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Assessment of Ocular Coherence Tomography Angiography Changes in Center and Non-center Involved Diabetic Macular Edema

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Abstract:

Background: Diabetes mellitus (DM) is one of the world's fastest-growing chronic illnesses. **Purpose:** To assess changes in center and non-center involved diabetic macular edema utilizing ocular coherence tomography angiography**. Patients and Methods:** This research was done on 21 diabetic cases (38 eyes), 15 females and 6 males with average age (57 ± 9) years old and mean duration of diabetes is 10 years. Cases with center involved diabetic macular edema (DME) are 27 cases while cases with non-center involved DME are 11 cases. Cases include 20 eyes with mild Nonproliferative Diabetic Retinopathy (NPDR), six eyes with moderate NPDR, 7 eyes with severe NPDR, and five eyes with Proliferative Diabetic Retinopathy PDR. The normality of distribution for the examined factors have been examined utilizing Shapiro test assuming normality at *P*-value above 0.05. Patients underwent Optical coherence tomography angiography (OCTA) exam and the results are studied using The Pearson correlation coefficient. **Results:** SVD was statistically significant higher in non-center involved DME (*p*-value below 0.05). There is greatly significant positive association between superficial and deep vessel density. There is no statistically significant relationship between type of diabetic macular edema with Age, sex, duration of D.M. or FAZ. **Conclusion:** Superficial Vessel Density **(**SVD) is higher in non-center involved DME than in center involved DME, while there is no statistical relation between type of DME and age, sex, duration of D.M. or FAZ.

Keywords: DME; SVD; DVD; Correlation coefficient.

Introduction:

Diabetes mellitus is one of the world's fastest-growing chronic illnesses. It is predicted that the number of persons had diabetes mellitus will elevate to 642 million by 2040 [(1).]

Diabetic retinopathy (DR) is a prevalent and particular micro vascular complication of diabetes mellitus that result in advanced visual impairment and even blindness. The occurrence of diabetic retinopathy is reported to be between thirty percent and forty-five percent in individuals with diabetes mellitus, and 0ne in ten has sight-threatening diabetic retinopathy. The diagnosis of diabetic retinopathy is depending on clinical fundoscopic investigation. It is divided into 2 categories: non-proliferative diabetic retinopathy, and proliferative diabetic retinopathy that is related to progress of neovascularization (NV) [(2)].

Diabetic macular edema is the primary etiology of diabetes-associated vision loss. Although it may be a complication of any stage of diabetic retinopathy, it more often influences cases in more progressed stages. DME occurs 2^{ry} to an elevation in the accessibility of retinal vessels 2^{ry} to endothelial damage, an elevation in the levels of vascular endothelial growth factor (VEGF) and an increase in the intraocular amount of inflammatory cytokines [(3)].

There are a rising number of imaging modalities that may be utilized in the diagnosis, screening, assessment, and management of diabetic retinopathy [(4)].

Optical coherence tomography angiography (OCTA), can work as a potential quick, non-invasive image modality as an assistant for evaluating micro vascular alterations in capillary level. It is implemented through obtaining recurrent optical coherence tomography B-scans at the same site to identify alterations in reflectant signals from the mobility of RBCs through blood vessels in the volumetric optical coherence tomography scans. It permits three dimensional & depth-resolved visualization of the retinal microvasculature through choosing various en face slabs from various retinal layers without intravenous dye injection. Microvascular alterations in the intermediate, deep, and superficial capillary plexuses may be assessed separately [(5)].

Regardless optical coherence tomography can demonstrate structural alterations and assist in observing cystic spaces in DME, optical coherence tomography angiography has reduced reliability in visualizing the capillary networks in eyes with DME [(6)].

This is due to the collected fluid can influence the segmentation abilities of optical coherence tomography, and in turn, the incorrect segmentation can result in a false interpretation of optical coherence tomography angiography images. Furthermore, diabetic macular edema has an inverse association with optical coherence tomography angiography signal intensity as the fluid weakens the reflected signal from the deep layer. It is also stated that the rate of flow voiding doesn't accurately correspond with the cystic space because the fluid can compress the vessels, consequently reducing flow under the detection restrictions of the optical coherence tomography angiography algorithms [(7)].

To overcome the segmentation concerns, manual adjustment of the deep capillary plexus or superficial capillary plexus boundary in the eyes with severe diabetic macular edema is done. It is verified that cases with DME show significant damage in the deep capillary plexus rather than superficial capillary plexus. In addition, it is well known that compared with diabetic macular edema eyes that reacted well to anti- vascular endothelial growth factor

therapy, poor responders exhibited extensive damage to the integrity of the deep capillary plexus, but not the superficial capillary plexus. This result shown that the deep capillary plexus could be crucial for the management response to anti- vascular endothelial growth factor management, proposing that the degree of deep capillary plexus loss evaluated through optical coherence tomography angiography might be a beneficial biomarker for expecting the management response of DME [(6)].

