The Egyptian Journal of Hospital Medicine (January 2021) Vol. 82 (3), Page 551-557

Comparison between the Foveal Avascular Zone and Macular Capillary Network Density in Diabetic Retinopathy and Normal Retina

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ABSTRACT

Background: Diabetic retinopathy (DR) is mostly a vascular disease where the development of macular oedema and proliferative retinopathy are major causes of visual impairment. Enlargement of the foveal avascular zone (FAZ) is associated with visual deterioration in patients with diabetic retinopathy.

Objective: To evaluate the foveal avascular zone (FAZ) and perifoveal capillary network density in the superficial retinal layer (SRL) and deep retinal layer (DRL) in patients with varying severities of diabetic retinopathy (DR).

Patients and methods: This is a prospective comparative randomized case-control study consisting of 77 eyes divided into two groups, each group underwent imaging using OCT-A device. Group one: 37 healthy control eyes, and group two: 40 eyes with DM of different degrees of diabetic retinopathy. Subjects were imaged between September 2019 and February 2020 at Kasr El-Ainy Teaching Hospital.

Results: The FAZ area at the levels of the superficial and deep vascular networks of eyes with DR were found to be larger compared with those of age-matched healthy controls, and as would be expected, control eyes had higher vascular density in both networks compared with the diabetic eyes. Furthermore, eyes with worse DR stage showed larger FAZ area and lower vascular density values. This study also showed that angiographic parameters, namely FAZ area and vessel density (VD) correlated with best corrected visual acuity.

Conclusion: Our study revealed that vascular density and FAZ area can be quantified in DR eyes in a rapid, automated, and noninvasive manner with OCTA. Also foveal avascular zone area and vascular density as measures of DMI correlate with visual acuity in patients with DR.

Keywords: Diabetic Retinopathy, FAZ, Macular Capillary Network Density, OCTA

INTRODUCTION

Diabetic retinopathy is the most common microvascular complication of diabetes, and remains a leading cause of blindness worldwide [(1)]. Diabetic retinopathy (DR) is mostly a vascular disease where the development of macular oedema and proliferative retinopathy are major causes of visual impairment. Over the last years a lot of work has been done on early diagnosis of DR and on looking for new ocular diagnostic tools useful in evaluating patients affected by diabetes [(2)].

The foveal avascular zone (FAZ) is extremely sensitive to biological events and tracking the morphology of this region can provide insights into possible pathologic processes, specifically FAZ enlargement in DR. Therefore, exploring the relationship between the FAZ characteristics and onset and progression of disease may offer an early diagnostic tool that might allow for early detection before irreversible changes occur [(3)]. Enlargement of the FAZ due to progressive capillary nonperfusion is associated with visual deterioration in patients with diabetic retinopathy. The FAZ area has long been considered an important clinical marker of advancing retinopathy [(1)].

In-vivo, the gold standard to screen for DR is dilated biomicroscopic fundus examination. Fluorescein angiography (FA) is more sensitive than examination to detect early microvascular changes. Since FA takes several minutes and requires the administration of an intravenous dye; the technique is not optimal for screening or frequent longitudinal assessments. In addition, leakage of fluorescein dye and the superimposition of capillaries from different retinal layers onto a single two dimensional FA image have hindered a more detailed investigation of the microvasculature by FA[(4)].

Introduction of optical coherence tomography angiography (OCTA) has allowed the opportunity both to study retinal vasculature without the need for dye injection and to image both the superficial and deep capillary plexuses. Moreover, OCTA is able to image and evaluate both the presence of retinal vascular abnormalities and neovascularizations associated to diabetes [(5)].

OCT-A images are mainly based on the detection of blood movement without the need of injecting intravenous contrast. It combines a suitable visualization for the analysis of the retinal vasculature, as angiographies, but non-invasively, using the tomography capture characteristics, which constitutes a more comfortable scenario for the patients. OCT-A images are typically taken at superficial and deep views of the eye fundus, which facilitates the subsequent vascular analysis; in addition, these images can be obtained at different levels of zoom, being 3 and 6 millimetres-wide (greater and smaller zooms) the most used configurations [(6)].

