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Vessel Density as a Biomarker for Progression of Diabetic Macular Edema: An Optical Coherence Tomography Angiography Study

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Abstract

Background: Diabetic macular edema development and progression is important prognostic factor for determining the final visual outcome and quality of life for each diabetic patient. OCTA vessel density is quantitative parameter that could be used to quantify and measure macular diabetic edema and ischemia. Our study used the VD values to follow-up these edema changes along the diabetic retinopathy course

Aim of Study: The aim is to use of optical coherence tomography angiography to quantify vessel density throughout the different stages of diabetic macular edema progression.

Material and Methods: OCTA images were obtained using the AngioVue (Optovue Inc., CA, USA). For quantitative analysis of the VD with the help of the manufacturer's automated software.

Study Design: Prospective, cross sectional, observational study.

Place and Duration of Study: University Hospitals in the period between March 2017 to March 2019.

Results: The study included 160 eyes of 135 diabetic patients, 61 (45%) females and 74 (55%) males. The values of VD of the SCP were significantly affected more than the DCP very early in the diabetic course (No DR stage) (p=0.040). Moving one stage more in the disease (mild to moderate NPDR with no edema stage) the deep layer got significantly more affected than the superficial layer (p=0.038). In the more advanced stages of the disease and as the macular edema develop and progress (spongy edema and CME) the two plexuses showed decreased VD values nearly to the same degree with the deep plexus affected slightly more (low VD values) than the superficial plexus.

Conclusion: Using the OCTA machine with AngioAnalytics parameters (vessel density) aided in the objective quantification of macular perfusion in diabetic eyes with and without macular edema.

Key Words: *FAZ area – Vessel density – Cystoid macular edema – Optical coherence tomography angiography.*

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Introduction

OPTICAL coherence tomography angiography (OCTA) is a new, non-invasive device which can detect motion contrast by one of the following three methods (1) Phase-based, (2) Amplitude-based, and (3) Complex amplitude-based, the third technique uses combination of the first two techniques. Red blood cells should move for a sufficient distance in order to be detected by the OCTA scans, this leads to a limitation in the OCTA devices which may not be able to differentiate between no flow and slow flow **[1,2].**

Two commercial platforms are present, the first one is the spectral domain OCT (SD-OCT), with a wavelength about 840nm, and the second one is the swept-source OCT (SS-OCT), with a longer wavelength approximately 1050nm.

OCTA image is en-face image which is produced by segmentation of the OCTA cube at certain depth then the data within the slab are converted to this en-face image **[3,4].**

Diabetic retinopathy (DR) is the leading cause of visual impairment worldwide. The disease is characterized by microaneurysms, capillary drop out, and ischemia, leading to neovascularization and/or macular edema, both of which can lead to severely impaired visual function. Early detection of DR is crucial for prevention of vision loss **[1-3].**

Abbreviations:

FAZ : Foveal avascular zone.
DCP : Deep capillary plexus.
SCP : Superficial capillary plexus.
VD : Vessel density.
NPDR : Non poliferative diabetic retinopathy.
VEGF : Vascular endothelial growth factor.
DR : Diabetic retinopathy.

Among the retinal changes, such as microaneurysms and hard exudates; macular ischemia is a major risk leading to decreased perifoveal capillary blood flow causing chronic ischemia of the retinal tissue **[4]**.

Several studies defined the importance of macular ischemia, which is considered a predictor of poor functional outcome in patients with diabetes mellitus (DM) **[4-6]**.

Retinal imaging is widely used by ophthalmologists to screen and follow-up DR and diabetic macular edema (DME). Fluorescein Angiography (FFA) is a gold standard for the analysis of the vascular and capillary bed since it provides a high sensitivity for a wide range of diabetic retinal changes two-dimensionally **[7,8]**.

In this study we aimed to use OCTA to quantify vascular capillary density as a biomarker to follow-up the progression of diabetic macular edema throughout the course starting with the no diabetic retinopathy stage, the non proliferative retinopathy with no macular edema stage, spongiform and cystoid edema stage.

Material and Methods

This cross sectional, observational study was conducted on 160 eyes from 135 diabetic patients in the period from March 2018 to March 2019.

