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Acircularity index and axis ratio of the foveal avascular zone in diabetic eyes and healthy controls measured by optical coherence tomography angiography ☆

Brian D. Krawitz [a,b], Shelley Mo [a,b], Lawrence S. Geyman [a,b], Steven A. Agemy [c], Nicole K. Scripsema [b], Patricia M. Garcia [b], Toco Y.P. Chui [a,b], Richard B. Rosen [a,b,*]

[a] Icahn School of Medicine at Mount Sinai, 1428 Madison Ave, New York, NY, USA
[b] New York Eye and Ear Infirmary of Mount Sinai, 310 East 14th Street, New York, NY, USA
[c] Department of Ophthalmology, SUNY Downstate Medical Center and SUNY Downstate College of Medicine, 50 Clarkson Ave, Brooklyn, NY 11203, USA

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ABSTRACT

Given the complexity of the current system used to stage diabetic retinopathy (DR) and the risks and limitations associated with intravenous fluorescein angiography (IVFA), noninvasive quantification of DR severity is desirable. We examined the utility of acircularity index and axis ratio of the foveal avascular zone (FAZ), metrics that can noninvasively quantify the severity of diabetic retinopathy without the need for axial length to correct for individual retinal magnification. A retrospective review was performed of type 2 diabetics and age-matched controls imaged with optical coherence tomography angiography (OCTA). Diabetic eyes were divided into three groups according to clinical features: No clinically observable diabetic retinopathy (NoDR), nonproliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). OCTAs of the superficial and deep vascular layers centered at the fovea were superimposed to form a full vascular layer on which the FAZ was manually traced. Acircularity index and axis ratio were calculated for each FAZ. Significant differences in acircularity index were observed between all groups except for controls vs. NoDR. Similar results were found for axis ratio, although there was no significant difference observed between NPDR and PDR. We demonstrate that acircularity index and axis ratio can be used to help noninvasively stage DR using OCTA, and show promise as methods to monitor disease progression and detect response to treatment.

1. Introduction

Diabetic retinopathy (DR) is the leading cause of blindness in working-age adults in developed countries (Zhang, Ferreyra, Grob, Bedell, & Zhang, 2013) and affects approximately 93 million people worldwide (Yau et al., 2012). While the majority of patients with DR do not experience visual symptoms until the later stages of disease, timely interventions may prevent visual decline (Aiello, 2003). In addition, recommendations for treatment and follow-up are guided by disease severity (Chakrabarti, Harper, & Keeffe, 2012). Consequently, early detection and accurate staging of DR are critical for determining optimal management.

The current gold standard for staging DR is the Early Treatment Diabetic Retinopathy Study (ETDRS) guidelines, which stratify disease severity based on quadrant analysis of dilated fundus exam, color fundus photography, and intravenous fluorescein angiography (IVFA) findings. Grading criteria include microaneurysms, exudates, cotton wool spots, retinal hemorrhages, and neovascularization (Group, 1981, 1991a, 1991b). However, the complete classification system is very complex and impractical in most clinical settings. In fact, many unpublished contemporary surveys have shown that most physicians do not use the full ETDRS severity scale for these reasons (Wilkinson et al., 2003). The implementation of IVFA has improved the identification of several vascular abnormalities such as capillary nonperfusion, neovascularization,

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* Corresponding author at: 310 East 14th Street, Suite 500 South Building, New York, NY 10003, USA.

E-mail addresses: brian.krawitz@icahn.mssm.edu (B.D. Krawitz), shelley.mo@icahn.mssm.edu (S. Mo), lawrence.geyman@mssm.edu (L.S. Geyman), sagemy@nyee.edu (S.A. Agemy), nscripsema@nyee.edu (N.K. Scripsema), pgarcia@nyee.edu (P.M. Garcia), ychui@nyee.edu (T.Y.P. Chui), rrosen@nyee.edu (R.B. Rosen).

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and leakage at the blood-retinal barrier (Ffytche, Shilling, Chisholm, & Federman, 1980; Novotny & Alvis, 1961; Rabb, Burton, Schatz, & Yannuzzi, 1978), and it is now the primary method used to assess the retinal vasculature. However, IVFA is limited in its resolution and provides incomplete morphological information about the retinal capillary networks, as demonstrated by lower capillary density values compared to histological images (Mendis et al., 2010). In addition, the procedure is invasive, time consuming, and is occasionally associated with adverse effects including nausea, pruritus, and even anaphylaxis in rare circumstances (Balbino, Silva, & Correia, 2012; Johnson, McDonald, & Schatz, 1998; Yannuzzi et al., 1986).

Optical coherence tomography angiography (OCTA) is a rapid, noninvasive technique that can be used to analyze the foveal microvasculature (Agemy et al., 2015; Di et al., 2015; Freiberg et al., 2015; Hwang et al., 2015; Kim et al., 2012; Mastropasqua et al., 2015; Takase et al., 2015). This modality employs a motion contrast image processing technique on sequential OCT images to generate perfusion maps without the need for extrinsic dye injection. Vascular metrics measured with OCTA have been shown to closely agree with histology (Mammo et al., 2015; Tan et al., 2015) as well as other *in vivo* imaging modalities (Hwang et al., 2015; Kim et al., 2012; Mo et al., 2016; Spaide, Klancnik, & Cooney, 2015). A number of studies have focused on quantifying the foveal avascular zone (FAZ), since capillary dropout from this region can be associated with significant visual impairment (Arend, Wolf, Harris, & Reim, 1995; Kim et al., 2012; Parodi, Visintin, Della Rupe, & Ravalico, 1995), and enlargement of the FAZ has been observed in DR, sickle cell retinopathy, and branch retinal vein occlusion (Arend et al., 1991; Bresnick et al., 1984; Conrath, Giorgi, Raccah, & Ridings, 2005; Mansour, Schachat, Bodiford, & Haymond, 1993; Parodi et al., 1995; Sanders, Brown, Rosenstein, & Magargal, 1991). As such, visualization and analysis of the FAZ has become a means of assessing macular perfusion and the extent of disease.

