DIABETIC MACULAR ISCHEMIA DIAGNOSIS: COMPARISON BETWEEN OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY AND FLUORESCEIN ANGIOGRAPHY

By

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ABSTRACT

Background: Diabetic retinopathy (DR) is a common complication of diabetes mellitus and is a leading cause of blindness worldwide. Diabetic macular ischemia is recognized as an important cause of visual disability. DMI is characterized by enlargement of the physiological capillary-free zone (FAZ).

Objective: To compare fluorescein angiography (FA) and optical coherence tomography angiography (OCTA) of foveal avascular zone (FAZ) in patients with diabetic retinopathy (DR) with and without diabetic macular ischemia (DMI).

Patients and methods: Our study included 60 patients with diabetic retinopathy, divided into 2 groups: Group I: 80 eyes of diabetic patients with diabetic retinopathy and DMI and Group II: 40 eyes of diabetic patients with. Diabetic retinopathy and no DMI (diagnosed clinically and FA). All of them underwent full history taking, complete ophthalmological examination including FFA & OCTA during the period from October 2017 to December 2018.

Results: Regarding the comparison of OCTA with FA in diagnosis of DMI according to ETDRS DMI grading. The present study found that moderate agreement between both devices (Kappa agreement k = 0.560 FAZ area was measured in DMI group and non DMI group. Group I Mean FAZ area ± SD was (0.57 ± 0.29 mm2) in OCTA6x6, (0.61 ± 0.28mm2) in FFA. Statistically, the difference in FAZ area between the OCTA and FFA was insignificant. The horizontal and vertical diameter was (650 ± 0.32Mm & 490 ±0.26) in OCTA6x6, (690 ± 0.25Mm & 530 ± 0.31Mm) in FFA. Statistically, the difference in horizontal and vertical diameter between the OCTA and FFA was insignificant.

Conclusion: OCT angiography was a valid, reliable and easy-to-use method to detect and quantify DMI changes without use of dye .with a moderate degree of agreement between FFA and OCTA in evaluating DMI.

Keywords: DMI, FAZ, OCTA.

INTRODUCTION

DMI has been reported to affect approximately 7% of patients with diabetic retinopathy. DMI is characterized by enlargement of the physiological capillary-free zone located at the center of the macula, also known as the foveal avascular zone (FAZ), along with perifoveal capillary dropout *(Liew et al., 2015)*.

According to the ETDRS, clinically, there is a correlation between DMI and poor prognosis that varies according to the severity of the macular ischemia *(Sim et al., 2013)*.

Various methods have been used to assess FAZ and perifoveal microcirculation: in vitro techniques on enucleated eyes as well as in vivo techniques, with fundus photography, and fluorescein angiography *(Fadzil et al., 2010)*.

FA has been the gold standard imaging modality since it was introduced in 1961 However, it requires venipuncture, and reports of anaphylaxis and death related to contrast injections, despite being rare, have been documented *(de Carlo et al., 2015)*.

Optical coherence tomography angiography (OCTA) is a newly available retinal vascular imaging technique, which is able to separately visualize superficial and deep macular capillary plexus *(Spaide et al., 2015)*.

OCTA has been used for 3D mapping at microcirculation level. It allows detection of retinal and choroidal structures via motion contrast imaging and high speed scanning, which detect blood flow by analysing signal decorrelations between scans *(Nagiel et al., 2015)*.

The aim of the current work was to compare FA with OCTA images of FAZ among individuals with DR with and without DMI.

PATIENTS AND METHODS

This was a comparative cross–sectional study. It was performed at Al- Sayd Galal Hospital, Al-Azhar University during the period from October 2017 to December 2018. Clinical data and images were obtained from one hundred twenty eyes of sixty patients divided into two groups: Group (I): Eighty eyes of diabetic patients with DMI proved by clinical examination and fluorescein angiography and Group (II): Forty eyes with no DMI by clinical examination and fluorescein angiography.

Inclusion criteria: Age of patient 18 years or more and Presence of DR in the studied eye. Clear view of the retina.

