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Optical coherence tomography angiography assessment of retinal microvascular changes in diabetic eyes in an urban safety-net hospital

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Abstract

PURPOSE: To determine whether quantitative optical coherence tomography angiography (OCTA) parameters can be used to distinguish among eyes at various stages of diabetic retinopathy (DR) in an urban safety-net hospital population.

DESIGN: Prospective cross-sectional study

PARTICIPANTS: 329 eyes from 329 patients were included in this study; 90 nondiabetic patients, 170 diabetic patients without retinopathy, 57 diabetes with mild to moderate NPDR, and 12 diabetes with severe NPDR to PDR.

METHODS: Patients underwent OCTA imaging and ultra-widefield fundus photography at Zuckerberg San Francisco General Hospital and Trauma Center between April and October 2018. For participants with diabetes, imaging was classified according to DR severity by a telemedicine reading center. Eight OCTA parameters were analyzed. Perfusion density (PD) and vessel length density (VD) were examined from both superficial and deep capillary plexus (SCP and DCP). The other four parameters were examined only from the SCP. Total extrafoveal avascular area (tEAA) was based on the area of absent capillary vessels. Foveal avascular zone (FAZ) related metrics consisted of FAZ area, FAZ circularity index (FAZ CI) and FAZ acircularity index (FAZ ACI).

MAIN OUTCOME MEASURES: Area under the curve (AUC) for OCTA parameters to distinguish among groups according to DR severity.

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Conflict of Interest: SL: none; CP: none; XL: none; JMS: consultant for Carl Zeiss Meditec, not related to the subject of this study.

RESULTS: All OCTA parameters demonstrated a significant relationship with DR severity ($p<0.05$). No significant difference was found when comparing non-diabetic participants versus the diabetes without retinopathy (DM no DR) group. FAZ area was the only metric that demonstrated a significant difference between genders, mean 0.29 (0.12) mm^2 in male and 0.34 (0.13) mm^2 in female groups ($p<0.001$). ROC curve analyses showed that tEAA had the highest AUC when comparing various stages of the disease.

CONCLUSIONS: In this urban, public hospital population, quantification of retinal vascular findings with OCTA imaging was a useful means of distinguishing patients according to DR severity. Because these results were similar to those of other tertiary referral centers, it would be reasonable to perform further DR-related OCTA studies in this population and expect generalizable results.

Precis

The study assessed the utility of optical coherence tomography angiography for evaluating diabetic retinopathy in an urban safety-net hospital serving the population of San Francisco. Quantitative parameters correlated well with retinopathy severity stages.

Introduction

Diabetes mellitus (DM) is known to lead to end-organ complications, including diabetic retinopathy, due to microvascular damage throughout the body. OCTA can detect microvascular changes of the retinal vessels. In the past, fluorescein angiography (FA) has been the gold standard for the investigation of multiple features of DR.[1] Recently, however, FA has been used less frequently in clinical practice because of its potential complications.[2] OCTA is noninvasive and convenient and thus is increasingly being used in the clinic setting.

OCTA provides a visual representation of retinal vessels with active blood flow, with better visualization of vascular details compared to fluorescein angiography, but it does not show leaking, pooling or staining of lesions. Because of these features, OCTA imaging allows for a quantitative measurement of various vascular characteristics in the macula, including the foveal avascular zone, vessel density and neovascularization.[3] OCTA also shows the details of multiple layers of the chorioretinal microvasculature: superficial capillary plexus (SCP), deep capillary plexus (DCP) and choroidal plexus. Because of this, it may be able to identify the location of vessel changes associated with early diabetic damage, such as microaneurysms,[4] venous collaterals, and absence of capillary flow.[5]

Various OCTA metrics have been used to assess diabetic macular ischemia, including the foveal avascular zone (FAZ) area,[6–12] FAZ circularity index (FAZ CI),[13–15] superficial perfusion density (SPD), superficial vessel density (SVD), deep perfusion density (DPD), deep vessel density (DVD)[9–11,14,16–21] and extrafoveal avascular area (EAA).[14,22–25] Additionally, FAZ acircularity index (FAZ ACI)[26] a novel metric, showed an ability to quantify DR severity without using axial length to correct for retinal magnification.