Swept-source OCT technology uses longer-wavelength infrared light with less sensitivity roll-off with depth compared to conventional spectral-domain

Received14: 10/ /2020
Accepted:2 /12 /2020

OCT. This allows a deeper penetration into tissue and better imaging through optical opacities. While this sensitivity benefit may be most apparent for choroidal vascular imaging, it also may be relevant to situations with marked retinal thickening, such as with severe macular oedema [(4)].

Aim of work was to evaluate the foveal avascular zone (FAZ) and perifoveal capillary network density in the superficial retinal layer (SRL) and deep retinal layer (DRL) in patients with varying severities of diabetic retinopathy (DR), and to compare the findings to those of normal individuals using optical coherence tomography angiography (OCTA).

PATIENTS AND METHODS

This is a prospective comparative randomized case-control study consisting of 77 eyes divided into two groups, each group underwent imaging using OCT-A device. Simple random sample was recruited and divided into two groups: Group one: 37 healthy control eyes, and group two: 40 eyes with different degrees of diabetic retinopathy. Subjects were imaged between September 2019 and February 2020 at Kasr El-Ainy Teaching Hospital on the RTVue XR Avanti AngioVue OCTA system (Optovue, Inc., Fremont, CA, USA).

Images (6 x 6 mm cube centered on the fovea) were taken for all subjects using OCT-A device. En face images of the retinal vasculature were generated from the superficial and deep retinal layers (SRL/DRL). Quantitative analysis of the vessel density (VD) and FAZ area was performed.

Ethical Considerations:

The study protocol had been approved by Medical Research Ethics Committee, Faculty of Medicine, Menoufia University. An informed consent had been taken from all the participants before taking any data or doing any investigations.

Inclusion criteria:

- In the diabetic group, all subjects had a known diagnosis of diabetes mellitus, previously confirmed by laboratory testing.
- In the control group all subjects deemed to be normal based on the absence of any previous ocular history, any systemic diseases, or any visual symptoms; a normal appearing retina on clinical examination.
- Patients of both groups were over 18 years of age.

Exclusion criteria:

- Cataract surgery within 6 months in the study eye.
- Refractive error of greater than +/−4D.
- Glaucoma or history of ocular hypertension (IOP > 21 mmHg).
- Neurodegenerative diseases (e.g., multiple sclerosis, Alzheimer's disease, and Parkinson's disease).
- Uncontrolled systemic blood pressure (BP ≥ 120/80 mmHg).
- Poor quality OCT-A images due to significant media opacity
- Baseline Clinical Examination and imaging

Both eyes of all participants were subjected to complete ophthalmological examination:

- Best corrected visual acuity (BCVA) and refraction.
- Slit lamp examination.
- Intraocular pressure with Goldmann applanation tonometry.
- Dilated fundus examination by binocular indirect slit-lamp biomicroscopy.
- OCTA examinations using (RTVue XR Avanti, Optovue, Inc., Fremont, CA).
- OCT Angiography with XR Avanti XR Avanti® AngioVue OCTA(Optovue Inc., Fremont, CA, USA) is a device with a high-speed of 70,000 axial scans per second, using a light source of 840 nm, and an axial resolution of 5 μm. The AngioVue OCTA system, based on the split spectrum amplitude decorrelation angiography algorithm (SSADA) (Version: 2015.1.0.90, Optovue, Inc., Fremont, CA, USA), uses blood flow as intrinsic contrast. The flow is detected as a variation over time in the speckle pattern formed by interference of light scattered from red blood cells (RBC) and adjacent tissue structure.
- AngioVue system is provided by an orthogonal registration algorithm called Motion Correlation technology (MCT) which minimizes motion artifacts produced by involuntary saccades and changes in fixation during data acquisition. The combination of motion-corrected OCT angiogram along with the corresponding OCT intensity en face image and OCT B-scans allows direct comparison of OCT structural and functional information.

Quantitative parameters:

Capillary vessel density: In both the superficial and deep capillary plexus levels were obtained using the ETDRS grid overlay centered on the FAZ area in both layers, then the computed software system automatically measured the vessel density of the SCP and DCP displayed as a percentage (areas showing flow divided by the total area of interest).

FAZ area: The software also features the ability to automatically delineate the FAZ area, preset as an area of absolute no flow, and calculate its area accordingly, giving an average of the FAZ area throughout the thickness of the inner two thirds of the fovea. In cases where the FAZ area was severely distorted rendering its automatic delineation inaccurate, the FAZ area was outlined manually then calculated.

