) imaging systems have been developed over the past 80 years; however, previous systems did not become part of daily practice due to several limitations (i.e., need for mydriasis, contact lens, limited resolution, clear ocular media).[4] The Optos fundus camera (Optos PLC, Dunfermline, Scotland, UK) is a device recently introduced in the market, which is based on a confocal scanning laser ophthalmoscope and an ellipsoid mirror and which allows the visualization of 200° of the retina in 1 single shot, with no need for contact lens and even without mydriasis. Nowadays, UWF FA is an invaluable tool in retinal vascular diseases, including diabetic retinopathy. Compared with both dilated fundus examination and traditional 7 standard fields protocol, UWF FA identified additional retinal lesions in up to 10% of eyes.[3] UWF FA is useful to visualize areas of peripheral ischemia, whose extent has been linked to disease severity.[5] To precisely quantify the amount of nonperfused areas and to investigate their relationship with other clinical or imaging variables, an ischemic index has recently been proposed.[6] Quantitative assessment of peripheral ischemia through the ischemic index has been applied to several ocular conditions, including vasculitis,[7] retinal vein occlusions,[6] and diabetic retinopathy.[5,8]

OCT angiography (OCT-A) is a novel technology that allows the visualization of the retinal vasculature and choroidal vascular network. It is a dye-free, rapid, and

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3-dimensional method, which is based on algorithms that convert multiple A-scans to OCT-A images.[9] OCT angiograms are co-registered with OCT B-scans, allowing for concurrent visualization of both retinal flow and structure. Images rely on the concept that in a firm eye the only structure with motion is blood flowing through vessels and contrast is generated based on the difference between moving cells in the vasculature and the static surrounding tissue. OCT-A revealed several alterations in patients affected by diabetic retinopathy, including enlargement of the foveal avascular zone (FAZ),[10] nonperfused areas,[11] microaneurysms,[11,12] intraretinal microvascular abnormalities,[12] and neovascularizations.[11] FAZ area enlargement reflects an ischemic process; notably, FAZ area is increased even in diabetic patients without retinopathy and its dimension reflects the disease severity.[13,14]

Because both FAZ enlargement and peripheral ischemia share a common pathogenic mechanism—that is, capillary nonperfusion[15]—it would be interesting to explore the correlation between peripheral and macular ischemia in diabetic eyes calculated with ischemic index and FAZ area, respectively. To the best of our knowledge, such relationship has been previously investigated only by a study by Sim et al,[8] in which a moderate correlation between FAZ area and peripheral ischemia was disclosed using only UWF FA. Although UWF FA is an excellent tool for the peripheral ischemia, it is less suitable to question the FAZ area due to leakage phenomena and superimposition of capillary networks. On the other hand, OCT-A dissociates superficial and deep capillary plexuses and, thus, it allows investigation of the different FAZ plexuses separately. Also, OCT-A is a dye-less technique free from vascular leakage.

The aim of this study was to investigate FAZ area by OCT-A in patients affected by diabetic retinopathy and its correlation with ischemic index.

Methods

Study Population

Consecutive patients with treatment-naïve diabetic retinopathy were prospectively recruited between October 2015 and January 2017 at the Medical Retina & Imaging Unit of the Department of Ophthalmology, University Vita-Salute, San Raffaele Hospital. The study was conducted in compliance with the Declaration of Helsinki and all patients signed a written general consent to participate in observational studies, which were approved by the ethics committee of San Raffaele Hospital. Inclusion criteria were diagnosis of type 1 or 2 diabetes mellitus, age $\geq$18 years, and refractive status between -6 and $+3$ diopters. Exclusion criteria were any other retinal disease; significant media opacity precluding proper image quality; previous ocular surgery other than uncomplicated cataract extraction and intraocular lens implantation performed $\leq$6 months before enrollment; previous posterior segment laser; or previous intravitreal injections. If both eyes fulfilled inclusion and exclusion criteria, 1 eye was randomly selected.

Patients underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA) on Snellen charts, anterior segment biomicroscopy, intraocular pressure measured with Goldmann applanation tonometry, indirect fundus examination, UWF color fundus images (Optos PLC, Dunfermline, Scotland, UK), UWF FA (Optos PLC, Dunfermline, Scotland, UK), spectral-domain OCT (Spectralis, HRA Heidelberg, Heidelberg, Germany) and 3 × 3-mm OCT-A (Angioplex, CIRRUS HD-OCT models 5000, Carl Zeiss Meditec, Inc, Dublin, CA) scans of the macula. BCVA was converted to the logarithm of the minimal angle of resolution (logMAR) for calculation purposes. Medical history and demographic data were also recorded.

Acquisition and Analysis of Ultra-widefield Images

All UWF FA images were acquired using the Optos California ultra-widefield retinal imaging system (Optos PLC, Dunfermline, Scotland, UK). The pupil was dilated with tropicamide 1% and UWF color fundus images were taken before FA execution. After intravenous injection of fluorescein dye (5 ml of 20% sodium fluorescein), UWF FA were obtained in the early (<60 seconds), middle (2 minutes and 30 seconds), and late phases (4−5 minutes). Both UWF color fundus images and FA were centered on the macula.

For each eye, the best UWF FA image in the arteriovenous phase (between 45 seconds and 2 minutes) was chosen to get the largest retina visualization and image clarity. The image was then exported as a jpeg file. Before image export, Optos Advance software was used to activate high-definition mode and set magnification at 1.5×, to have reduced background area with no loss of retinal surface, and enhancement at 1.6×, to obtain sharper boundaries between perfused and nonperfused areas; conversely, brightness and gamma were left unchanged. Ischemic index was calculated by 2 independent operators (MVC, AR) with ImageJ software and using a previously described methodology.[6] Briefly, total retinal area and nonperfused areas were encircled by means of the polygon selection tool. Ischemic index was defined as the ratio of nonperfused areas to total retinal area (Fig 1A).

A third masked operator (EC) independently reviewed the UWF images and graded diabetic retinopathy according to the severity scale proposed by Wilkinson et al.[16]

Spectral-domain OCT Measurements of Retinal Thickness

Mean central macular thickness (CMT) was obtained for each patient (Spectralis spectral-domain OCT; 19 horizontal lines [6 × 6-mm area] centered on the fovea, each with 9 averaged OCT B-scans−1024 A-scans per line at 240-μm intervals).

Acquisition and Analysis of OCT Angiography Images

All OCT-A images were acquired with the Cirrus HD-OCT (Angioplex, CIRRUS HD-OCT models 5000, Carl Zeiss Meditec, Inc, Dublin, CA). All 3 × 3-mm OCT-A images were acquired in the macular area. Automatic segmentation of full-thickness (internal limiting membrane to Bruch's membrane) retina vasculatures and superficial and deep capillary plexuses was evaluated by a single operator (AR) and manually adjusted in case of segmentation errors. Images were exported to the National Institutes of Health ImageJ 1.50 (National Institutes of Health, Bethesda, MD) software and analyzed by 2 independent masked operators (AR, MVC).

The FAZ area was manually measured using a previously published method.[17,18] Briefly, FAZ area was manually outlined through the polygon selection tool in all 3 selected plexuses (full-thickness, superficial, and deep), and its dimension was expressed in millimeters squared (Fig 1B).