BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X

Online ISSN 2357-0016

Original article

Retinal Microvascular Changes of Subclinical Diabetic Retinopathy Using Optical Coherence Tomography Angiography

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Received:

Accepted

Abstract

Background: Patients with subclinical diabetic retinopathy (DR) are those who are diagnosed with diabetes mellitus (DM) with duration of 4–8 years, with no frank manifestations of DR, neither on clinical examination nor by the common diagnostic tools. **This study aimed to** evaluate retinal and choriocapillary parameters in subclinical diabetic patients using optical coherence tomography angiography (OCTA). **Methods:** This was a cross-sectional observational study that included a total of 145 eyes. The patients were divided into two groups: The eyes were categorized into two groups: Group A: That included 105 eyes with diabetes (Cases group). Group B: That included 40 eyes of healthy individuals (Control group). **Results**: FAZ area in SCP was significantly higher in the case group compared to the control group. There was an insignificant correlation between disease duration and FAZ area in SCP, between disease duration and superficial density and between disease duration and macular thickness. There was a negative significant correlation between disease duration and the whole region (r=- 0.312, P=0.001). **Conclusion:** OCTA provides a non-invasive objective tool with depth-resolved imaging that enables detailed enface visualization of the superficial and deep retinal vasculature. The subclinical diabetic retinopathy was associated with decrease in superficial capillary density, deep capillary density and increase in the macular thickness as compared to the healthy eyes. However, the limitations of OCTA to scan peripheral retinal vascular changes still can't eliminate the role of FFA in the diagnosis and follow-up of retinal vein occlusion.

Keywords: Retinal Microvascular Changes; Subclinical Diabetic Retinopathy; OCTA.

Introduction

Patients with subclinical diabetic retinopathy (DR) are those who are diagnosed with diabetes mellitus (DM) with duration of 4–8 years, with no frank manifestations of DR, neither on clinical examination nor by the common diagnostic tools. DR is the specific microvascular complication of DM and affects one in three patients with DM. DR remains a leading cause of vision loss in the working adult population (1).

Advances in retinal photographic techniques and image analysis allowed objective and precise in-vivo measurement of retinal vascular changes. In particular, quantitative assessment of retinopathy signs and measurement of retinal vascular caliber have greatly increased our knowledge of early microcirculation alterations in prediabetes, diabetes, and diabetic macrocirculation and microcirculation complications (2). Fluorescein angiography and color fundus photography have been used to establish quantitative indices of perfusion in DR (3, 4). However, these imaging modalities do not resolve retinal capillaries reliably and cannot detect subtle changes (5).

Optical coherence tomography (OCT) became a part of the standard of care in ophthalmology. It provided cross-sectional and three-dimensional imaging of the anterior segment, retina, and optic nerve head with micrometer scale-depth resolution. Structural OCT enhances the clinician's ability to detect and monitor fluid exudation associated with vascular diseases (6). It is however unable to directly detect capillary dropout or pathological vessel growth (neovascularization) that constitutes the major vascular changes associated with DR. These features, among other vascular abnormalities are assessed clinically by using fluorescein or indocyanine green angiography (7).

To overcome the conventional structural inability of OCT to provide direct blood flow information, several optical coherence tomography angiography (OCTA) methods have been developed (8). Quantification of retinal perfusion using OCTA has been reported in normal individuals (9, 10) and retinal vascular diseases. OCTA provided a novel method for noninvasively imaging the capillary network and the foveal avascular zone (FAZ) (11). In addition, OCTA can use a split-spectrum amplitude-decorrelation angiography algorithm to detect erythrocyte movement. The currently commercially available OCTA machines allow a four-section division of the retina–choroid complex: superficial capillary plexus, deep capillary plexus, outer retinal layers, and choriocapillaris. A new software update allowed quantification of the vascular density (VD) around the macula. VD was defined as the percentage of the sample area occupied by vessel lumens following binary reconstruction of images. In-vivo quantification of VD and the FAZ area

may be useful in detecting and monitoring the progression of retinal vascular changes caused by diabetes and other forms of retinopathy (12).

The purpose of this study was to evaluate retinal and choriocapillary parameters in subclinical diabetic patients using optical coherence tomography angiography (OCTA).