Manual segmentation of FAZ area in SRL and DRL was performed by single observer using ImageJ software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). The FAZ area was defined as the area inside the central border of the capillary network, which was

outlined manually the SRL and DRL in accordance with our previously described technique.

Qualitative Vessel Analysis: The OCTA images were segmented and evaluated for changes at the level of the superficial capillary plexus, the deep capillary plexus and choriocapillaris.

Foveal and Parafoveal Retinal Thickness Analysis: Central macular thickness was automatically calculated by the software on the OCTA 6 × 6 mm^2 volume scan (XR Avanti®; Optovue, Inc., Fremont, CA, USA) from ILM to retinal pigment epithelium (RPE). A circular region of interest (ROI) centered on the center of the foveal avascular zone with a diameter of 3 mm was considered for retinal thickness analysis: central foveal area (1 mm of diameter) and parafoveal area that constitutes the remaining part inside the ROI (total parafoveal area or temporal, superior, nasal, and inferior quadrants). In The current study we used OCTA integrated automated algorithms to examine macular vascular density and FAZ area in eyes with DR compared with healthy controls.

Statistical methods

Data were coded and entered using the statistical package for the social sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using analysis of variance (ANOVA) for more than 2 means; with multiple comparisons post hoc test or unpaired t test to compare 2 means in normally distributed quantitative variables while non-parametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables. For comparing categorical data, Chi square (χ^2) test was performed. P-values less than 0.05 were considered as statistically significant.

RESULTS

In our study the number of right eyes in diabetic patients was 21 and left eyes was 19 representing 52.5% and 47.5% respectively of the total number of cases. The mean age of the diabetic patients was 49.00 years ± SD 10.60. The mean BCVA in diabetic group was 0.46 ± SD 0.28. The mean DM duration, mean HBA1C and mean hypertension (HTN) duration are shown in table 1.

Table (1): Represents mean DM duration, mean HBA1C and mean HTN duration.

	Diabetic	
	Mean	Standard Deviation
DM duration	14.10	6.22
HBA1C	8.11	1.60
HTN (years)	6.79	5.39

In the diabetic group 19 patients had hypertension 47.5%. Diabetic group was subdivided into mild, moderate (Mod), and severe NPDR, and PDR (Table 2).

Table (2): Summarize data of diabetic group.

		Diabetic	
		Count	%
HTN	Yes	19	47.5%
	No	21	52.5%
DM Type	Type 1	6	15.0%
	Type 2	34	85.0%
Retinopathy	Mild NPDR	15	37.5%
	Mod NPDR	12	30.0%
	Severe NPDR	5	12.5%
	PDR	8	20.0%

The BCVA of diabetic patients was statistically significantly lower than the controlled group. While, there was no statistically significant difference between them regarding age (Table 3).

Table (3): Sex, age data of two groups and mean visual acuity of two groups.

		Groups				
		Diabetic N=40		Control N=37		P value
		Count	%	Count	%	
Sex	Male	11	27.5%	15	40.5%	0.227
	Female	29	72.5%	22	59.5%	
		Mean	Standard Deviation	Mean	Standard Deviation	
Age		49.00	10.60	45.19	13.66	0.178
BCVA		0.46	0.28	0.94	0.06	< 0.001

Retinal thickness was significantly higher in fovea, perifovea and in parafovea in diabetic group (Table 4).

Table (4): Comparison of retinal thickness in diabetic and control group

	Diabetic N=40		Control N=37		
	Mean	Standard Deviation	Mean	Standard Deviation	P value
Fovea (OCT thickness ILM-RPE)	360.15	183.24	249.32	16.91	< 0.001
Parafovea (OCT thickness ILM-RPE)	380.73	103.95	326.65	8.26	0.002
Temp para (OCT thickness ILM-RPE)	372.45	108.31	316.89	8.96	0.002
Sup para (OCT thickness ILM-RPE)	388.10	104.88	330.46	8.78	0.001
Nasal para (OCT thickness ILM-RPE)	388.50	115.75	330.81	9.37	0.003
Inf para (OCT thickness ILM-RPE)	375.43	103.14	328.49	8.37	0.007
Perifovea (OCT thickness ILM-RPE)	328.35	67.70	283.38	5.36	< 0.001

Vascular density in SRL was highly significantly lower in diabetic group in all quadrants except fovea (Table 5).