Many publications describing the findings and features of OCTA imaging in diabetic retinopathy have come from tertiary referral centers and university hospitals.[9,22,26] Urban safety-net hospitals are government-funded institutions that provide healthcare for patients

unable to access private insurance, often socioeconomically challenged and marginalized populations. It is not generally known whether the early microvascular changes of diabetic eye disease manifest differently in this patient population. In the present study, we evaluated OCTA findings in diabetic and non-diabetic patients in this at-risk population to determine whether quantitative OCTA parameters were able to distinguish among non-DM eyes, those from patients with DM without retinopathy, and eyes with varying levels of DR.

Methods

In this prospective cross-sectional study, participants without diabetes and participants with diabetes with or without DR were recruited from Zuckerberg San Francisco General Hospital and Trauma Center, a publicly funded safety-net hospital serving the City and County of San Francisco, from April to October 2018. The study was approved by the Human Research Protection Program (HRPP) at the University of California, San Francisco (UCSF). The UCSF HRPP granted a waiver of consent, affirming that patient welfare would not be adversely affected by waiving informed consent. All research adhered to the tenets of the Declaration of Helsinki. OCTA imaging on diabetic patients was collected from patients participating in a telemedicine-based DR screening program, and OCTA from non-diabetic patients was collected from patients undergoing comprehensive eye exams. The latter group of patients' main clinical conditions included but were not limited to dry eye, presbyopia, and glaucoma suspect status. Ultra-widefield fundus photography (Optos Daytona, Optos PLC, Dunfermline, UK) and OCTA were obtained in all qualifying subjects.

Exclusion criteria for participants without diabetes included any history of ocular injury, ocular disease that could affect the retinal microvasculature such as retinal vascular occlusion, glaucoma, or vitreomacular disease.

OCTA imaging was performed with a Cirrus™ HD-OCT 5000 with AngioPlex OCT Angiography (Carl Zeiss Meditec, Dublin, CA). Both eyes of each participant were imaged with a scan comprising 245 clusters of B-scans repeated four times, in which each B-scan consisted of 245 A-scans. The resulting OCT volume scan had dimensions of 3 × 3 × 2 mm centered at the fovea. The effect of eye motion-related artifacts was minimized by the use of FastTrac eye tracking software. Images were selected for inclusion based on having signal strength greater than 7, minimal motion artifacts, decentration from the foveal center of less than 20 microns, and minimal evidence of obscuration by media opacities.

The Optical Micro Angiography algorithm was applied to the volumetric data sets, and the images were exported for analysis in Cirrus software 11.0, ImageJ (National Institutes of Health, Bethesda, MD, USA), and MATLAB (R2018b; MathWorks, Inc., Natick, MA, USA).

The inner retina was included in the analysis. This was identified on the scans as the tissue between the inner limiting membrane and an offset 110 pm from the retinal pigment epithelium layer.[13] The SCP was defined as the superficial 70% of the inner retina, and the deeper 30% remaining was the DCP. A model-based method was used to remove

decorrelation tails from the DCP en face image. All these steps were performed within the software commercially available on the OCTA device.

OCTA parameters were classified into three categories: foveal avascular zone-related metrics, consisting of FAZ area, FAZ ACI and FAZ CI; vessel density-related metrics, consisting of SPD, SVD, DPD and DVD; and a nonperfusion metric, the total extrafoveal avascular area (tEAA).

CIRRUS 11.0 software automatically calculated the FAZ area, FAZ CI, perfusion density, and vessel density of the SCP (Figure 1). The FAZ measures were based solely on the SCP because it is expected that there is a single capillary plexus at the border of the FAZ.