The study was performed according to principles of the Declaration of Helsinki. All subjects provided written informed consent to get involved in this study.

Inclusion criteria:

The study reviewed healthy patients and diabetic patients who were divided as follow:

1- Group I: 40 eyes of patients with diabetes mellitus for more than 5 years duration with no clinically detected Diabetic retinopathy (No DR Group).

2- Group II: 40 eyes of patients diagnosed with mild to moderate non proliferative diabetic retinopathy without diabetic macular Edema (NPDR Group).

3- Group III: 40 eyes diagnosed with diabetic retinopathy associated with Spongy macular edema (Spongy edema Group).

4- Group IV: 40 eyes diagnosed with diabetic retinopathy associated with Cystoid macular edema (CME Group).

Exclusion criteria:

- Patients with severe complications of diabetic retinopathy as vitreous hemorrhage or neovascular glaucoma.
- Patients who received any kind of treatment for diabetic retinopathy as laser photocoagulation, intravitreal injection.
- Patients with concomitant retinal disease (e.g., dystrophy, vascular occlusion, or age related macular degeneration).
- Patients with any media opacity affecting quality of imaging studies as corneal opacity, dense cataract.
- Patients with motion artifacts preventing the accurate analysis of the microvascularization were excluded.

Image acquisition:

OCT angiography images were obtained using the AngioVue (Optovue Inc., CA, USA), images were centered on the fovea after pupillary dilation, each cube consisting of 304 clusters of two repeated B-scans each contains 304 A-scans **[9]**.

We used the flow density map software Angio Analytics, an automatic quantification tool that measured flow area, non flow area, and flow area density **[10]**. Angio Analytics evaluated and then reported the relative density of flow as a percentage of the total evaluated area **[11]**. With Angio Analytics software, VD is calculated by first extracting a binary image of the vessels from the grayscale OCTA en face image, and then computing the percentage of pixels of vessels in the defined sectors **[12]**. Automated measurement of the FAZ area was obtained using the new non flow area measurement option **[13]**. An avascular area defined by automatic border detection was quantified in square millimeters (mm^2) **[14]**.

Results

Statistical analyses were performed using SPSS Statistics version 20 (IBM, Armonk, NY). Chi-square test (χ^2) was used to study association between qualitative variables. A p-value ≤ 0.05 was considered to be statistically significant.

This cross sectional observational study included 160 eyes of 135 diabetic patients, 61 (45%) females and 74 (55%) males. The mean age of the participants was 57.9±13.4 years. Patients whether type I or type II diabetics were included in the study with diabetes duration of more than 5 years

and irrespective of their method of diabetic control whether oral hypoglycemic drugs or insulin intake.

The No DR group had significantly higher SCP VD than any of the other groups. The SCP VD of the NPDR with no DME group was not significantly different from the spongy group (p=0.22), but was significantly higher than CME (p<0.001). The SCP VD of the spongy group was not significantly different from the CME group (p=0.175). (Table 1).

The No DR group had significantly higher DCP VD than any of the other groups. The DCP VD of the NPDR group was not significantly different from the spongy group (p=0.846), but was significantly higher than CME (p=0.003) and significantly lower than the control group (p<0.001). The DCP VD of the spongy group was not significantly different from the CME group (p=0.473), but was significantly lower than the control group (p<0.001) (Table 2).