Table (5): Comparison of vascular density in SRL in both groups

	Diabetic N=40		Control N=37		
	Mean	Standard Deviation	Mean	Standard Deviation	P value
Fovea (OCTA sup vascular density)	20.80	9.08	21.33	6.47	0.768
Parafovea (OCTA sup vascular density)	43.37	7.90	53.15	4.87	< 0.001
Temp para (OCTA sup vascular density)	44.11	6.84	53.45	3.83	< 0.001
Sup para (OCTA sup vascular density)	43.92	8.51	53.95	4.97	< 0.001
Nasal para (OCTA sup vascular density)	42.69	7.27	52.11	5.45	< 0.001
Inf para (OCTA sup vascular density)	44.59	7.13	53.12	5.61	< 0.001
Perifovea (OCTA sup vascular density)	45.10	4.82	50.49	3.93	< 0.001

Vascular density in DRL in diabetic group was highly significantly lower in all quadrants. Subfoveal choroidal density was significantly lower in diabetic group (Table 6).

Table (6): Comparison between vascular density in DRL in both groups

	Diabetic N=40		Control N=37		
	Mean	Standard Deviation	Mean	Standard Deviation	P value
Fovea (OCTA deep vascular density)	30.34	10.45	40.80	5.46	< 0.001
Parafovea (OCTA deep vascular density)	49.86	5.82	57.58	2.78	< 0.001
Temp para (OCTA deep vascular density)	50.91	6.02	58.98	2.57	< 0.001
Sup para (OCTA deep vascular density)	48.68	7.03	57.57	3.66	< 0.001
Nasal para (OCTA deep vascular density)	50.00	6.37	57.76	3.09	< 0.001
Inf para (OCTA deep vascular density)	49.84	5.80	56.04	3.84	< 0.001
Perifovea (OCTA deep vascular density)	46.18	5.85	56.20	5.53	< 0.001
Subfoveal choroidal density	1.94	0.19	2.15	0.11	< 0.001

FAZ, sup FAZ and deep FAZ areas were significantly higher in diabetic group (Table 7).

Table (7): Comparison of FAZ area in diabetic and control group

	Diabetic N=40		Control N=37		
	Mean	tandard Deviation	Mean	tandard Deviation	P value
Auto FAZ	0.31	0.13	0.25	0.08	0.010
Sup FAZ	0.41	0.24	0.25	0.08	< 0.001
Deep FAZ	0.49	0.28	0.27	0.08	< 0.001

Comparison of FAZ area in SRL and DRL and Auto FAZ between control group and different stages of DR showed highly significant difference. Also mean FAZ area increased with severity of diabetic retinopathy in both SRL and DRL (Table 8).

Table (8): Comparison of FAZ area in different stages of diabetes

	Retinopathy groups										
	Control		Mild NPDR		Mod NPDR		Severe NPDR		PDR		P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Auto FAZ	0.25	0.08	0.21	0.10	0.40	0.10	0.34	0.05	0.34	0.12	< 0.001
Sup FAZ	0.25	0.08	0.32	0.30	0.47	0.16	0.50	0.19	0.48	0.09	< 0.001
Deep FAZ	0.27	0.08	0.30	0.24	0.53	0.20	0.65	0.17	0.74	0.24	< 0.001

On using post hoc test to compare the results in table 8, there was statistically significant difference compared to control group in moderate, severe NPDR and PDR. There was also statistically significant changes when comparing mild to moderate and mild to PDR only (Table 9).

Table (9): Post hoc pair wise comparison of control group and subgroups of DR sup FAZ

	P value
control-Mild NPDR	1.000
control-Mod NPDR	0.005
control-Severe NPDR	0.034
control-PDR	0.004
Mild NPDR-Mod NPDR	0.045
Mild NPDR-Severe NPDR	0.117
Mild NPDR-PDR	0.028
Mod NPDR-Severe NPDR	1.000
Mod NPDR-PDR	1.000
Severe NPDR-PDR	1.000

FAZ area was significantly enlarged in the deep network compared with controls in moderate, severe NPDR and PDR. There was also a significant difference between PDR and mild NPDR, mod and mild NPDR and severe and mild NPDR (Table 10).