The FAZ CI was calculated as the ratio of the measured area of the FAZ to the expected area of a perfect circle, which has the same perimeter as the FAZ, with a range of 0.0 to 1.0. The closer this metric is to zero, the more irregular is the shape of the FAZ.

$$\text{FAZ CI} = \text{area of measured FAZ} / \text{area of equal perimeter circle}$$ [27]

The FAZ ACI was calculated as the ratio of the measured perimeter of the FAZ to the expected perimeter of the perfect circle, which has the same area as the FAZ.[26] A value closer to 1.0 is a more circular shape.

$$\text{FAZ ACI} = \text{perimeter of measured FAZ} / \text{perimeter of equal area circle}$$

The perfusion density (PD) was calculated as the total area of perfused vasculature per unit area in a region of measurement using the following formula:[9]

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

The vessel density or vessel length density (VD) was the total length of perfused vasculature per unit area in a region of measurement using the following formula:[9]

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

In the DCP, ImageJ was used to calculate DPD and DVD. DCP en face images were created in ImageJ with a binary slab that assigns a 1 (perfused) or 0 (background) to each pixel. The images were binarized and computed with a vascular density plugin application for obtaining DVD. After binarizing, a skeletonized slab was created, representing vessels one pixel in width, and then they were taken into “AnalyzeSkeleton” mode in ImageJ for calculating the vessel length density. The total extrafoveal avascular area (tEAA) was defined as the area outside the FAZ characterized by a dark zone without any flow signal larger than 0.02 mm.[2] To calculate this, the SCP image was imported into ImageJ, and the dark/nonperfused areas outside the FAZ were manually demarcated. Then, MATLAB software was used to determine the sum of the avascular areas within the entire 3 × 3 mm

scan area, excluding the FAZ. tEAA was only considered in the SCP due to limited quality of the images in the DCP.

Age, duration of diabetes, and hemoglobin A1c (HbA1c) level, when available, were noted for each participant from the patient medical record. Best-corrected visual acuity (BCVA) was measured for each eye using the Snellen chart and converted into logMAR VA. DR severity was graded from the color fundus photos by the department's DR screening program reading center. DR severity for each patient was assigned into one of four groups: nondiabetic participants (control), diabetes patients without retinopathy (DM no DR), mild to moderate non-proliferative diabetic retinopathy (NPDR), and patients with severe NPDR to proliferative stages of DR (SNPDR/PDR).

SPSS version 24 (IBM, New York, USA) was used to perform the statistical analysis. A p-value of less than 0.05 was considered statistically significant for all statistical tests. The study selected one eye from each patient. If a participant had both eyes imaged with equal quality, the right eye was included in the study. A one-way ANOVA was used to analyze whether there was a significant difference in the OCTA parameters between at least two of the four patient groups. If the p-value of the one-way ANOVA was less than 0.05, an additional multiple comparison test (Bonferroni) was used to determine where the significant difference was located.

Spearman rank-order correlation analysis was used to test the correlation between the OCTA parameters and the level of retinopathy severity, with the four groups ranked in ascending order of DR severity: control, DM no DR, NPDR, and SNPDR/PDR.

With the specificity fixed at 95%, receiver operating characteristic (ROC) analysis was used to determine the diagnostic efficacy of the all OCTA parameters. Efficacy was defined as the ability to distinguish between participants with diabetes from control individuals, patients with mild to moderate NPDR from those without retinopathy, and patients with severe NPDR and PDR from patients with mild NPDR. This was analyzed for all OCTA parameters. The ROC curve was plotted by computing the sensitivity and specificity using each symmetric value of the rating variable as a possible cut point. The area under the curve (AUC) was then computed using the trapezoidal rule.

Results

601 patients were recruited for this study. Of those recruited, 329 patients met eligibility criteria and were included in this analysis. The remainder were excluded because of poor quality scans due to various factors such as staff learning curve in obtaining the images, limited cooperation and other general condition of subjects, reduced signal strength due to ocular media opacity, and image quality limitations of the device. The study included one eye each from 90 non-diabetic individuals (control group), 170 diabetic patients without retinopathy (DM no DR), 57 patients with mild to moderate nonproliferative diabetic retinopathy (NPDR), and 12 patients with more severe retinopathy (SNPDR/PDR). The overall image quality of the included images was high, with 80% having a signal strength of 10, 15% with signal strength 9, and less than 5% having a strength of 7 or 8. Patient

demographics are presented in Table 1. Almost all diabetic patients had type 2 diabetes. The mean value of each OCTA parameter is shown in Figure 2. All eight OCTA parameters showed statistically significantly different means between the control and severe NPDR/PDR groups. Except for FAZ area, all OCTA parameter means were statistically significantly different when comparing the control and NPDR groups. Of the eight OCTA parameters, no significant differences were found in comparing the control and DM no DR groups.