Exclusion criteria: Macular edema with retinal thickness preventing good visualization of the FAZ by OCTA. Retinal diseases (age-related macular degeneration, macular hole, foveoschisis, and foveal hypoplasia). History of vitreoretinal surgery. Subjects that presented motion artifacts during OCTA or poor signal strength.

The patients in this study were undergoing a complete ophthalmologic examination including: measurement of best-corrected visual acuity by landolt notation then converted to log MAR, Slit-lamp ant-segment examinations to detect any opacity of the media or any diabetic complication, IOP measurement using Goldman applanation tonometer, fundus examination by direct and indirect ophthalmoscope. Fluorescein angiography, Swept-Source optical coherence tomography angiography for macular assessment.

Diabetic retinopathy grading of the retinopathy was based on the early Treatment Diabetic Retinopathy Study (ETDRS) classification, endorsed in 2003 by the American Academy of Ophthalmology Guidelines Committee

and widely used in clinical trials *(Wilkinson et al., 2003).*

Standard fluorescein angiograms were analyzed quantitatively and qualitatively by two independent masked readers' retina specialists who assessed macular perfusion according to ETDRS classification. Early-to-mid phase images were considered for the evaluation of macular perfusion; late frames were used to grade macular edema. Quantitative analysis of FAZ included measurement of maximum vertical and horizontal diameters (μm) as well as FAZ area (mm2) for each fluorescein angiogram. The Image J suite was used to analyze FFA images. Qualitative analysis was classified based on standard reference photos from the ETDRS DMI grading system with special regards to FAZ alterations.

OCTA was done by the same device (DRI Triton Plus, Topcon Systems, Tokyo, Japan). Technique was explained to the patient. Chin height, imaging instrument and chin rest was adjusted to approximate position. The subject was asked to look at internal fixation target and a circular scan 6x6 with a circle diameter of 320x320 mm was centered on macula around. OCTA is a 3D imaging modality that provides high-quality static images of the retinal and choroidal vasculature without the need for any dye Injections "dye free study of the chorioretinal vasculature". Sequential B-scans are taken of the SAME retinal location and then subjected to analysis to determine if there was any change in the amplitude or phase of the scan. If changes are detected, this signifies movement in the retinal tissue of this location. The obtained signal can then be amplified (SSADA—split spectrum amplitude decorrelation angiography) and digitally processed to provide an en face view of the vasculature at different layers of the retina.

Images obtained from the IMAGE net 6 database were analyzed from a quantitative and qualitative point of view by two independent masked readers' retina specialists who assessed macular perfusion according to ETDRS classification. En face SS-OCTA images were generated for the Superficial capillary plexus (SCP) only, to allow for better comparison with corresponding FFA images. Manual segmentation was performed for each scan.

Statistical Methods was performed using Microsoft® Excel® version 22 and Statistical Package for the Social Sciences (SPSS®) for Windows® version 15.0. Continuous data were presented as range, mean and standard deviation (if parametric) after t-test. Dichotomous or categorical data were presented as number and percentage, Chi-squared test and McNemar's test (for categorical variables). Significance level was set at 0.05.

RESULTS

In group I the mean age + SD was 58.03 ± 4.98 years. This group included fourteen males and twenty six females In group II the mean age + SD was 57.26 ± 6.13 years. This group included seven males and thirteen females. The differences between the two groups as regards the age and sex were statistically insignificant.

The presence of DMI in mild, moderate, severe NPDR are average (13.75%, 36.25%, 21.25%) consequently and in PDR is (28.75%), but the absence of ischemia are (70%, 15%, 0%) consequently. And in PDR is (15%). There was statistically significant between severity of diabetes and ischaemia of FAZ.

The mean BCVA ± SD was 0.47 ± 0.36 in group I, 0.58 ± 0.23 in group II. Statistically mean BCVA in these two groups were significant **(Table 1)**.