Table (10): Post hoc pair wise comparison of control group and subgroups of DR deep FAZ

	P value
Mild NPDR-control	1.000
Mild NPDR-Mod NPDR	0.017
Mild NPDR-Severe NPDR	0.013
Mild NPDR-PDR	0.001
control-Mod NPDR	0.007
control-Severe NPDR	0.009
control-PDR	< 0.001
Mod NPDR-Severe NPDR	1.000
Mod NPDR-PDR	1.000
Severe NPDR-PDR	1.000

DISCUSSION

In our study we used a commercially available OCTA system and integrated automated algorithms to examine macular vascular density and FAZ area in eyes with varying levels of DR severity compared with healthy controls. The FAZ area at the levels of the superficial and deep vascular networks of eyes with DR were found to be larger compared with those of age-matched healthy controls. As would be expected, the control eyes had higher vascular density in both networks compared with the diabetic eyes. Furthermore, eyes with worse DR stage showed larger FAZ area and lower vascular density values. This study also showed that angiographic parameters, namely FAZ area and VD correlated with visual acuity. Healthy control participants were age matched to the diabetic cohort.

Alterations in the FAZ in DR have been well characterized using FA. **Sim *et al.*** [7] showed that FAZ area increases as DMI severity progresses and is most profound in PDR. Unfortunately when using FA, only the superficial vascular network is visualized and it is not possible to characterize FAZ changes in the deep network [8]**.** With OCTA, we are now able to examine the deep network, and FAZ measurements in both the superficial and deep networks, which have been shown to be repeatable and reproducible biomarkers for DR [9]**.**

In our study the mean FAZ area in SRL in control group was 0.25 mm^2 and in diabetic group was 0.41 mm^2 and the difference was statistically highly significant. In DRL mean FAZ area was 0.27 mm^2 in control group and 0.49 mm^2 in study group, which also showed statistically highly significant difference. Several studies using OCTA have shown that FAZ area is larger at both the level of superficial and deep vascular networks in eyes with DR compared with healthy eyes. Examples of those studies are **Salz *et al.*** [10] who quantified FAZ and the perifoveal intercapillary area in diabetic eyes. The mean area of FAZ was statistically significant larger in all the diabetic groups compared to the control group ($p < 0.05$ for all), and **Coscas *et al.*** [11] who investigated the foveal microvasculature in NPDR. The mean area of FAZ was statistically significant enlarged in both SRL and DRL, when comparing the diabetic group to the control group ($p < 0.05$).

Interestingly, studies also showed that even in diabetic patients without clinically detectable DR, FAZ area was enlarged compared with healthy eyes. Example of this was **de Carlo *et al.*** [12, 13] who studied early microvascular changes in NDR patients, The mean area of FAZ was larger in the diabetic group, 0.35 $\pm$ 0.10 mm^2, compared to the control group, 0.29 $\pm$ 0.14 mm^2 ($p = 0.04$). Also, **Dimitrova *et al.*** [14] who compared retinal and choriocapillary vascular flow parameters in NDR patients and healthy individuals. The mean area of FAZ, only measured in SRL, was larger in the NDR group, 0.37 $\pm$ 0.11 mm^2, compared to the control group,0.31 $\pm$ 0.10 mm^2 ($p = 0.02$).

In our study we subdivided the study group according to degrees of diabetic retinopathy as classified by the Early Treatment DR Study (ETDRS), where DR can be divided into mild, moderate, severe non-proliferative DR(NPDR), and proliferative DR (PDR) [15].

Previous studies investigated FAZ area in SRL and DRL had variable results compared to our study. **Mastropasqua *et al.*** [2] stated that mean FAZ area with OCTA was 0.285±0.128 mm^2 in the control group and 0.235±0.055 mm^2 in patients affected by diabetes and without DR. Considering patients affected by DR, FAZ area was 0.284±0.099 mm^2, 0.399±0.156 mm^2 and 0.417±0.120 mm^2 in mild NPDR group, moderate and severe NPDR group and PDR group, respectively ($P<0.001$). After comparing patient groups with control group, FAZ area was statistically significantly increased in moderate or severe NPDR group ($P=0.050$, post hoc analysis) and PDR group ($P=0.025$) which agree with our results.