Patients and methods

This was a cross-sectional observational study that included a total of 145 eyes. The study was conducted at Ophthalmology Department, Benha University and Memorial Institute of Ophthalmology, Egypt.

This cross-sectional study was conducted at Benha University Hospital, during the period from January 2023 to October 2023,

A written informed consent was obtained from all the participants before inclusion in the study. The whole study design was approved by the local ethics committee, Faculty of Medicine, Benha University.

Inclusion criteria were controlled diabetic patients with type two DM, duration of DM ≥ 8 years, no frank ocular signs of DR, age between 30-60 years, best corrected visual acuity (BCVA) better than 6/18 in the examination and glycosylated hemoglobin HbA1c not exceed 8.5%.

Exclusion criteria were eyes with ocular disease as retinal, choroidal pathology, glaucoma, uveitis, history of intraocular surgery, other systemic disorders that affect posterior segment (Systemic lupus erythematosis, anemia, and leukemia), high errors of refraction and media opacity.

Grouping: The eyes were categorized into two groups: **Group A**: That included 105 eyes with diabetes (Cases group). **Group B**: That included 40 eyes of healthy individuals (Control group).

All studied cases were subjected to the following: Detailed history taking, including [General History and ophthalmic history: History of ocular trauma, ocular surgery, intravitreal injection or LASER therapy and onset, course, duration of diminution of vision]. **Ophthalmic examination:** Assessment of the visual acuity (VA)**,** Slit lamp biomicroscopy, patient's refractive error, measurement of intraocular pressure and posterior segment examination. **Images Analysis:** FFA images and OCTA images.

Assessment of the visual acuity (VA) [Unaided visual acuity and Best corrected visual acuity]. Were done using Landolt's VA chart and then transformed for statistical analysis to logarithm of minimal angle of resolution units (Log MAR).

Slit lamp biomicroscopy: By the slit lamp biomicroscopy (Haag Streit BP 900) (Haag-Streit, Koeniz, Switzerland) to assess:

Corneal clarity (opacities, scars, and descemetoceles), AC for depth and regularity, Pupil shape, size, regularity, and reactivity, Lens: any signs of exfoliation, dehiscence of zonules, subluxation, and grading of nuclear hardness using LOCS lll classification system, complications of diabetes such as (recurrent styes, xanthelasma, accelerated senile cataract, rubeosisiridis).

Patient's refractive error: using opcon RM-800 autorefractometer.

Measurement of intraocular pressure (IOP): IOP was measured using Goldmann Applanation Tonometer.

Posterior segment examination using indirect ophthalmoscope and slit lamp biomicroscopy with auxiliary contact lens.

Multimodal imaging procedures including:

Color & red-free fundus photography: is a specialized low-power microscope with an attached camera. Its optical design is based on the indirect ophthalmoscope.it is used to document the characteristics of diabetic retinopathy (damage to the retina from diabetes) such as macular edema and microaneurysms.

Fundus fluorescein angiography: This was done after pupillary dilatation and intravenous injection of 5 ml of 10% fluorescein sodium.

OCT scans: The images were done as it was performed using a 6x6 mm scan centered on the fovea in all cases and 3 x 3 mm in some cases to reveal more resolution. The macula was assessed in 2 zones; the superficial plexus extending from the internal limiting membrane to the inner plexiform layer and the deep plexus extending from the inner plexiform layer to the outer plexiform layer.

OCTA images:

The measured quantitative FAZ parameters included the central vessel-free area (FAZ); the fovea; the central 1 mm diameter ring, and the parafovea; the annulus centered on the fovea with inner and outer ring diameters of 1 mm and 3 mm, respectively.

The built-in angio-analytics software quantitatively analyzed the retinal microcirculation parameters as mean values evaluated within an area 1.5 mm radius from the center for the parafovea, 3 mm for the perifovea, excluding the central foveal 0.5 mm radius area. Quantitative parameters were expressed as vessel density defined as the total length of the perfused vessels per unit area within a measured area that was calculated after skeletonization of the binarized image; the perfusion index (parafovea and perifovea) described the total area of perfused vasculature per unit area within a region of measurement, as well as FAZ area, perimeter, and circularity index. FAZ boundaries were automatically outlined

along the innermost capillaries after which the area and perimeter of this zone were calculated. FAZ circularity was measured using the equation: circularity = 4πA/P2, where A is the area and P is the perimeter. Using this equation, as the circularity value approaches 1 it indicates a smooth regular shape and if it becomes closer to zero it indicates more irregular FAZ.