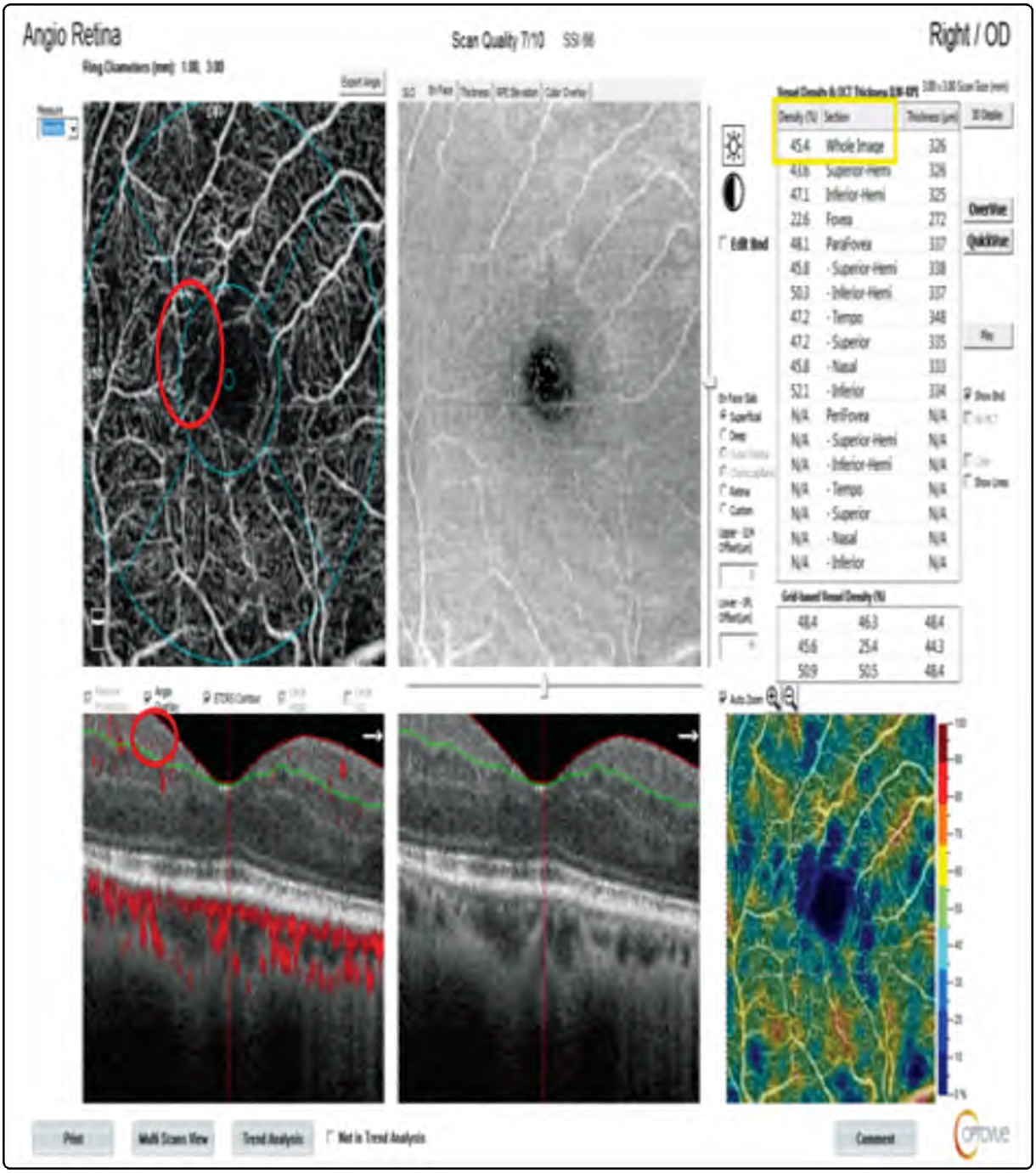

Fig. (1-A): This is a 3 x 3mm OCTA Angio Reina scan is centered on the right macula of 55 male with moderate NPDR with no DME at the level of the SCP. The calculated VD (yellow rectangular here = 45.4%) show reduction of the perfusion density, the angiogram shows areas of capillary drop out (red circle) corresponds with no flow in the B-scan Angio overlay (red circle). Interruption of the FAZ in the area of capillary non perfusion is also noted.