Table 2 presents the correlation coefficient between OCTA parameters and severity group. All the OCTA parameters demonstrated a significant relationship with severity of the DR ($p<0.05$).

Figure 3 shows the mean OCTA parameters by gender. We found a statistically significant difference in FAZ area between the male (0.29 (0.12) mm^2) and the female (0.34 (0.13) mm^2) groups ($p<0.001$).

Figure 4 demonstrates the ROC curve which showed that tEAA had the highest area under the curve (AUC) in all pairs of comparison, meaning it was the OCTA parameter most able to distinguish between DR severity groups. The AUC for each tEAA ROC curve distinguishing control from DM no DR, DM no DR from NPDR, and NPDR from SNPDR/PDR was 0.66 (95%CI, 0.60–0.73), 0.76 (95%CI, 0.66–0.83), and 0.93 (95%CI, 0.86–1.00), respectively. FAZ ACI, FAZ CI, DPD and DVD showed the second highest diagnostic efficacy, with the AUC of 0.59 in distinguishing control from eyes with DM no DR. FAZ area showed the lowest efficacy in differentiating patients among groups.

Discussion

This study quantitatively evaluated differences among diabetic and non-diabetic patients at an urban safety-net hospital using three aspects of OCTA imaging: FAZ-related metrics, vessel density-related metrics, and capillary nonperfusion area-related metrics.[9,22,26] All OCTA metrics in our population showed similar trends in DR as has been seen in other reports from tertiary medical centers. The findings were based on analysis of high-quality images, as 95% of the included images had a signal strength of 9 or 10.[28]

We observed an increase in FAZ area as the severity of disease increased, which is consistent with previous literature.[13] In this study, this was statistically significant in the control group compared with the SNPDR/PDR group. Some investigators have reported that eyes with DR have a larger FAZ area compared to controls and patients with DM without DR.[6,7,9,16,17,23] These findings suggest that OCTA may be useful for early detection of microvascular changes that appear prior to what is detectable with fundus photography. However, some studies involving patients with DM type 1 found no significant difference in FAZ area between groups.[10,11]

In this study, FAZ CI and FAZ ACI showed similar results when comparing control versus NPDR and SNPDR/PDR. We did not find a significant difference in the control versus DM no DR group. Durbin et al. also demonstrated no significant difference between control and diabetic patients for both FAZ area and FAZ CI.[13] Krawitz et al. found a significant

difference in acircularity index between all groups except for the control group versus DM no DR group.[26] We found a correlation of FAZ-related metrics with disease severity. This is consistent with previous literature.[11]

The vessel density (VD) of SCP and DCP decreased in more severe disease. Differences between groups were statistically significant when comparing control versus DM no DR. The perfusion density (PD) of SCP and DCP also demonstrated a similar trend with the vessel density. Comparing VD and PD, VD was superior in differentiating among groups. In addition, all vascular density metrics were negatively correlated with disease severity. Several studies also showed similar results.[9,18,20,23,29]

Ashraf et al. showed that FAZ area, DCP vessel density (DPD in our study) and FAZ ACI were the best parameters to distinguish between DR severity groups, compared to other metrics such as SCP vessel density (SPD in our study), skeletonized vessel density (SVD and DVD in our study), fractal dimension and intersection and average vessel diameter.[30] Other literature from Alam et al. comparing various parameters stated that blood vessel density showed the best classification accuracy and was improved when combined with vessel tortuosity, vessel caliber, vessel perimeter index, FAZ area and FAZ CI.[31,32]