Macular angiographic changes and FAZ quantitative parameters (macular thickness, Retinal vascular density) were processed and analyzed in 3×3 and 6×6 mm2 macular scans. Differential retinal capillary vessel density and perfusion density values were calculated using the OCTA angio-analytics software in the central, inner, full, and outer regions.

Approval code: MS 19-2-2021

Statistical analysis

The data collected were analyzed with SPSS version 27 for (IBM, SPSS Inc, Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test and ANOVA (F) test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. Pearson correlation coefficient – was calculated to indicate the strength and direction of association between two numerical variables. A two tailed P value < 0.05 was considered statistically significant.

Results

There was no significant difference between both groups as regard age and sex. There was an insignificant difference between case and control as regards the affected eye. The mean HbA1C was significantly higher in the case group compared to the control group (p<0.001). FAZ area in SCP was significantly higher in the case group compared to the control group. **Table 1**

Regarding superficial density, whole region, fovea, parafovea, temporal, superior, Nasal, and inferior were significantly lower in the case group compared to the control group (P<0.001). Regarding deep density (%), the whole region, parafovea, temporal, superior, Nasal, and inferior were significantly lower in the case group compared to the control group (P<0.001). Fovea was insignificantly different between the case and control group. Regarding macular thickness (µm), whole region, Fovea, parafovea, temporal, superior, Nasal, and inferior were significantly higher in the case group compared to the control group (P<0.001). **Table 2**

Microaneurysm SCP occurred in 11(35.7%) of eyes in the case group. Microaneurysm DCP occurred in 17(25%) of eyes in the case group. FAZ irregularities did not occur in any patient. FAZ area in SCP was

insignificantly different between both groups (Diabetic controlled and Diabetic uncontrolled). **Table 3**

Superficial density, Deep density and Macular thickness whole region, Fovea, Parafovea, Temporal, Superior, Nasal, and Inferior were insignificantly different between both groups ((Diabetic controlled and Diabetic uncontrolled). **Table 4**

There was an insignificant correlation between disease duration and FAZ area in SCP, between disease duration and Superficial density and between disease duration and macular thickness. There was a negative significant correlation between disease duration and the whole region (r=- 0.312, P=0.001). **Table 5**

Control group: 32 years old female candidate. **Figure 1**

Fifty-two years old male diabetic patient for 10 years on oral medications, BCVA 0.8, HbA1c 7 %. **Figure 2**

Table 1: Analysis of the demographic data, ocular examination and FAZ area (Vascular density) in SCP in the two study groups.

		Cases group (N=105)	Control group (N=40)	**P value**
Age (Years)		48.98 ± 9.14	46.20 ± 7.66	
OD		49(46.7 %)	20 (50 %)	0.719
OS		56(53.3 %)	20 (50 %)	
Disease duration (years)		8 (1 - 20)	-----	---
BCVA		0.3 (0.2 – 1)	----	----
HbA1C (%)		8.69 ± 1.62	5.35 ± 0.64	< 0.001*
Diabetic	Controlled	8 (7.6 %)	---	---
control	Uncontrolled	97 (92.4 %)	---	---
FAZ area in SCP (VD)		0.329 ± 0.103	0.274 ± 0.058	0.010*

Data are expressed as mean ± SD, median (Range) or number (percent), FAZ: foveal avascular zone, *: statistically significant as P value <0.05.

Table 2: Analysis of Superficial density, deep density and macular thickness in the two study groups.