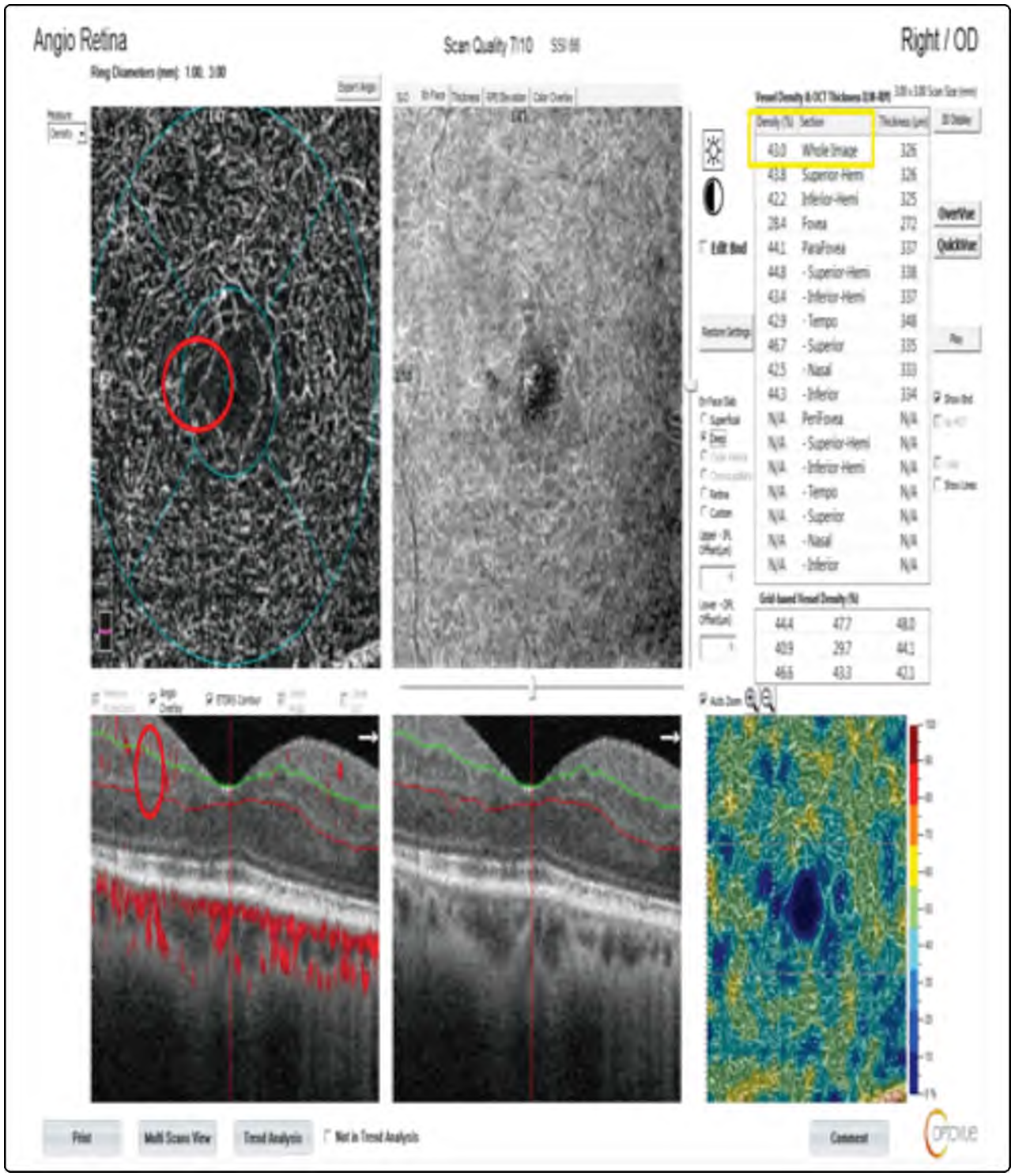

Fig. (1-B): A 3 x 3mm OCTA Angio Reina scan is centered on the right macula of same previous patient at the level of the DCP. The calculated VD (yellow rectangular here = 43.00%) show reduction of the perfusion density (more than the SCP VD evidencing that DCP is affected early in the diabetic retinopathy process), the angiogram shows areas of capillary drop out (red circle) corresponds with no flow in the B-scan Angio overlay (red circle).