Table (1): **Analysis of demographic data, correlations between severity of diabetes and presence of DMI and correlations between severity of diabetes and presence of DMI in the two study groups**

Parameters \ Groups		DMI (N=40)		No DMI (N=20)		Test of significance
Age (years)		58.03 ± 4.98		57.26 ± 6.13		t=0.631 P = 0.529
Gender	Male	14	35%	7	35%	x2=0 P < 0.001
	Female	26	65%	13	65%	

		DMI (N=80)		No DMI (N=40)		
Type of DR	PDR	23	28.75%	6	15%	x2= 33.803 P < 0.001
	MILD NPDR	11	13.75%	28	70%	
	Moderate NPDR	29	36.25%	6	15%	
	Severe NPDR	17	21.25%	0	0%	
BCVA		0.47 ± 0.36		0.58 ± 0.23		Z=-5.211 P < 0.001

Qualitative analysis of FAZ (absent, questionable, mild, moderate, severe, ungradable) based on ETDRS DMI grading system by OCTA and FFA showed statistically significant between two devices (P < 0.001) with moderate agreement (K=0.560) **(Table 2)**.

Table (2): Comparison of the grade of DMI with OCTA

Grades in DMI cases / Groups	DMI by OCTA (N=80)	DMI by FFA (N=80)	Test of significance
Absent	20 (25%)	16 (20%)	k = 0.560 P < 0.001
Questionable	7 (8.75%)	10 (12.5%)	
Mild	12 (15%)	18 (22.5%)	
Moderate	10 (12.5%)	9 (11.25%)	
Severe	25 (31.25%)	22 (27.5%)	
Ungradable	6 (7.5%)	5 (6.25%)	

Mean FAZ area ± SD was (0.57 ± 0.29 mm2) in OCTA, (0.61 ± 0.28mm2) in FFA. Statistically, the difference in FAZ area between the OCTA and FFA was insignificant. Mean horizontal and vertical diameter was (650 ± 0.32Mm & 490 ±0.26) in OCTA, (690 ± 0.25Mm & 530 ± 0.31Mm) in FFA. Statistically, the difference in horizontal and vertical diameter between the OCTA and FFA was insignificant **(Table 3)**.

**Table (3): Comparison between (FAZ area &horizontal and vertical diameter) by OCTA and FFA in DMI group**

Parameters / Groups	No DMI by OCTA (N=40)	No DMI by FFA (N=40)	Test of significance
FAZ area (mm2)	0.22 ± 0.38	0.19 ± 0.43	z = 1.927 P = 0.641
Horizontal (Mm)	240 ± 40	230 ± 54	z = 0.926 P = 0.350
Vertical (Mm)	200 ± 36	185 ± 38	z = 2.209 P = 0.074