	Cases group (N=105)	Control group (N=40)	P value
Whole region	43.79 ± 5.24	52.80 ± 2.23	< 0.001*
Fovea	16.05 ± 7.10	31.71 ± 3	< 0.001*
Parafovea	46.26 ± 5.69	54.04 ± 2.24	< 0.001*
Temporal	46.01 ± 5.72	53.22 ± 2.89	< 0.001*
Superior	46.34 ± 7.30	55.82 ± 2.72	< 0.001*
Nasal	45.43 ± 6.72	54.47 ± 2.81	< 0.001*
Inferior	46.97 ± 6.26	55.97 ± 1.83	< 0.001*
Deep density			
Whole region	49.32 ± 4.51	58.42 ± 1.53	< 0.001*
Fovea	30.80 ± 7.92	30.83 ± 5.45	0.985
Parafovea	52.31 ± 5.16	60.49 ± 2.39	< 0.001*
Temporal	52.37 ± 7.46	59.01 ± 2.25	< 0.001*
Superior	52.29 ± 5.46	60.53 ± 7.32	< 0.001*
Nasal	52.86 ± 5.52	59.67 ± 2.94	< 0.001*
Inferior	51.25 ± 5.76	61.81 ± 1.49	< 0.001*
Macular thickness			
Whole region	317.20 ± 19.60	304.79 ± 23.10	0.002*
Fovea	272.39 ± 23.46	261.73 ± 18.73	0.011*
Parafovea	340.52 ± 16.07	329.96 ± 20.91	0.001*
Temporal	332.16 ± 17.98	321.26 ± 19.58	0.002*
Superior	335.26 ± 19.03	327.45 ± 22.60	0.038*
Nasal	334.83 ± 15.73	326.13 ± 23.29	< 0.001*
Inferior	331.80 ± 16.50	322.60 ± 17.09	0.003*

Data are expressed as mean ± SD, median (Range) or number (percent), *: statistically significant as P value <0.05.

Table 3: Qualitative analysis, the FAZ area in SCP in the cases group

Items	Cases group N = 105	
	Number	Percent
FAZ irregularities	0	0
Microaneurysm SCP	11	35.7
Microaneurysm DCP	17	25
	Diabetic controlled. (N=8)	**Diabetic uncontrolled(N=97)**	P value
FAZ area in SCP (VD)	0.255 ± 0.104	0.335 ± 0.130	0.093

Data are expressed as mean ± SD, median (Range) or number (percent),

Table 4: Analysis of Superficial density, deep density and Macular thickness in the cases group (according to diabetic control)

	Diabetic controlled (N=8)	Diabetic uncontrolled (N=97)	P value
Whole region	44.44 ± 2.86	43.73 ± 5.40	0.717
Fovea	16.25 ± 5.60	16.04 ± 7.23	0.935
Parafovea	46.19 ± 4.63	46.26 ± 5.79	0.971
Temporal	45.60 ± 3.92	46.04 ± 5.86	0.835
Superior	45.60 ± 4.71	46.40 ± 7.48	0.767
Nasal	45.59 ± 6.21	45.42 ± 6.80	0.946
Inferior	47.45 ± 5.70	46.94 ± 6.33	0.824
Deep density			
Whole region	50.83 ± 2.89	49.19 ± 4.60	0.326
Fovea	33.26 ± 7.29	30.59 ± 7.97	0.362
Parafovea	53.88 ± 3.18	52.18 ± 5.28	0.374
Temporal	55.85 ± 4.82	52.08 ± 7.59	0.171
Superior	53.71 ± 4.55	52.17 ± 5.53	0.447
Nasal	54.63 ± 3.66	52.71 ± 5.64	0.348
Inferior	51.81 ± 2.78	51.20 ± 5.95	0.774
Macular thickness			
Whole region	316.50 ± 16.90	317.26 ± 19.89	0.916
Fovea	265.75 ± 11.41	272.94 ± 24.14	0.407
Parafovea	343.88 ± 10.51	340.25 ± 16.45	0.542
Temporal	333.75 ± 10.22	332.03 ± 18.50	0.796
Superior	339.25 ± 13.58	334.93 ± 19.42	0.539
Nasal	338.75 ± 9.47	334.51 ± 16.13	0.466
Inferior	335.50 ± 10.58	331.49 ± 16.89	0.512

Data are expressed as mean ± SD, median (Range) or number (percent), *: statistically significant as P value <0.05

Table 5: Correlation between disease duration (years) and FAZ area, Superficial density, Deep density and macular thickness in SCP (VD).

