Foveal Avascular Zone and Parafoveal Vessel Density Measurements as Markers for Macular Ischemia in Minimally Treated Diabetic Retinopathy Using Optical Coherence Tomography Angiography

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Background

Diabetic retinopathy (DR) is a leading cause of blindness worldwide[1], with various mechanisms resulting in visual impairment including vitreous hemorrhage, macular edema, tractional retinal detachment and macular ischemia. While the other etiologies within DR can potentially be reversed or treated, diabetic macular ischemia (DMI) is irreversible and vision-threatening. DMI plays an important role in the progression of DR as increasing macular hypoxia leads to the production of vascular endothelial growth factor (VEGF)[2]. DMI is difficult to detect and monitor as traditional methods of imaging via fluorescein angiography fail to provide fine detail for DMI.

Optical coherence tomography angiography (OCTA) is a non-invasive imaging modality that can diagnose and monitor progression of DMI in asymptomatic patients[3]. The use of OCTA parameters such as foveal avascular zone (FAZ) and parafoveal vessel density (VD) to evaluate DMI has been demonstrated previously as early biomarkers for DR[4,5]. Previous studies have shown cross-sectional correlations between FAZ and VD with best-corrected visual acuity. One year longitudinal studies have also been conducted validating OCTA markers.

Purpose

To investigate FAZ and parafoveal VD and its correlation with DR parameters using OCTA in patients with minimally treated DR without macular edema, and ultimately to understand DMI in a cross-sectional and longitudinal manner.

Eliminating macular edema allows to obtain more accurate measurements of DMI. By including minimally treated patients, we also hope to study DMI without the influence of treatment that will influence VEGF.

Methods

Design

Observational, retrospective, cross-sectional single center imaging study with longitudinal sub-analysis

Subjects

Cross-sectional analysis: 70 eyes of 43 adult patients with minimally treated DR, longitudinal sub-analysis: 41 eyes of 25 patients from the original cross-sectional analysis (average follow-up time from first OCTA scan to last was 2.5 years)

Inclusion Criteria

Patients with treatment-naïve non-proliferative DR (NPDR) without macular edema and treated but quiescent (>1 year) proliferative DR (PDR) without macular edema who underwent OCTA imaging

Exclusion Criteria

Presence of diabetic macular edema at the time of last OCTA scan, significant media opacity, concurrent vascular conditions (ex retinal vein occlusion), history of macula involving tractional and/or rhegmatogenous retinal detachment, or macular neovascularization (ex wet age-related macular degeneration)

Imaging Modalities and Acquisition

The angiographic data was obtained using 2 different OCTA imaging devices using 6x6mm scan protocols, including Carl Zeiss PLEX Elite 9000 and Carl Zeiss Cirrus AngioVue, using superficial and total retinal slabs.

Imaging Processing and FAZ/Vessel Metric Calculations

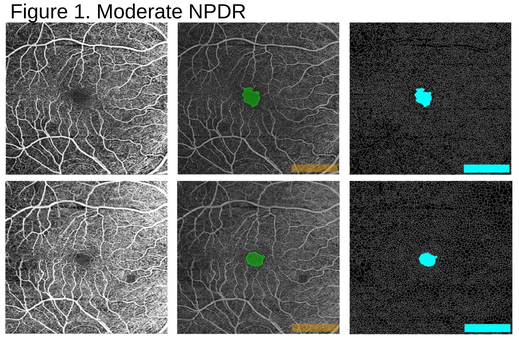
The FAZ for each OCTA scan was manually outlined by two graders (PI and AM) (Figure 1). The FAZ and (non-skeletonized) VD were analyzed using the OCTA analysis toolbox (OAT) software.

Methods

Clinical biomarkers collected

Visual acuity (VA), central subfoveal thickness (CST), disorganization of retinal inner layers (DRIL), ellipsoid zone (EZ) disruption, hyperreflective foci (HRF), formation of epiretinal membranes (ERM) and microaneurysms (MA).