Cases:
Case (1): Print out of SS-OCTA scan and FFA in diabetic pt with DMI:
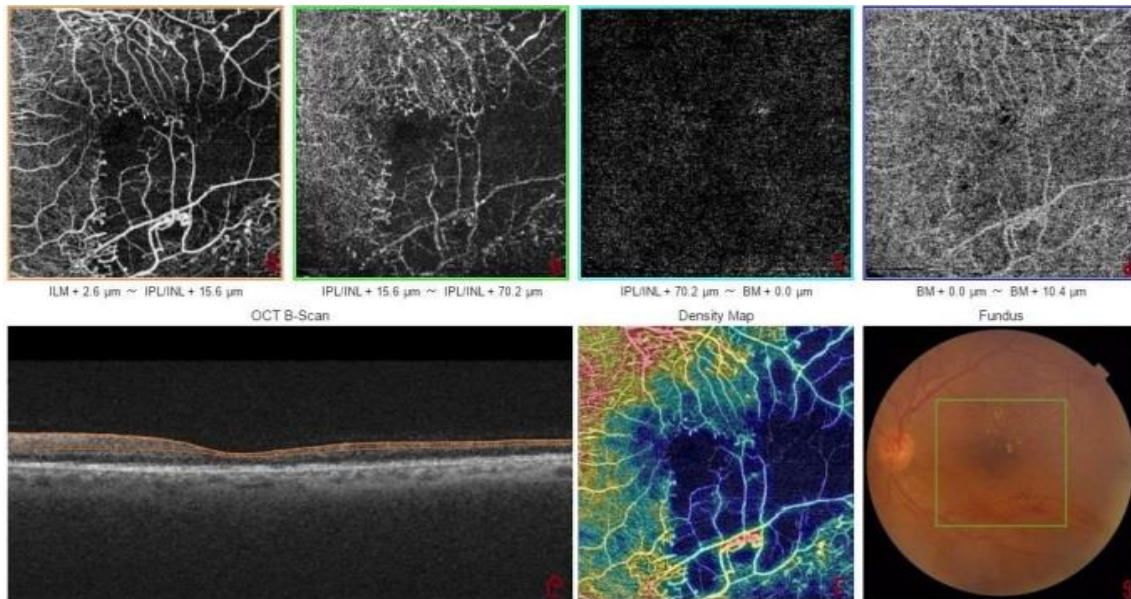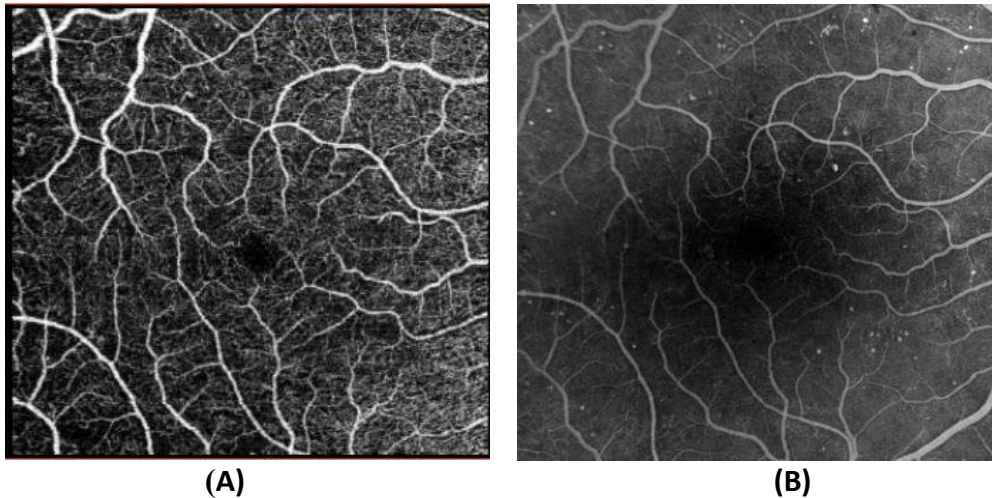

Figure (1): a. Superficial capillary plexus b.Deep capillary plexus c.Outer retina d.Choriocapillaris e.B-scan of macula f. Map Density g.Fundus
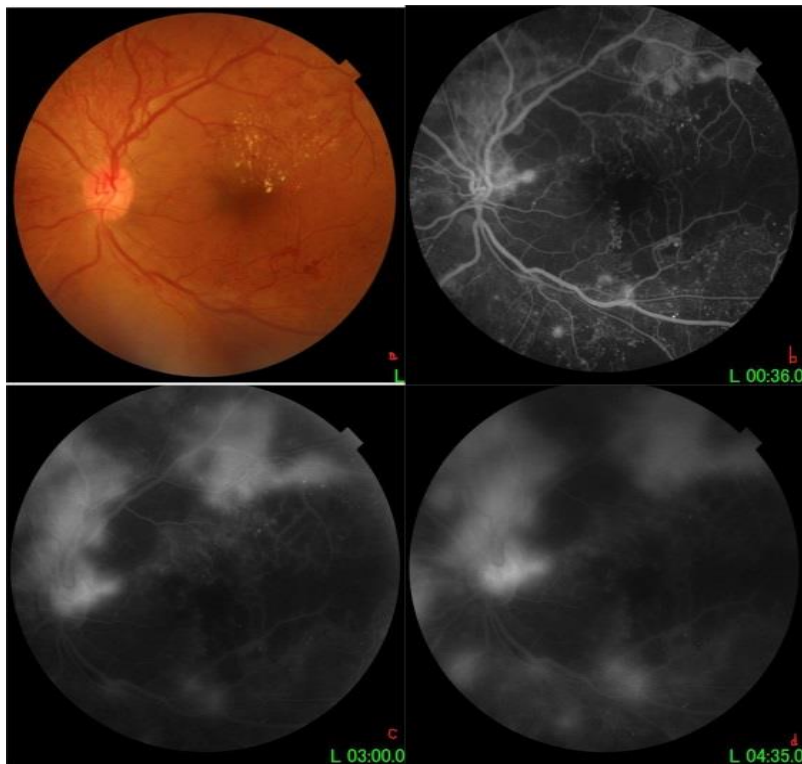
Figure (2): a. Colour fundus photo. b. Early ateriovenous phase. c. Recirculation phase. d. Late phase