Variables	**Disease duration (Cases group) (N= 105)**	
	rs	**P**
FAZ area in SCP (VD)	- 0.013	0.889
Superficial density		
Whole region	0.123	0.213
Fovea	0.144	0.105
Parafovea	0.061	0.534
Temporal	0.145	0.139
Superior	0.017	0.865
Nasal	- 0.014	0.889
Inferior	0.005	0.988
Deep density		
Whole region	**- 0.312**	**0.001***
Fovea	0.075	0.452
Parafovea	- 0.122	0.222
Temporal	- 0.054	0.588
Superior	- 0.100	0.318
Nasal	- 0.164	0.099
Inferior	- 0.153	0.273
Macular thickness		
Whole region	- 0.105	0.292
Fovea	- 0.107	0.278
Parafovea	0.015	0.881
Temporal	0.005	0.984
Superior	0.040	0.688
Nasal	- 0.012	0.902
Inferior	0.007	0.940

rs: (Spearman's correlation.,2004), foveal avascular zone (FAZ), *: Statistically significant ($p < 0.05$)

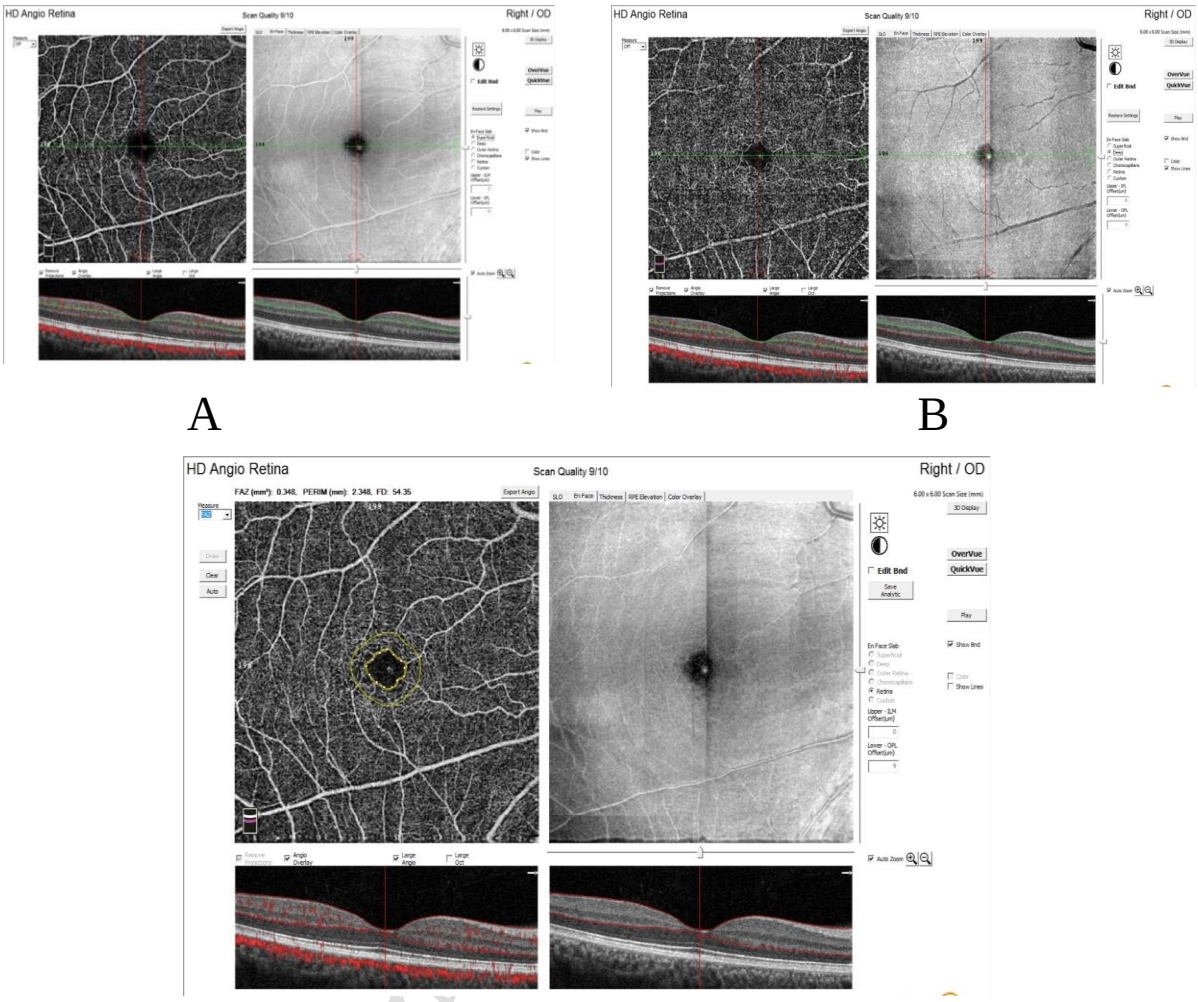

Figure 1: (A)shows a superficial vessel density map , (B) shows a deep vessel density map , (C) shows FAZ. map.