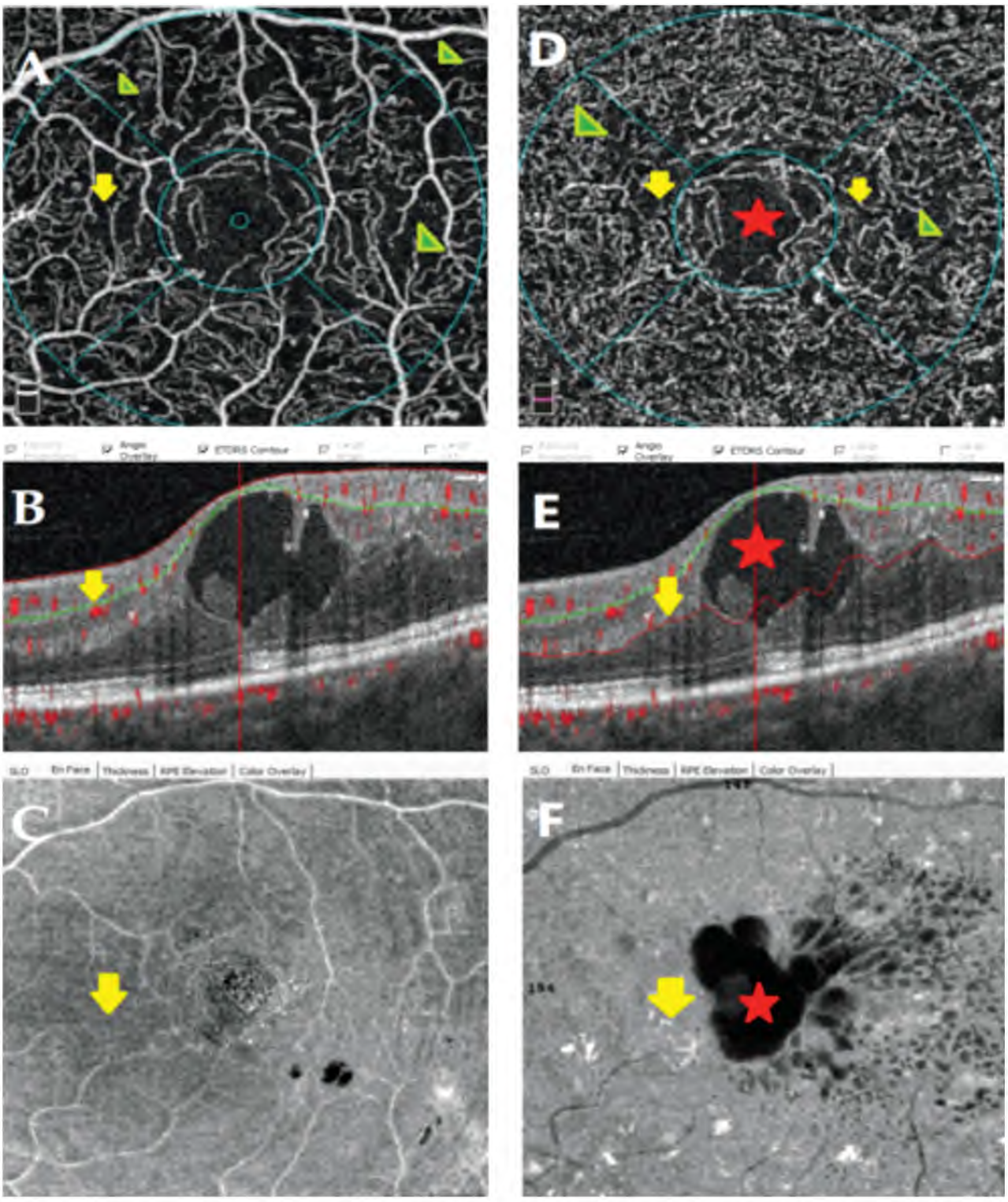

Fig. (2A)