Concerning capillary non-perfusion area, we investigated OCTA parameters to determine which might be best as a substitute for FA in grading diabetic macular ischemia. In our study, tEAA significantly increased as severity of disease increased, except when comparing the control group versus the DM no DR group. We found positive correlations between tEAA and disease severity, which is similar to a prior report.[24] Furthermore, tEAA showed the greatest diagnostic efficacy among OCTA parameters in differentiating the multiple stages of DR. It has been suggested that this type of nonperfusion-related parameter is likely more sensitive to early-stage capillary dropout than vascular density-based methods and also FAZ-based methods.[22]

Even though OCTA parameters correlated well with the severity of DR in this study, based on our limited sample size, especially in the more advanced DR groups, we cannot recommend that OCTA could replace clinical grading. At the present time, OCTA can serve an adjunct role in providing greater detail about a patient's microvascular changes from DR.

Limitations of this study include no correction for axial length, which might affect the FAZ area[33] calculation, and the relatively small number of patients in the NPDR and SNPDR/PDR groups. This occurred because the majority of participants were recruited from the DR screening clinic and not the retina referral clinic. Additional studies could include patients from the retina clinic with more severe diabetic retinopathy and could collect axial length from participants. Another limitation is the less precise imaging of the deep vascular layers of the retina, known to be important in DR, due to the technical specifications of the spectral-domain OCTA machine that was available for use in this study. Further improvement of OCTA technology is still needed, particularly in the applications of automated vessel quantifying software.

Conclusions

This study found that OCTA imaging in an urban safety-net hospital diabetic population yielded similar efficacy in distinguishing among DR severity groups as in previously reported studies from tertiary referral centers. This finding suggests that it would be reasonable to perform further DR-related OCTA studies in this population and that the results of such studies could be generalizable. Our results suggest that OCTA metrics are well correlated with DR disease severity and also suggest that FAZ area, in particular, is useful for studying gender differences in anatomical vasculature.

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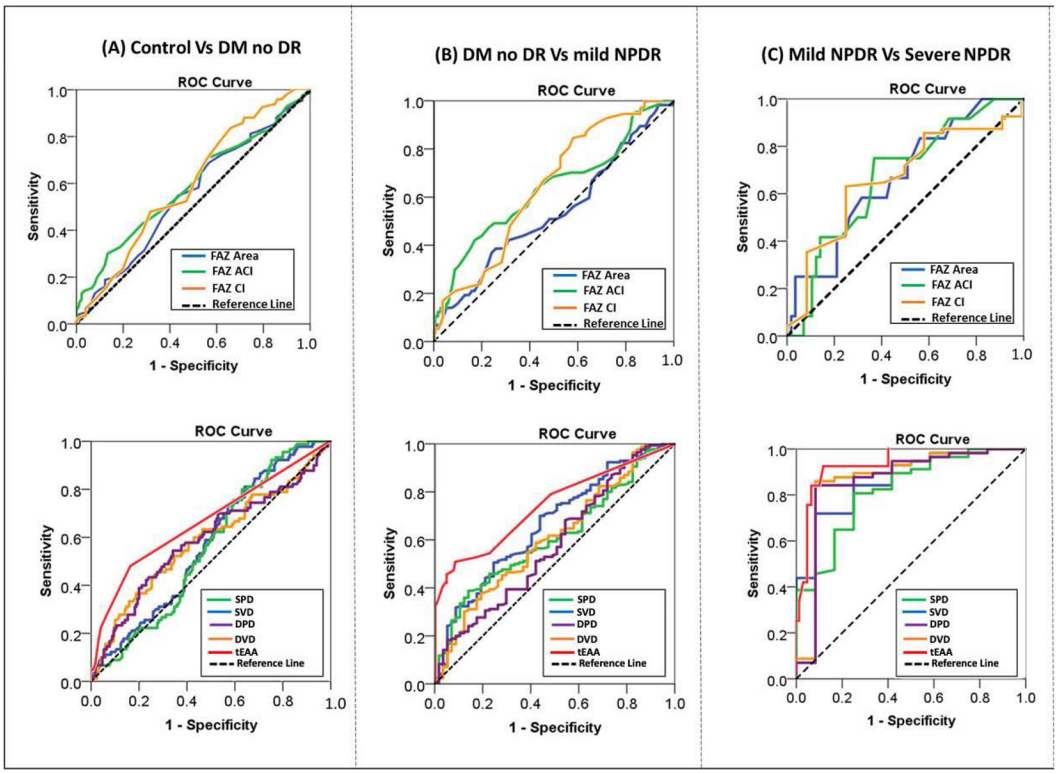