Several studies have demonstrated quantitative differences of FAZ dimensions in DR compared to controls using IVFA (Bresnick et al., 1984; Conrath et al., 2005; Mansour et al., 1993) and more recently, OCTA (Di et al., 2015; Freiberg et al., 2015; Hwang et al., 2015; Kim et al., 2012; Takase et al., 2015). These FAZ metrics generally require axial length measurement to correct for individual retinal magnification (Bennett, Rudnicka, & Edgar, 1994; Popovic, Knutsson, Thaung, Owner-Petersen, & Sjostrand, 2011), which adds an additional step for accurate calculations and is not always available. In this study, we calculated two metrics that do not require axial length correction in healthy and diabetic eyes using OCTA. We measured acircularity index, a metric that was first described by Tam et al. in conjunction with adaptive optics imaging to quantify the irregularity of the FAZ (Tam et al., 2011). We also measured the axis ratio of the FAZ. We demonstrate how these simple, noninvasive methods can be applied as potential biomarkers for characterizing DR severity and may help identify vascular changes before the onset of funduscopically visible disease.

2. Materials and methods

2.1. Study population

A retrospective review of diabetic patients and healthy controls was conducted at the New York Eye and Ear Infirmary of Mount Sinai. The work was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by our Institutional Review Board. Diabetic eyes were divided into 3 groups according to stage of disease on the day of imaging determined by extensive chart review: no clinically observable diabetic retinopathy (NoDR), nonproliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). An in-house retina specialist (SA) further classified eyes with NPDR into mild, moderate, and severe disease according to the ETDRS system (Group, 1981, 1991a, 1991b) by analyzing dilated fundus examination findings, color funduscopic images, and IVFA images within 6 months of OCTA acquisition. One eye from each subject was included. In subjects with both eyes imaged, a single eye was randomly chosen. Best corrected visual acuity (BCVA) at the time of OCTA imaging was documented. Eyes were excluded if there was additional retinal vascular pathology present including venous or arterial occlusions, as well as systemic vascular conditions including sickle cell disease, HIV, or uncontrolled hypertension.

2.2. OCTA acquisition and image processing

OCTA imaging was performed using a commercial spectral domain OCT system (Avanti RTVue-XR; Optovue, Fremont, CA). Macular $10 \times 10^{\circ}$ ($\sim 3 \times 3$ mm) scans centered at the fovea were obtained from each subject. OCTA perfusion maps were generated using the split-spectrum amplitude decorrelation angiography (SSADA) algorithm as previously described (Agemy et al., 2015; Jia et al., 2012; Spaide et al., 2015). After image acquisition, automatic OCT layer segmentation was performed using the built in Optovue software. In brief, the inner retinal blood vessels were separated into the superficial and deep layers. The superficial layer consists of blood vessels from the inner limiting membrane (ILM) to the posterior boundary of the inner plexiform layer (IPL), whereas the deep layer consists of blood vessels between the posterior boundary of the IPL and the posterior boundary of the outer plexiform layer (OPL). The software selects the maximum decorrelation value to generate an en face angiogram at each layer.

These superficial and deep perfusion maps were then superimposed to generate full thickness angiograms of the inner retina using custom software on MATLAB (The MathWorks Inc., Natick, MA). This full thickness vascular layer included all large vessels and capillaries located between the ILM and the posterior boundary of the OPL, and was designed to resemble the two-dimensional view provided by conventional fluorescein angiography (Spaide et al., 2015). Previously published data by our group have demonstrated the value of this map for dependable FAZ analysis, with FAZ metrics including acircularity index, area, and perimeter on the full OCTA layer agreeing closely with high resolution adaptive optics imaging (Mo et al., 2016). Furthermore, while we found that the superficial and full layer FAZ margin is typically identical in control subjects, superficial capillary dropout in diseased patients can lead to regions where the FAZ is bordered by deeper capillaries (Kim et al., 2012) (Fig. 1). Additionally, capillaries that bridge the superficial and deep layers or are shifted by cystic changes are not entirely captured by the superficial segmentation, further supporting the use of the full layer to reliably trace the FAZ.

Images with poor signal strength or motion artifacts substantial enough to disrupt clear delineation of the FAZ were excluded. Patients with large exudates that obscured the FAZ border or significant macular edema that obliterated the margin were also excluded. On images acceptable for inclusion, signal strength index was documented and the FAZ was manually traced by an expert grader (BK) using Adobe Photoshop CS6 (Adobe Systems Inc., San Jose, CA) (Fig. 2A). A second independent grader (SM) traced a subset of 10 randomly selected FAZs from each of the control, NoDR, NPDR, and PDR groups for intergrader agreement analysis. Acircularity index and axis ratio of the FAZ were computed using MATLAB. Acircularity index was defined as the ratio of the

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