Figure 1. Moderate NPDR



Top Right: First visit 6x6 mm OCTA superficial slab. Top Middle: First visit with outlined FAZ. Top Left: Non-skeletonized vessel density index. Follow-up visit in 1 year. Bottom Right: Follow-up 6x6 OCTA superficial slab. Top Middle: Follow-up visit with outlined FAZ. Bottom Left: Non-skeletonized vessel density index

Results

Cross-sectional analysis: Baseline characteristics

Demographics	N
Eyes	70
Right/Left	38/32
Mild NPDR	28
Moderate NPDR	20
Severe NPDR	5
PDR	17
Patients	43
Average Age	64.9 years
Average Duration of DM	26.5 years
Females/Males	22/21
Type 1/Type 2	9/34
Average A1C	7.9

Cross-sectional analysis: Relationship among clinical biomarkers (VA, CST, DRIL, EZ disruption, HRF, MA, ERM) and OCTA biomarkers (surrogates for DMI; FAZ and VD)

Superficial and total FAZ area were positively correlated with logMAR VA and negatively correlated with CST. Superficial FAZ had a positive correlation to foveal EZ disruption. However, there was no correlation between superficial FAZ and DRIL, HRF, MA or ERM. Total VD had a negative correlation with logMAR VA but VD had no other correlations to other biomarkers (Table).

Clinical biomarker	P value			
	Total FAZ	Superficial FAZ	Total VD	Superficial VD
LogMAR VA	0.03	0.001	0.021	0.107
CST	<0.001	<0.001	0.74	0.98
DRIL	NA	0.14	0.38	0.11
EZ disruption	NA	0.03	0.25	0.36
HRF	NA	0.12	0.154	0.49
MA	NA	0.9	0.38	0.41
ERM	NA	0.7	NA	NA

Commercial Relationship Disclosure

AM: None; PI: None; HS: None; HT: None; AYA: None; CB: Employee: Apellis, Consultant: OcuTerra, Ocuphire Pharma, Alcon; AJW: Grants: Apellis, Genentech; ML: Consultant: Beacon Therapeutics; NKW: Research support to institution: Zeiss, Topcon, Nidek, Speaker fees: Nidek, Consultant: Topcon, Complement Therapeutics, Olix Pharma, Iolyx Pharmaceuticals, Hubble, Saliogen, Syncona, Equity Interest: OcuDyne, Gyroscope, Employee: Beacon Therapeutics

Results

Longitudinal sub-analysis: Relationship among initial OCTA/surrogate biomarkers (FAZ and VD) and final clinical biomarkers (VA and CST)

The initial total retinal FAZ was positively correlated with final logMAR, although initial superficial FAZ did not correlate with final logMAR VA. Initial superficial and total retinal FAZ were also negatively correlated with final CST. Initial total retinal VD negatively correlated with final logMAR VA, although initial superficial VD did not correlate with final logMAR VA. Initial superficial and total retinal VD also did not correlate to final CST (Table).

Initial OCTA biomarker	P value	
	Final logMAR VA	Final CST
Initial total FAZ	0.029	0.001
Initial superficial FA	0.066	0.003
Initial total VD	0.021	0.123
Initial superficial VD	0.821	0.913

Longitudinal sub-analysis: Comparison in relationship among initial OCTA biomarkers (FAZ, VD) and final clinical biomarkers (VA, CST) between NPDR and PDR eyes

Sub-analysis did not find any significant findings (Table).

Initial OCTA biomarker	P value			
	NPDR eyes (n=53)		PDR eyes (n=17)	
	Final logMAR VA	Final CST	Final logMAR VA	Final CST
Initial total FAZ	0.274	<0.001	0.28	0.45
Initial superficial FA	0.079	0.002	0.16	0.42
Initial total VD	0.46	0.32	0.85	0.39
Initial superficial VD	0.55	0.29	0.82	0.67

Conclusion

Superficial and total FAZ areas are associated with VA and CST, relating to DMI in DR. VD did not have strong correlations to other biomarkers as FAZ had. In fact, initial total FAZ area may be a predictor for long-term final VA and CST. Sub-analysis amongst NPDR and PDR eyes did not reveal significant correlations between initial surrogates and final biomarkers. In conclusion, automated calculations of FAZ can be ideal markers for DMI with good correlations to clinical biomarkers as well as predictive for future VA. This study is unique to look at surrogates for DMI and correlate with multiple clinical biomarkers aside from BCVA. In additional, our longitudinal sub-analysis has the longest follow-up period in the current literature. Limitations include the retrospective and cross-sectional nature of the study along with a relatively small sample size with DR stages not equally balanced. Further studies with larger populations and longer longitudinal duration may be able to provide more robust information of DMI.

References

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