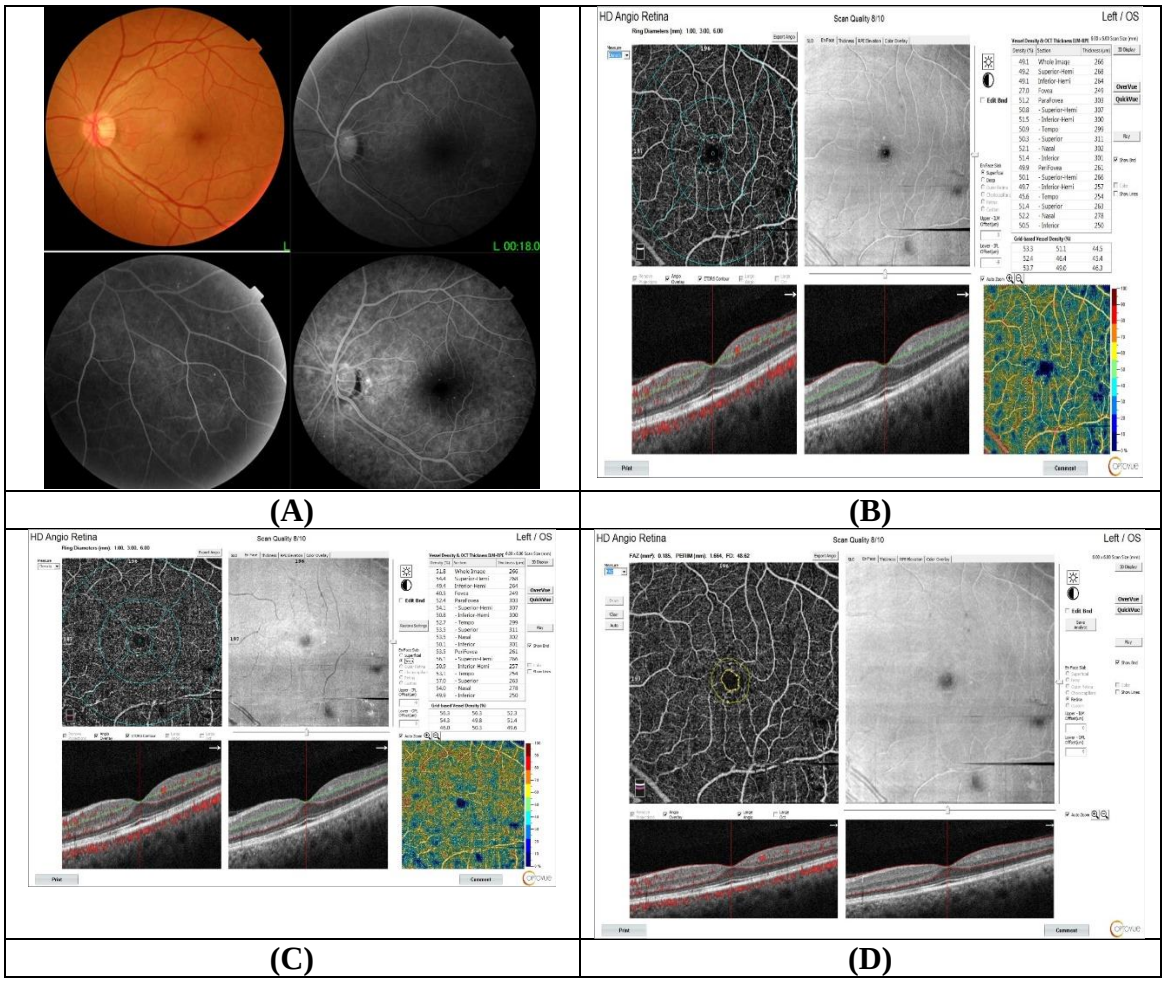

Figure 2: (A) shows FFA. Of left eye, (B) superficial vessel density map, (C) deep vessel density map and (D) FAZ. map

Discussion

In the current study, the mean age in the cases group was 48.98 ± 9.14 years while the mean age in the control group was 44.20 ± 7.66 years, with no statistically significant difference between the two groups (P= 0.094). There were 69.5% and 60% females in the cases and the control group, with no statistically significant difference between the two groups (p= 0.276).

This agreed with Ahmed et al. who included 44 eyes of 44 patients having early/mild non-proliferative diabetic retinopathy and 30 eyes of 30 age- and gender-matched healthy controls. There was no significant difference between groups regarding age and gender (p = 0.17 and 0.26, respectively), with a higher prevalence of female gender in the two groups (13).

In the current study, the mean FAZ area in SCP in the diabetic group was 0.329 ± 0.103 that was statistically significantly higher as compared to the control group (0.274 ± 0.058) (p= 0.010).

Within the same line, regarding the FAZ, Fernández-Espinosa et al. observed a significantly greater area at the SCP level in the DM2 group; however, no significant differences were found in DCP. Despite not reaching statistical significance in the DCP, we observed that the FAZ area increased in both plexuses in the DM2 group compared to the control group (14).

However, the current study disagreed with Yoon et al. who showed that the area, perimeter, and acircularity of FAZ were not different between the two groups, with and without DR (15).

FAZ metrics could even be measured more easily with OCTA than fluorescein angiography as there is no masking effect by dye leakage (16). Several studies have demonstrated significant quantitative differences in the FAZ in DR patients compared to normal controls. Notably, the FAZ becomes enlarged as a result of lost integrity of blood vessels (17-19).

In the current study, no FAZ irregularities were reported. This disagreed with Freiborg et al. who showed that the outline of FAZ becomes more irregular due to widened inter-capillary gaps; these vascular abnormalities are more evident in the deep than the superficial capillary plexus (17).