Figure 1. OCTA image acquisition from superficial capillary plexus

Each row shows a representative subject from each group of participants: control; diabetes without retinopathy; mild to moderate non-proliferative diabetic retinopathy; and severe non-proliferative diabetic retinopathy to proliferative diabetic retinopathy. Each column presents the values of quantitative OCTA parameters in the superficial capillary plexus: FAZ area, foveal avascular zone area; SPD, superficial perfusion density; SVD, superficial vessel density; tEAA, total extrafoveal avascular area, which is the summation of areas highlighted in red, each of which represents a non-perfusion area equal or greater than 0.02 mm^2 in area.

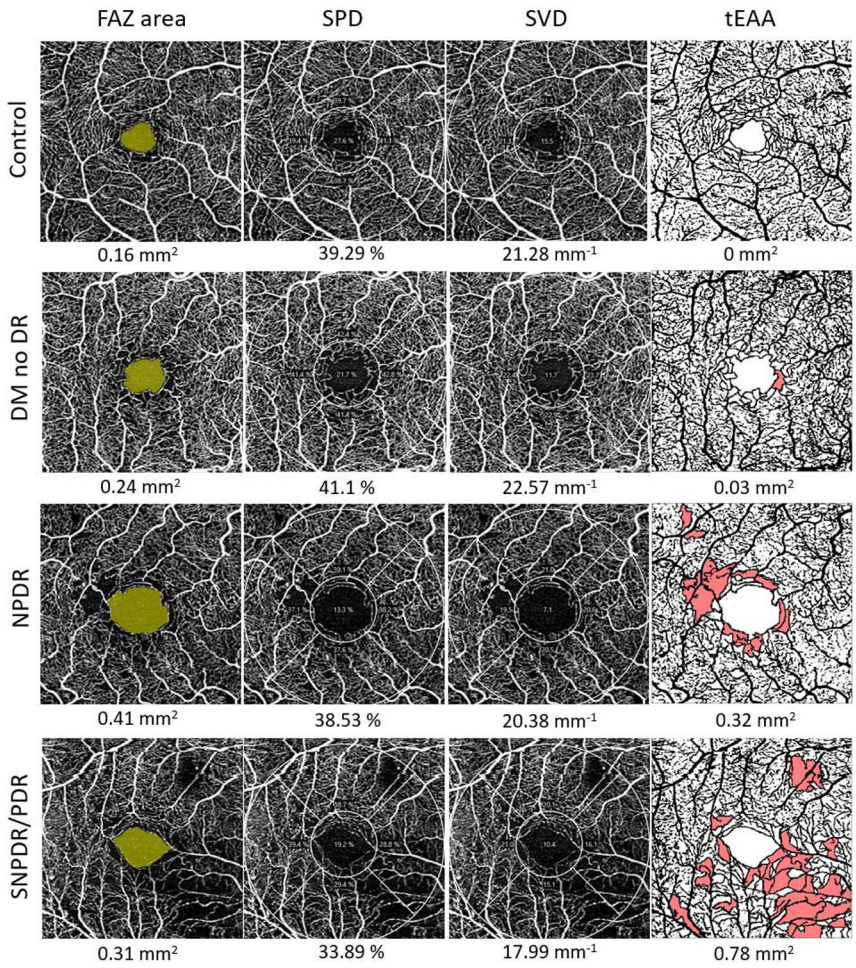

Figure 2. Mean OCTA parameters in each patient group

Bar graphs demonstrating quantitative OCTA parameters in the four patient groups: (A) mean FAZ (foveal avascular zone) area, (B) mean foveal avascular zone acircularity index (FAZ ACI), (C) mean foveal avascular zone circularity index (FAZ CI), (D) mean total extrafoveal avascular area (tEAA), (E) mean superficial perfusion density (SPD), (F) mean superficial vessel density (SVD), (G) mean deep perfusion density (DPD), (H) mean deep vessel density (DVD). Error bar, ±2SD; ** = statistically significantly different, $p<0.001$.