Another study by **Carnevali *et al.*** [16] who analysed retinal vascular plexuses and choriocapillaries in patients with type 1 DM without DR. In SRL, the mean area of FAZ was 0.22 $\pm$ 0.10 mm^2 in the diabetic group, and 0.25 $\pm$ 0.10 mm^2 in the control group ($p = 0.34$). In DRL, the mean area of FAZ was 0.75 $\pm$ 0.20 mm^2 in the diabetic group and 0.76 $\pm$ 0.23 mm^2 in the control group ($p = 0.81$) which was statistically non-significant which agrees with our results in early stages of DR. Also our results agrees also with **Goudot *et al.*** [17] who studied parafoveal capillaries in NDR patients. Mean area of FAZ in the SRL (NDR: 0.32 $\pm$ 0.13 mm^2, controls: 0.29 $\pm$ 0.15 mm^2, $p = 0.31$), in DRL (NDR: 0.44 $\pm$ 0.15 mm^2, controls: 0.40 $\pm$ 0.14 mm^2, $p = 0.20$), which was statistically non-significant.

Our results disagree with **Bhanushali *et al.*** [18] who investigated the correlation between retinal vascular features and severity of DR in type 2 diabetes where he illustrated that the mean area of FAZ was larger in the DR groups compared to the control group ($p = 0.001$), but FAZ-area did not differ between the DR groups. This may be due to using different method to measure the FAZ area in SRL and DRL, also his study used 3x3 images and lastly our study is among Egyptian population.

In summary, we found increasing values in the area of FAZ along with increasing severity of DR, but this was only statistically significant in a few studies. Therefore, area of FAZ may be used as a part of the diagnostic procedure for DR in the future, but may be unsuitable as a parameter used alone [19].

In our study we also compared subfoveal choroidal vascular density between control and diabetic groups and there was statistically significant decrease in diabetic group compared to control group These results were consistent with **Choi *et al.*** [20] who investigated choriocapillaris alterations in different stages of DR which were common not only in PDR and NPDR but also in diabetics without retinopathy. This finding suggests that CC alterations also occur early in diabetes and may play a role in the pathogenesis of DR. Choriocapillaris flow impairment at different stages of DR merits further investigation. While our results disagree with **Carnevali *et al.*** [16] where VD ratio of choriocapillaries were statistically insignificant between diabetic group and control group.

Previous studies also have correlated FAZ area with visual function using various imaging methods in patients with DR. One study using FA found a negative correlation between FAZ area and best-corrected visual acuity after adjusting for the presence of DME. Recently, **Freiberg *et al.*** [21] demonstrated that the maximum FAZ diameter measured by OCTA in both the superficial and deep vascular networks correlated positively with best-corrected visual acuity.

Our results showed a correlation between FAZ area and visual acuity, where eyes with worse vision had larger FAZ areas. We further explored the correlation of vascular density with visual acuity and found a positive correlation at the level of both the superficial and deep vascular networks.

Regarding retinal thickness we compared control group and diabetic group and there was statistically significant increase in retinal thickness in diabetic group compared to control group in all

quadrants of ETDRS, which was consistent with previous studies. We also studied the effect of duration of diabetes on FAZ area and found to correlate directly while duration of diabetes correlates inversely with VD.

CONCLUSION

Our study revealed that vascular density and FAZ area can be quantified in DR eyes in a rapid, automated, and noninvasive manner with OCTA. Also foveal avascular zone area and vascular density as measures of DMI correlate with visual acuity in patients with DR.

Quantitative OCTA metrics may be useful as image acquisition and processing improves. The impact of these novel vascular biomarkers in the clinical setting remains unclear, but there is potential for metrics like vascular density and FAZ area to supplement and even replace more well-established, participative markers of ocular diabetic disease activity.

As OCTA technology evolves, inclusion of this imaging tool in future prospective studies will be essential in determining its potential impact on clinical care.