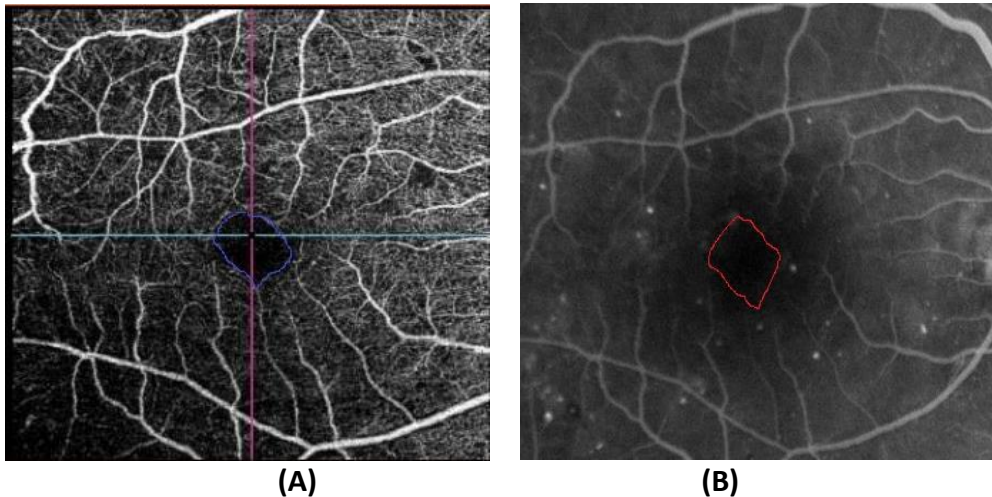**Case (2): Compare Superficial capillary plexus and early phase of FFA**

(A)   (B)

Figure (3): Optical coherence tomography angiography (OCTA), (A) early phase of fluorescein angiography (FA) (B)

Showed foveal avascular zone (FAZ) area on OCTA angiogram segmented at the level of the superficial retinal vasculature showed mild grading of DMI (outline definitely destroyed for less than one half the original circumference). (B) FAZ area on fluorescein angiography (FA) questionable (outline not smoothly round or oval, but visible irregularities, not definitely abnormal).
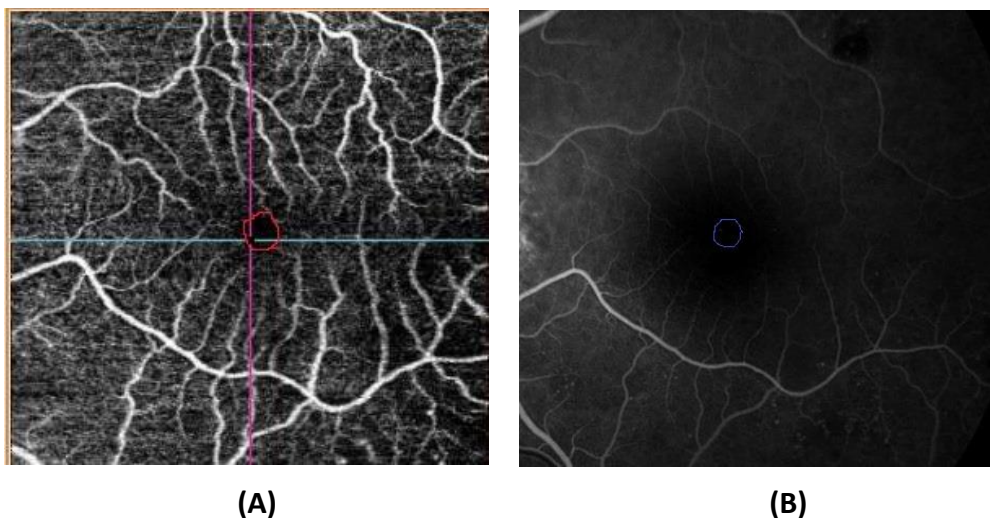
Case (3): Compare Superficial capillary plexus and early phase of FFA.