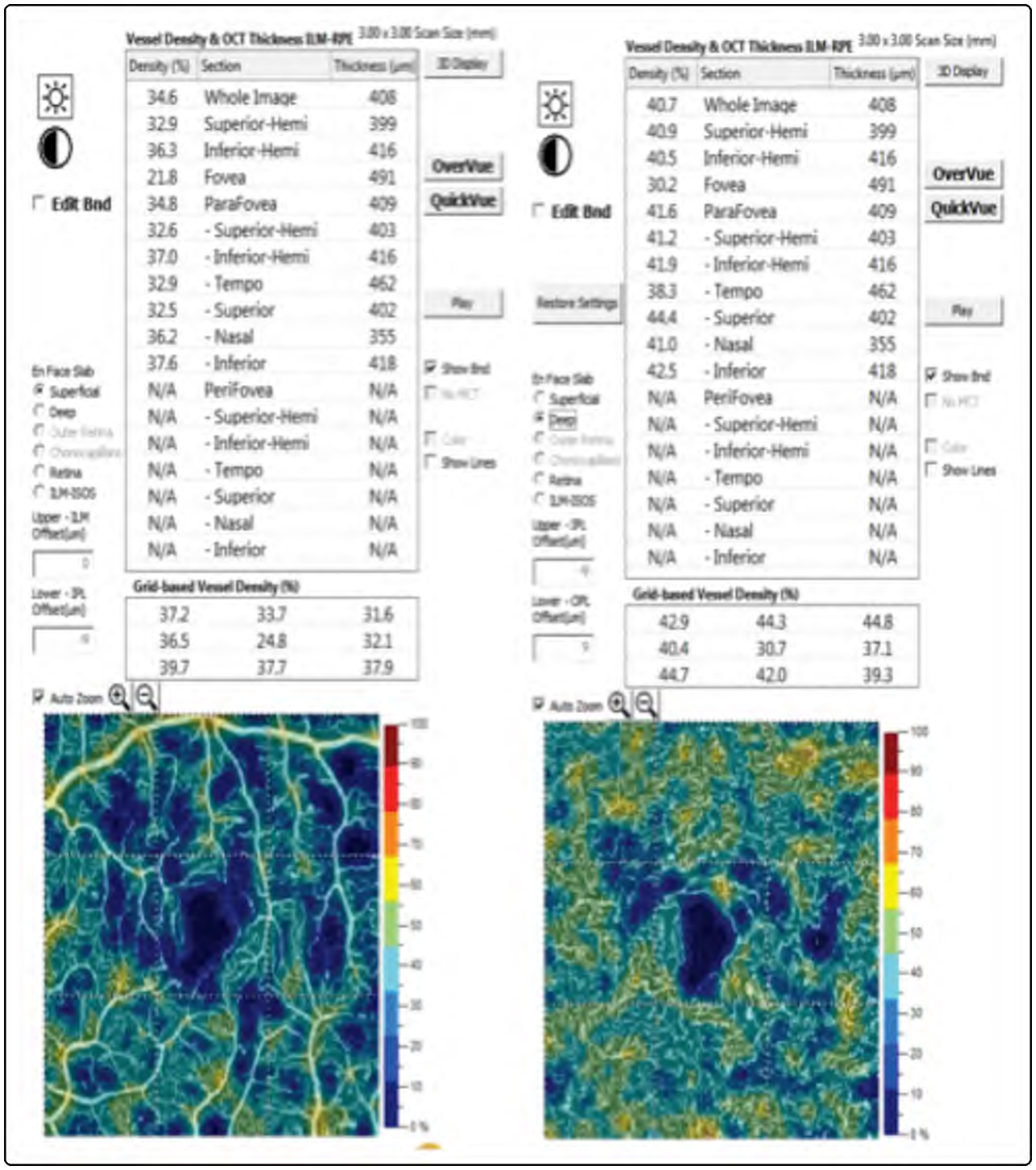

Fig. (2): (A,B): 3 x 3 OCTA angiogram of the SCP (A) and the DCP (D) with (star) represent CME spaces while (arrow) Represent ischemic area. (B) And (E) B-scan angio overlay OCT show segmentation at the SCP and DCP level with cystoids spaces more at the level of the DCP. (C) and (F) En-face image show cystoids spaces as hyporeflective spaces (red star) with oval borders while the non perfused areas not hyporeflective with irregular borders (yellow arrow). Yellow arrows also showed on the angio overly with no flow areas in the SCP and DCP (B) and (E). (D) The DCP has lost its normal pattern. (G) A decrease in capillary density was found in the SCP (VD 34.6%) and DCP (VD 40.7%) representing associated ischemic maculopathy. Cystoid spaces are surrounded by many other areas of flow void (yellow arrows indicate the non perfusion areas located on the edges of the cystoids spaces, showing the co-localization between the cystoid spaces and capillary non perfusion) (Green triangles of parafoveal capillary non flow).