*__Patient and methods__:

This is a cross sectional research to assess ocular coherence tomography angiography changes in center and non-center involved diabetic macular edema. This study was done on 21 diabetic patients (38 eyes), 15 females and 6 males with average age (57 ± 9) years old and mean duration of diabetes is 10 years. Cases with center involved DME are 27 cases while cases with non-center involved DME are 11 cases. Cases include 20 eyes with mild NPDR, six eyes with moderate NPDR, 7 eyes with severe NPDR, and 5 eyes with PDR. The rest of clinical and demographic data are listed in (**table 1).** Cases came to the ophthalmology department, Benha university hospital, Benha, Egypt during the period between June and December 2023. All participants in this study signed their written consent to participate. This research has been permitted through ethical committee of Faculty of Medicine- Benha University {M.S.347.2023}.

The study has been done by using the OPTOVue OCT angiography (Avanti scanner, USA). This instrument can perform 70.000 A- scan/second utilizing a light source centered on 840 nm and a bandwidth of 50 nm. The tissue resolution is five millimeters axially and width of the beam is fifteen millimeters. It can achieve several recurrent B-scans at the same retinal site and the attained structural information are compared to observe signal alterations owing to the flowing erythrocytes (movement contrast). This allows us to visualize the fundus and assess both FAZ and vessel density without dye injection but only by detection of the erythrocytes motion.

__*Sample size:__

Utilizing G power, Version 3.1.9.4, [(8)] for size of the sample calculation, depending on information from [(9)] which assess, utilizing optical coherence tomography angiography, the effect of intravitreal dexamethasone (DEX) implant on quantitative vascular measurements in cases had diabetic macular edema. The effect size in this research was 0.4considered to be (large) utilizing Cohen's (1988) criteria. With a significance criterion of $\alpha = .05$ and power = .80. The minimum size of the sample needed with this effect size is N = 38 for (Anova: difference between many independent groups). **As showing (figure, 1)**

__Settings:__ The study will include patients attending to banha university hospital outpatient clinic diagnosed with diabetic retinopathy.

__Inclusion criteria:__ Age group: 30-70 years, previously diagnosed with DME and eyes with visual acuity more than 6/60.

__Exclusion criteria:__ History of macular photocoagulation, history of vitreoretinal operation, the existence of significant epiretinal membrane or vitreomacular traction, concurrent ocular illnesses like uveitis, optic neuropathy or glaucoma, Existence of macular edema 2^{ry} to other etiologies compared to diabetic retinopathy (e.g. retinal vascular occlusion), Presence of any dense media opacity and Uncooperative patients.

An informed consent has been taken from all cases who participated in this research and the confidentiality of the participants affirmed for the study. The ethical committee of Benha faculty of medicine approved this study (No). Every patient who fulfilled the inclusion criteria underwent all the following procedures:

- Detailed history taking including: Name, Age, Sex, Present history and past history of ocular and systemic diseases.
- Ocular examination including: Uncorrected and best-corrected visual acuity, anterior segment slit lamp investigation, Pupil investigation, Intra-ocular pressure measurement. And Fundus examination.
- OCT angiography imaging using the Avanti RTVue XR System (OPTOVUE) for:
- Macular scans of 6mm × 6mm centered at the fovea collecting the following measurements (Foveal avascular zone, deep vessel density and superficial vessel density).
- Peripapillary scans of 4.5 millimeters × 4.5 millimeters centered at the disc.
- For each case, the evaluation of DM control using HbA1c.

***Data management and statistical analysis: -**

- The gathered information has been documented followed by showed, and statistically examined through computer utilizing Statistical Package for the Social Sciences (SPSS) 25.0 for windows (SPSS Inc., Chicago, IL, USA) as follow:
- Coding and editing.
- Information entry in computer.
- Information has been summarized and presented in tables and graph.
- The normality of distribution for the examined factors were examined utilizing Shapiro test assuming normality at *P*-value above 0.05.
- The gathered information has been summarized in relation to median and Inter Quartile Range (IQR) as appropriate for nonparametric information and mean ± Standard Deviation (SD) as proper for parametric information, Frequency, and distribution for qualitative information.
- The statistical significance of the variance between the studied groups has been assessed utilizing Student t test as appropriate for parametric data.
- Spearman correlation has been performed.
- All tests were 2 sided. The accepted level of significance in this work was (*p*-value below 0.05), p not more than 0.001 has been considered highly statistically Significant (HS), and *p*-value above 0.05 has been considered non-statistically Significant (NS).