REFERENCE

1. **Lynch G, Romo J, Linderman R *et al.* (2018):** Within-subject assessment of foveal avascular zone enlargement in different stages of diabetic retinopathy using en face OCT reflectance and OCT angiography. Biomed Opt Express, 9(12): 5982–5996.
2. **Mastropasqua R, Toto L, Mastropasqua A *et al.* (2017):** Foveal avascular zone area and parafoveal vessel density measurements in different stages of diabetic retinopathy by optical coherence tomography angiography. Int J Ophthalmol., 10(10):1545-1551.
3. **Bates N, Tian J, Smiddy W *et al.* (2018):** Relationship between the morphology of the foveal avascular zone, retinal structure, and macular circulation in patients with diabetes mellitus. Scientific Reports, 8: 5355-66.
4. **Al- Sheikh M, Akil H, Pfau M *et al.* (2016):** Swept-source OCT angiography imaging of the foveal avascular zone and macular capillary network density in diabetic retinopathy. Investigative Ophthalmology & Visual Science, 57(8):3907-3913.
5. **Ishibazawa A, Nagaoka T, Takahashi A *et al.* (2015):** Optical coherence tomography angiography in diabetic retinopathy: a prospective pilot study. Am J Ophthalmol., 160(1):35-44.e1.
6. **Díaz M, Novo J, Cutrín P *et al.* (2019):** Automatic segmentation of the foveal avascular zone in ophthalmological OCT-A images. https://pubmed.ncbi.nlm.nih.gov/30794594/
7. **Sim D, Keane P, Zarranz-Ventura J *et al.* (2013):** The effects of macular ischemia on visual acuity in diabetic retinopathy. Invest Ophthalmol Vis Sci., 54: 2353-2360.
8. **Mendis K, Balaratnasingam C, Yu A *et al.* (2010):** Correlation of histologic and clinical images to determine the diagnostic value of fluorescein angiography for studying retinal capillary detail. Invest Ophthalmol Vis Sci., 51(11):5864-5869.
9. **Gao S, Jia Y, Liu L *et al.* (2016):** Compensation for reflectance variation in vessel density quantification by optical coherence tomography angiography. Invest Ophthalmol Vis Sci., 57: 4485-4492.
10. **Salz D, de Carlo T, Adhi M *et al.* (2016):** Select features of diabetic retinopathy on swept-source optical coherence tomographic angiography compared with fluorescein angiography and normal eyes. JAMA Ophthalmol., 134: 644-650.
11. **Coscas G, Lupidi M, Coscas F *et al.* (2018):** Optical coherence tomography angiography in healthy subjects and diabetic patients. Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde, 239(2-3), 61–73.
12. **de Carlo T, Chin A, Bonini F *et al.* (2015):** Detection of microvascular changes in eyes of patients with diabetes but not clinical diabetic retinopathy using optical coherence tomography angiography. Retina (Philadelphia, Pa.), 236: 4–2370.
13. **de Carlo T, Romano A, Waheed N *et al.* (2015):** A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous, 1(5): 1-15.
14. **Dimitrova G, Chihara E, Takahashi H *et al.* (2017):** Quantitative retinal optical coherence tomography angiography in patients with diabetes without diabetic retinopathy. Investigative Ophthalmology & Visual Science, 58: 190-196.
15. **Classification of Diabetic Retinopathy from Fluorescein Angiograms (1991):** ETDRS report number 11. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology, 98: 807-822.
16. **Carnevali A, Sacconi R, Corbelli E *et al.* (2017):** Optical coherence tomography angiography analysis of retinal vascular plexuses and choriocapillaris in patients with type 1 diabetes without diabetic retinopathy. Acta Diabetol., 54: 695–702.
17. **Goudot M, Sikorav A, Semoun O *et al.* (2017):** Parafoveal OCT angiography features in diabetic patients without clinical diabetic retinopathy: a qualitative and quantitative analysis. J Ophthalmol., 2017: 8676091.
18. **Bhanushali D, Anegondi N, Gadde S *et al.* (2016):** Linking retinal microvasculature features with severity of diabetic retinopathy using optical coherence tomography angiography. Invest Ophthalmol Vis Sci., 57: 519–525.
19. **Tey K, Teo K, Tan A *et al.* (2019):** Optical coherence tomography angiography in diabetic retinopathy: a review of current applications. Eye Vis (Lond), 6:37-46.
20. **Choi W, Waheed N, Moult E *et al.* (2017):** Ultrahigh speed swept source optical coherence tomography angiography of retinal and choriocapillaris alterations in diabetic patients with and without retinopathy. Retina, 37(1):11-21.
21. **Freiberg F, Pfau M, Wons J *et al.* (2016):** Optical coherence tomography angiography of the foveal avascular zone in diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol., 254: 1051-1058.