Table (1): Superficial Capillary Plexus vessel density values % in different grades of Diabetic Retinopathy.

Groups	SCP VD (%) X ± SD	Median	K	*p*-value	Post Hoc
No DR (Group I)	51.78±2.32	51.98	118.66	<0.001	*p*1<0.001
NPDR (Group II)	42.31±3.78	43.10			*p*2<0.001
Spongy (Group III)	40.28±4.13	40.65			*p*3<0.001 *p*4 0.22
CME (Group IV)	37.68±5.47	37.60			*p*5<0.001 *p*6 0.175

p1: NO DR Vs NPDR. *p*4: NPDR Vs Spongy.
p2: No DR Vs Spongy. *p*5: NPDR Vs CME.
p3: No DR Vs CME. *p*6: Spongy Vs CME.

Table (2): Deep Capillary Plexus vessel density values % in different grades of Diabetic Retinopathy.

Groups	DCP VD (%) X ± SD	Median	K	*p*-value	Post Hoc
No DR (Group I)	58.93±1.77	59.46	127.71	<0.001	*p*1<0.001
NPDR (Group II)	44.73±4.25	44.27			*p*2<0.001
Spongy (Group III)	43.17±5.71	41.30			*p*3<0.001 *p*4 0.846
CME (Group IV)	40.95±4.70	40.45			*p*5 0.003 *p*6 0.473

*p*1: NO DR Vs NPDR. *p*4: NPDR Vs Spongy.
*p*2: No DR Vs Spongy. *p*5: NPDR Vs CME.
*p*3: No DR Vs CME. *p*6: Spongy Vs CME.

Discussion

We conducted a cross sectional study to evaluate the role of OCTA in describing the retinal structural damages observed in diabetic macular edema through following the earlier stages of diabetic retinopathy passing by non clinically detected DR to the mild and moderate NPDR with no evidenced DME.

Our results also indicated that diabetic eyes with mild to moderate NPDR without macular edema exhibited significantly lower macular vessel density (VD) (whole image) values at the level of both the superficial and deep retinal networks in 3 x 3mm Angio Retina scans (*p*=<0.001).

Our results also showed that diabetic eyes with no clinically detected diabetic retinopathy didn't have significant lower macular vessel density (whole image) values at the level of both the superficial (*p*=0.365) and deep (*p*=0.395) capillary plexuses in 3 x 3mm Angio Retina scans. These results are similar to those of Mathilde et al., who evaluated the capacity of the OCTA for detecting infraclinical lesions in parafoveal capillaries in diabetic patients without diabetic retinopathy (DR) and compared with age- and gender-matched non diabetic controls including Qualitative analysis and Quantitative analysis measured parafoveal capillary density. They concluded that neither the qualitative nor quantitative parameters were significantly different between both groups. On the SCP, (*p*=0.31). On the DCP, (*p*=0.20) **[15]**.

Our results revealed significant differences in vessel density values between diabetic eyes with Cystoid Edema and those without Macular Edema (No DR and the NPDR groups) at the level of DCP (*p*=<0.001 and *p*=0.03) respectively. These results are similar to those of Mané et al., who studied the OCTA changes in diabetic cystoid macular edema. The VD of the superficial capillary plexus and deep capillary plexus was measured using AngioAnalytics software. He noted that the intraretinal cystoid spaces were surrounded by capillary-flow void areas in the superficial capillary plexus in 71% of cases and in the deep capillary plexus in 96% of cases. The deep capillary plexus had lost its regular pattern in all cases. The capillary density was decreased in both plexus (mean decrease of 223.0% in the superficial capillary plexus and 212.4% in the deep capillary plexus vs. normal) **[16]**.

Our results revealed that the values of vessel density of the superficial capillary plexus were significantly affected more than the deep capillary plexus very early in the diabetic course (No DR stage) (*p*=0.040). Moving one stage more in the disease (mild to moderate NPDR with no edema stage) the deep layer got significantly more affected than the superficial layer (*p*=0.038). In the more advanced stages of the disease and as the macular edema develop and progress (spongy edema and CME) the two plexuses showed decreased vessel density values nearly to the same degree with the deep plexus affected slightly more (low VD values) than the superficial plexus. These results are similar to those of Ishibazawa et al., Who evaluated how octa depicts clinical fundus findings in patients with dr. They measured the area of retinal non perfusion near the macula in 7 eyes and found a difference between the extent of non perfused areas in superficial and deep plexuses **[17]**.