(A)   (B)

Figure (4): Optical coherence tomography angiography (OCTA) (A) early phase of fluorescein angiography (FA) (B)

Blue line representing the FAZ area on OCTA angiogram segmented at the level of the superficial retinal vasculature (A). Red line delimits foveal avascular zone (FAZ) area on fluorescein angiography at 0:53 min. (B) both images showed moderate grades of DMI (outline destroyed for one half or more of the original circumference, but some remnants remain).

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Case (4): Compare Superficial capillary plexus OF OCTA and early phase of FFA.

(A)   (B)

Figure (5): optical coherence tomography angiography (A), early phase of fluorescein angiography (B)

Left eye of showed quantitive and qualitative analysis of (FAZ) area on the superficial retinal vasculature of optical coherence tomography angiography versus fluorescein angiography. red line representing the FAZ area (mm2) on optical coherence tomography angiography (OCTA) about 0.19 ± 0.40 (A), blue line delimits foveal avascular zone (FAZ) area (mm2) on fluorescein angiography about 0.18 ± 0.39 (B). Both images showed absent of DMI (no alteration of the capillary outline).

DISCUSSION

The newly used SS-OCT technology provided a scanning wavelength of 1050 nm with high resolution images, and also a sweeping range about 100nm, when compared to spectral-domain OCT (SD-OCT) with 850 nm scanning wavelength *(Mansouri et al., 2013)*.

Our current study used SS-OCTA technology to evaluate the FAZ shape and size in comparison with FA image at the same time in different grades of DR with and without DMI. Furthermore, we detected a correlation between FAZ alterations and BCVA. In addition we correlated the disruption of FAZ with DR severity. There was a statistically insignificant difference between FAZ area, horizontal and vertical diameter measurements by FFA and SCP in OCTA among diabetic patient with and without DMI which also noted by *Garcia et al. (2016)*, who compared FA images with SCP of OCTA image in FAZ area size and also did not indicate significant difference between area measurements obtained with FA and OCTA in patients diagnosed with DMI and patient without DMI.

In the present study, there was statistically significant correlation by ETDRS DMI grading between OCTA and FFA patients diagnosed with DMI and other without DMI. This was supported by *Bradley et al. (2016)*, who compared FAZ shape by EDTRS grading protocols between FA and OCTA and showed a

mean of 60.4% of patients had no difference in DMI grades, 33.3% with a one-grade difference, and 2.1% with a two-grade difference between FA and OCT angiography images. A total of 4.2% of images were upgradable.

This study showed that there was a statistically significant correlation between macular ischemia and BCVA which was supported by *Freiberg et al. (2015)* who showed that FAZ enlarged in eyes with diabetic retinopathy and the enlargement of the FAZ correlated with reduced visual acuity.

Our present study data were in accordance with the study of *Garcia et al. (2016)* who used OCTA and FA in quantitative analysis of FAZ and showed significant difference between FA and OCTA in patients without DMI.

In our study, we measured FAZ area in DMI group and non DMI group and showed that the difference in FAZ area between the OCTA and FFA was insignificant, which also noted by *La Mantia et al. (2019)*.

In contrast to our study, *La Mantia et al. (2019)* reported a good agreement between FFA and both SS-OCTA for both vertical diameter and foveal avascular zone area measurements. The difference in horizontal and vertical diameter between the OCTA and FFA was insignificant.

Cennamo et al. (2017) shown good agreement between FFA and SD-OCTA in the evaluation of DMI using the ETDRS protocol.

Miwa et al. (2016) demonstrated that FAZ areas in OCT angiograms in the superficial layer were smaller than those

in the fluorescein angiography images which also noted by our study.

One of limitation of our study, we could not measure the functional blood flow to assess the perfusion because of limited SS-OCTA software. So, we only measured area and horizontal and vertical diameters of FAZ, other limitation all of the results were obtained during a single appointment, and there was no follow-up. We showed that there were moderate degrees of agreement between FFA and OCTA in evaluating DMI.