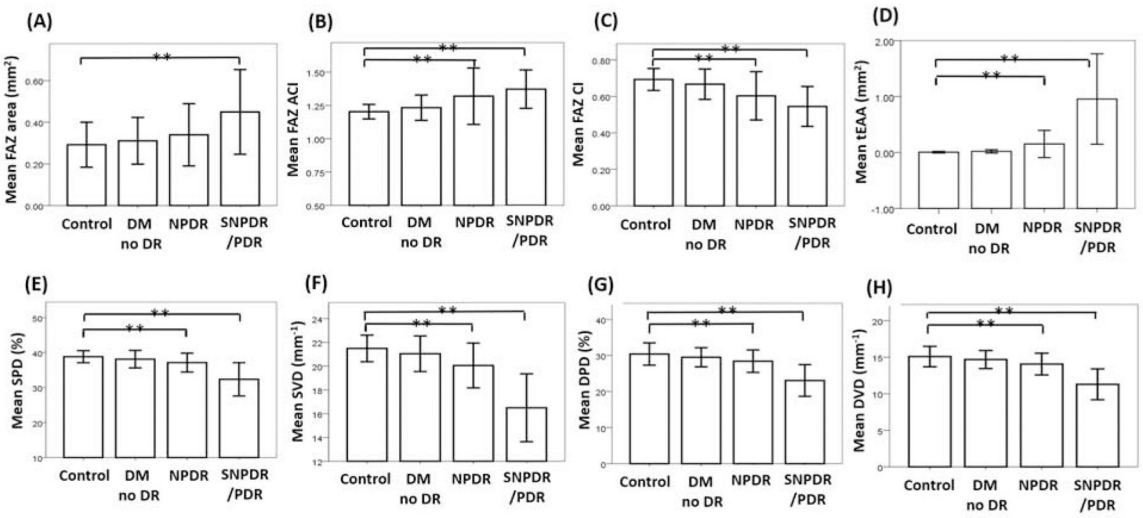

Figure 3. Mean value of OCTA parameters by gender groups

Mean foveal avascular zone area comparing male and female. Error bar, ±2SD; ** = statistically significantly different, p<0.001.