In the current study, Microaneurysm (MA) was shown in 35.7% in the SCP and was shown in 25% of the DCP.

This percentage was lower as compared to Fernández-Espinosa et al. (2022) who showed that MA was described in both plexuses in 80% of the patients, but 55% and 64% were described in SCP and CP, respectively (14).

Other authors, such as Lupidi et al., have studied anatomical alterations in DM patients in different plexuses. They studied DM1 and DM2 patients with non-proliferative RD and no DME, pooling different stages. They described abnormalities in both SCP and DCP. They found a higher number of linear vascular dilatations and a smaller number of microaneurysms (20).

In the current study, choriocapillaris hypo or non-perfusion was not reported in the current study. This came in accordance with Fernández-Espinosa et al. (2022) who were not able to find a hypo or non-perfusion in the DCP in the DM2 group (14)

In the current study, the superficial density showed a statistically significant decrease in the cases group as compared to the control group in all the areas (Whole region, Foveal region, Parafoveal region, Temporal region, superior region, nasal region and inferior region). The deep density showed a statistically significant decrease in the cases group as compared to the control group in all the areas (Whole region, Parafoveal region, Temporal region, superior region, nasal region and inferior region), but not the foveal region.

This agreed with Fernández-Espinosa et al. (2022) who reported that by the OCTA results, there was a decrease in VD in all areas of the SCP of the DM2 group (C, S, T, N and I) and most areas of the CC (S, T, N and I) with significant differences with respect to the healthy controls (14).

In a previous study, it was found that the parafoveal vessel density analyzed in both superficial and deep retinal plexuses was significantly reduced in diabetic patients with moderate to severe non-proliferative changes (42.48 ± 3.06 and 42.34 ± 2.35) in comparison to controls (52.91 ± 5.19 and 50.38 ± 5.42) ($p < 0.001$) (21).