CONCLUSION

6X6 analysis protocols appeared to be reproducible. It was necessary to have imaging system with wide field of view for increasing the possibility to visualize the peripheral region vascular networks. SS-OCTA is recommended as good biomarker in clinical researches.

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مقارنة ما بين التصوير البصرى المقطعى المترابط للأوعية الدموية والتصوير بمادة الفلوريسين فى تشخيص ضعف التغذية الدموية لمركز الإبصار لدى مرضى السكر

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خلفيــة البحــث: يعتبــر الإعــتلال الشــبكي الســكري مــن أشــهر المضــاعفات لمــرض السكر ويعــد الســبب الرئيســي لفقــدان البصــر علــي مســتوى العــالم. ويتميــز نقــص ترويــة المقولــة الســكري بتضــخم المنــاطق الخاليــة مــن الأوعيــة الدمويــة لــذلك يُعــد مــن الأســباب المهمة للإعاقة البصرية.

الهــدف مــن البحــث: تهــدف دراســتنا للمقارنــة بــين تشــخيص نقــص ترويــة المقولــة الســكري بجهاز التصــوير بمــادة الفلوريســين وجهــاز التصــوير البصــري المقطعــي المتــرابط للأوعيــة الدمويــة وذلــك فــي المرضــى المصــابون بالإعتلال الشــبكي السكري.

المرضــي وطــرق البحــث: وتشــتمل الدراســة علــي ٦٠ مريضــاً (١٢٠ عــين) تــم تقسيمهم الــي مجمــوعتين: المجموعــة الاولــي تحتــوى علــي (80عــين) مــن مرضــي الســكر والــذي يعــانون مــن نقــص ترويــة المقولــة الســكري والمجموعــة الثانيــة تحتــوي علــي (40 عــين) مــن مرضــي الســكر وهــم لايعــانون مــن نقــص ترويــة المقولــة الســكري وتــم التقســيم المبــدئي عــن طريــق الفحــص الإكلينيكــي والفحــص باســتخدام مــادة الفلوريســين, وقــد تــم أخــذ التــاريخ المرضــي الكامــل لجميــع المرضــي مــع عمــل جميــع الفحوصات الرمدية لهم.

نتــائج البحــث: المقارنــة بــين المجمــوعتين طبقــا لأفضــل رؤيــة يصــل اليهــا مريــض نقــص ترويــة المقولــة الســكري باســتخدام النظــارة (0.36 ± 0.47) وهيــا أقــل مقارنــة بــين المرضــي الــذين لايعــانون مــن نقــص ترويــة المقولــة الســكري (0.23 ± 0.58) كمــا بينــت علاقــة بــين زيــادة مــدة الإصــابة بمــرض الســكر, تــدهور نســبة الســكر التراكمــي بحــدوث نقــص الترويــة المقــولي الســكري. وأظهــرت هــذه الدراســة علاقــة بــين درجــة تفــاقم الإعــتلال الشــبكي الســكري وزيــادة حــدوث نقــص ترويــة المقولــة

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السكري. وقد أوضحت هذه الدراسة المقارنة بين إستخدام جهاز التصوير الأوعية الدموية بمادة الفلوريسين وجهاز التصوير البصري المقطعي المترابط للأوعية الدموية توافق متوسط بين الجهازين حيث إن قياس مساحة وطول المنطقة الخالية من الأوعية الدموية باستخدام الجهازين قد أوضح إختلافا غير ملاحظ إحصائيا.

الإستنتاج: جهاز التصوير البصري المقطعي المترابط للأوعية الدموية ويسهُل إستخدامه في قياس التغيرات التي تحدث في مقولة الإبصار وذلك بدون حقن. كما وجد توافق متوسط بين إستخدام الجهازين ولكن, وبسبب المضاعفات الناتجه عن إستخدام الصبغة فإنه ليس الجهاز المفضل خاصة في تشخيص من الإعتلال الشبكي السكري.

الكلمات الدالة: منطقة الأوعية الدموية النقرة, نقص الترويـة البقعية السكري, تصوير الأوعية بالتصوير المقطعي البصري.