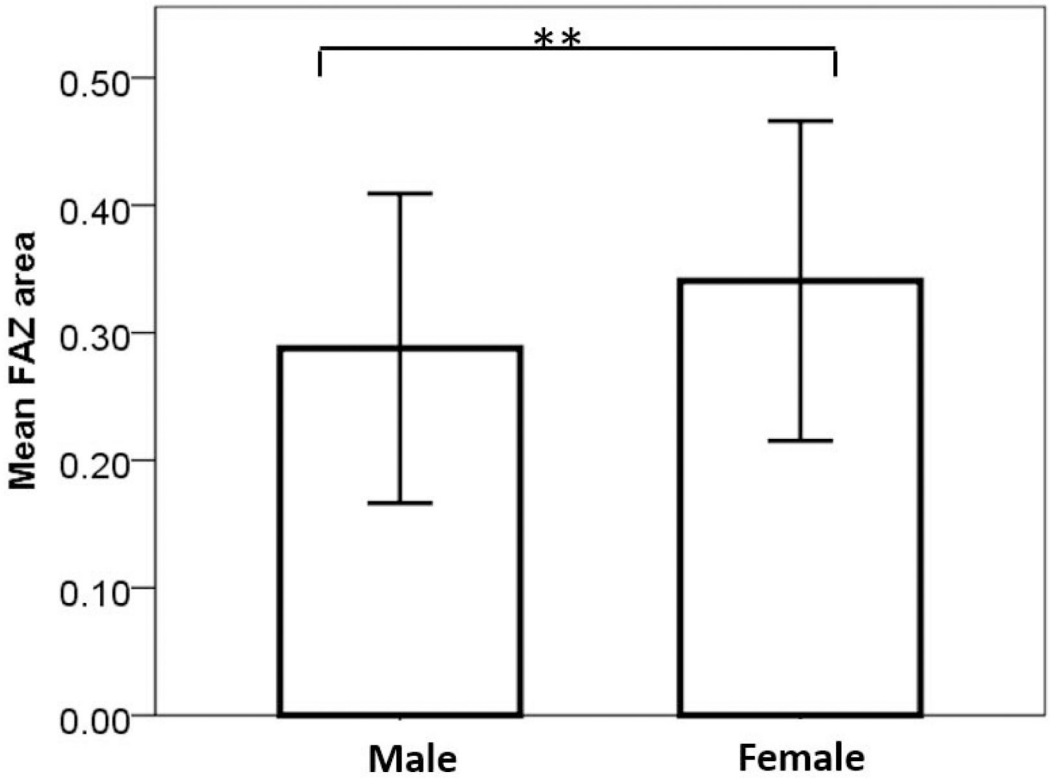

Figure 4. Receiver Operating Characteristic (ROC) Curves

Comparisons of OCTA parameters by group are shown. (A) Control versus DM no DR, (B) DM no DR versus NPDR, and (C) NPDR versus SNPDR/PDR. The first row shows FAZ-related metrics: foveal avascular zone area (FAZ area), foveal avascular zone acircularity index (FAZ ACI), and foveal avascular zone circularity index (FAZ CI). The second row shows vessel density-related metrics and tEAA: superficial perfusion density (SPD), superficial vessel density (SVD), deep perfusion density (DPD), deep vessel density (DVD), and total extrafoveal avascular area (tEAA).

Table 1:

Characteristics of subjects and eyes

Clinical Values	Control (N=90)	DM no DR (N=170)	NPDR (N=57)	SNPDR/PDR (N=12)
Age, mean (SD), y	49.6 (15.3)	55.4 (11.2)	54.6 (11.0)	48 (10.3)
Male No. (%)	36 (40)	78 (45.9)	33 (57.9)	8 (66.7)
Type I Diabetes No. (%)	NA	1 (0.6)	1(1.8)	1 (8.3)
Type II Diabetes No. (%)	NA	161(94.1)	53 (93)	11 (91.7)
Hispanic No. (%)	34 (37.8)	87 (51.2)	27 (47.4)	6 (50)
HbA1c level, mean (SD), %	NA	8.4 (0.1)	9.2 (2.3)	10.1 (2.9)
Diabetes duration, mean (SD), y	NA	6.4 (8.6)	10.8 (4.9)	15.8 (8.2)
Hypertension No. (%)	NA	88(51.8)	34(59.6)	5(41.7)
LogMAR VA OD, mean (SD)	0.05 (0.09)	0.09 (0.12)	0.11 (0.14)	0.21 (0.27)
LogMAR VA OS, mean (SD)	0.07 (0.12)	0.10 (0.13)	0.11 (0.14)	0.19 (0.28)

Abbreviations: DM no DR, diabetes without retinopathy; NPDR, mild to moderate nonproliferative diabetic retinopathy; SNPDR/PDR, severe non-proliferative diabetic retinopathy to proliferative diabetic retinopathy; HbA1c, glycated hemoglobin; logMAR, logarithm of minimum angle of resolution; VA, visual acuity; OD, oculus dexter, right eye; OS, oculus sinister, left eye

Table 2:

Correlation coefficient between OCTA parameters and severity group

OCTA parameter	tEAA	FAZ area	FAZ ACI	FAZ CI	SPD	SVD	DPD	DVD
Correlation coefficient	0.54 **(p<0.001)**	0.14 **(p=0.009)**	0.30 **(p<0.001)**	−0.30 **(p<0.001)**	−0.26 **(p<0.001)**	−0.34 **(p<0.001)**	−0.27 **(p<0.001)**	−0.29 **(p<0.001)**

Abbreviations: tEAA, total extrafoveal avascular area; FAZ area, foveal avascular zone area; FAZ ACI, foveal avascular zone acircularity index; FAZ CI, foveal avascular zone circularity index; SPD, superficial perfusion density; SVD, superficial vessel length density; DPD, deep perfusion density; DVD, deep vessel length density.