However, Ong et al. described the utility of VD evaluation, the FAZ, and the vessel length density at the SCP to distinguish healthy subjects and the different stages of non-proliferative DR (NPDR). They suggested that SCP changes are more reliable due to the lower noise and artifacts in OCTA acquisition. They found less variability in the vessel length skeleton at the DCP in moderate to severe NPDR (22).

In the current study, the Macular thickness showed a statistically significant increase in the cases group as compared to the control group in all the areas (Whole region, Foveal region, Parafoveal region, temporal region, superior region, nasal region, and inferior region).

In agreement with our study Kim et al. report an increased CT in patients with increasing severity of DR, and while the exact mechanism they state is unknown (23), there is conflicting evidence on the change in retinal blood flow and pulsatile ocular blood flow in subjects with diabetes (24).

The current results partially agreed with ElShazly et al. who showed that there was a statistically significant decrease in the parafoveal macular thickness in the diabetic group compared with the control group (the superior–-hemi parafoveal thickness was 310.94±10.84 vs. 321.71±11.2 μm, respectively, P=0.001, while the inferior–hemi parafoveal thickness was 304.71±11.04 vs. 320.82±11.25 μm, respectively, P=0.001) (25).

In contrast with our study, Querques et al. identified choroidal thinning despite the disease stage, even in diabetic patients without DR (26), Sudhalkar et al. described a progressive thinning of CT with increasing severity of DR (27), Regatieri et al. states that it is unclear whether the choroidal thinning is primary or secondary to retinal ischemia (28).

In the current study, there was no significant association between the diabetes duration or the degree of diabetic control with FAZ area, superficial density, deep density or macular thickness.

This agreed with Li et al. who showed that although DM duration was a significant risk factor for microvascular abnormalities, they found no correlations between OCTA parameters and HbA1c or blood glucose in univariate or multivariable models. In their study, the assessed T2DM patients had a relatively short period of diabetes (71.5%, ≤10 years), and less than half of the patients (43.3%) had poor glycemic control (HbA1c > 10%) (29)

The level of glycemic control and tolerance to diabetes are independent contributing factors for the development of DR. However, glucose levels, glycated albumin, and glycated hemoglobin (HbA1c), well-known serum biomarkers for glycemic control (30, 31), have limited correlation with initial microvascular changes (32). Pancreatic β-cell function and insulin

sensitivity are assessed by various markers, such as C-peptide and insulin levels, and homeostasis model assessment (HOMA) values (33, 34). Among these serum biomarkers, low insulin levels and HOMA values have been shown to have an inverse correlation with the levels of macular microvascular impairment (32).

On the other hand, our findings were in disagreement with previous research by Czakó et al., who found that DM duration was strongly associated with decreased retinal VD after interaction analysis with the effects of systemic risk factors (35).

Also, the current results were opposite to Qian et al., who reported a negative correlation between DM duration and OCTA metrics such as SCP-VD and SCP-PD in 1118 DM patients (36).

Furthermore, larger FAZ and lower retinal capillary densities in children and adolescents with diabetes were observed in a case–control study, and these changes are associated with DM duration and poor glycemic control (37).

Conclusion

OCTA provides a non-invasive objective tool with depth-resolved imaging that enables detailed enface visualization of the superficial and deep retinal vasculature. The subclinical diabetic retinopathy was associated with decrease in superficial capillary density, deep capillary density and increase in the macular thickness as compared to the healthy eyes. The degree of diabetic control and the disease duration didn't affect the tested retinal parameters. However, the limitations of OCTA to scan peripheral retinal vascular changes still can't eliminate the role of FFA in the diagnosis and follow-up of retinal vein occlusion.

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To cite this article: Ayser A. Fayed, Mohamed A. AL Said , Ahmed A. Tabl , Ghada S. Mohamed , Jehad A. Emam. Retinal Microvascular Changes of Subclinical Diabetic Retinopathy Using Optical Coherence Tomography Angiography. BMFJ XXX, DOI: 10.21608/bmfj.2024.315375.2178