However our study proved that diabetic eyes with Cystoid Edema had significantly lower VD values when compared with eyes without macular edema (No DR or NPDR with *p*=<0.001 and *p*= 0.003 respectively) at the level of DCP and we were able to correlate between macular edema and capillary non perfusion, we could not judge whether decreased macular perfusion in diabetic eyes is

due to edema or an initiator for edema, as we lacked baseline VD values for the studied eyes before developing edema.

Conclusion:

OCTA could detect infraclinical quantitative or qualitative differences in macular capillaries of diabetic patients without DR in comparison with controls. Results from this study suggested that superficial and deep retinal vessel density in the diabetic patients without DR is decreased as compared to healthy subjects. The differences between the control and diabetic group's associations of OCTA parameters with the subjects' systemic characteristics suggests altered autoregulation of the retinal blood vessels in diabetic patients without DR.

We revealed that the integrity of the DCP is important not only for the occurrence of DME but also for its progression. Therefore, the extent of DCP loss assessed by OCTA could be a useful diagnostic tool for predicting the treatment response to anti- vascular endothelial growth factors (VEGF) agents.

It's recommended to Use these OCTA biomarkers to predict visual function in such eyes and for monitoring treatment response.

Further studies are needed to document the same patient over the long period of DR progression state since the current study lacked the follow-up of the reported changes over time.

Competing interests:

Authors have declared that no competing interests exist.

Authors' contributions:

This work was carried out in collaboration among all authors. Authors MW and MA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript.

Authors AE, EN and ME managed the analyses of the study. Author HE managed the literature searches.

All authors read and approved the final manuscript.

Consent:

All patients were informed of the nature of the study and gave written informed consent before enrollment. The study was approved by the Ethics Committee of University.

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تقييم الارتشاح السكرى بالماقولة باستخدام التصوير المقطعى المترابط للأوعية الدموية للشبكية

سيظل الارتشاح الشبكى السكرى واحد من أهم الأسباب المسببة لفقدان الابصار فى العاليم. لقد اعتمد الرواد الاوائل فى أبحاث الشبكية على تصوير قاع العين بصيغة الفلورسين لتشخيص أمراض الأوعية الدموية بالشبكية وبالرغم من اعتباره هو الرئيسى فى تقييم الدورة الدموية بالشبكية إلا أنه تبين أنه لا يمكن تصوير جميع الشعيرات الدموية بالشبكية باستخدام صبغة الفلورسين وخصوصاً الموجودة بالطبقات العميقة.

التصوير المقطعى البصرى المترابط هو طريقة سهلة للحصول على صور مقطعية للشبكية بجودة عالية وعلى مدار الأعوام تطورت تطبيقاته بصورة ملحوظة. تصوير الأوعية الدموية بال الضوئى المقطعى المترابط هو طريقة حديثة لتصوير الأوعية الدموية للشبكية بطريقة غير تدخلية عن طريق تصوير حركة كرات الدم الحمراء وباستخدام تكنولوجيا تصحيح الحركة للحصول على صور. ان نقص تروية الشعيرات الدموية بشبكية العين له دور كبير فى التسبب بالارتشاح الشبكى السكرى بالماقولة.

أظهر التصوير المقطعى الترابطى للأوعية الدموية القدرة على تشخيص وحساب درجة نقص تروية الماقولة كما أظهرت الدراسة وجود ارتباط بين وجود تغيرات التركيب التشريحى للماقولة على مستوى الطبقات الداخلية فى صورة عدم انتظام هذه الطبقات ووجود الارتشاحات السكرية مروراً بمراحلها من الصورة الاسفنجية إلى الصورة المتكيسة وكذلك تشخيص المراحل الأولى ما قبل ظهور الارشاح السكرى بصورة إكلينيكية وكذلك نقص تروية الماقولة فى المراحل الأولى من مرض الشبكى السكرى وذلك قبل ظهور الارشتاح بالماقولة.