Results:

According to differences of the studied patients' superficial vessel density according to their demographic data and history of present illness, we found that: Mean of SVD in male group equals 44.71 while SD equals 6.70, Mean of SVD in patients < 60-year-old equals 47.19 While SD equals 3.65, An insignificant variance has been observed in superficial vessel density values in studied cases in relation to age, sex, D.M treatment, the rest of clinical and demographic data are listed in (**table 2)**.

*According to differences of the studied patients' superficial vessel density according to type of DME we found that: Mean of SVD in non-center involved DME equals 48.59 While SD equals 3.24, Mean of SVD in center involved DME equals

45.72 While SD equals 3.85**, SVD was statistically significant higher in non-center involved DME (p value < 0.05) table 3.**

*According to differences of the studied patients' superficial vessel density according to type of DME we found that: Mean of SVD in non-center involved DME equals 48.59 While SD equals 3.24, Mean of SVD in center involved DME equals 45.72 While SD equals 3.85**, SVD was statistically significant higher in non-center involved DME (*p* value < 0.05)** in **(table, 3).**

*According to differences of the studied patients' deep vessel density according to type of DME, we found that: There was no statistically significant relation between the DVD and the type of DME of the studied group, There was no statistically significant relation between the DVD and the side of the affected eye of the studied group, The rest of clinical and demographic data are listed in **(table, 3).**

*According to Spearman correlation between the studied patients' superficial vessel density and different variables, we found that: **There is highly significant positive correlation between superficial and deep vessel density,** the rest of clinical and demographic data are listed in **(table, 4).**

*there is no statistically significant relationship between type of diabetic macular edema with Age, sex, duration of D.M. or FAZ as described in **(table, 4).**

Table 1. Demographic data and history of present illness of the studied patients

Variable N.=21		**N.**	**%**
Age (years)	Mean &SD	57.3	9.69
	<60	12	57.2%
	≥60	9	42.8%
Sex	Male	6	28.6%
	Female	15	71.4%
Hypertension	Yes	14	66.7%
	No	7	33.3%
DM treatment	Oral	11	52.4%
	Insulin	10	47.6%
Type of DME	Center involved	27	71.05%
	Non center involved	11	28.9%
		Mean or Median	**SD or IQR**
DM duration (years)		10	10.16
Hypertension duration(years)		10.7	8.80

SD: standard deviation; **IQR:** Inter Quartile range

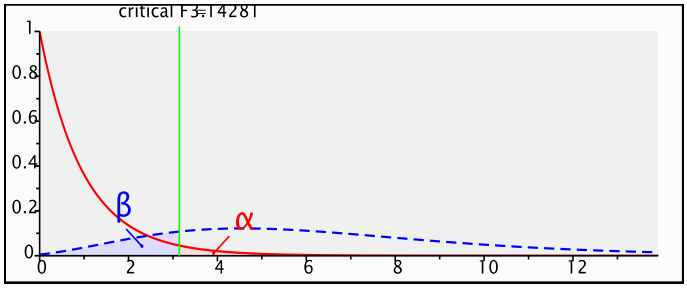

Figure (1): Sample size determination using the G*Power software

Table 2: Differences in Superficial and Deep Vessel Density and Diabetic Macular Edema Involvement Based on Demographic Data and History of Present Illness.

Variable N.=21		**Superficial vessel density (%)Mean SD**		**Student t-test**	***P* value**
Age groups	<60	47.19	3.65	.664	.515
	≥60	45.81	5.86		
Sex	Male	44.71	6.70	1.186	.250
	Female	47.35	3.56		
Hypertension	Yes	47.55	3.60	.948	.356
	No	45.30	6.780		
DM treatment	Oral	46.50	4.56	.462	.651
	Insulin	45.31	5.89		
Variable N.=21		**Deep vessel density (%) Mean SD**		**Student t-test**	**P value**
Age groups	<60	44.81	5.68	.183	.857
	≥60	44.33	6.36		
Sex	Male	41.13	4.20	1.824	.084
	Female	46.00	5.92		
Hypertension	Yes	44.15	4.27	1.661	.115
	No	48.78	7.886		
DM treatment	Oral	43.84	5.025	.210	.836
	Insulin	44.46	7.169		
Variable N.=21		**Center involved DME**	**Non center involved DME**	**Student t-test**	**P value**
Age groups	<60	8	4	.269	.604
		66.7%	33.3%		
	≥60	5	4		
		55.6%	44.4%		
Sex	Male	3	3	.505	.477
		50.0%	50.0%		
	Female	10	5		
		66.7%	33.3%		
DM duration (Median (IQR))		10.0 ،(8.5-16)	11 (10-19)	.522	.601
FAZ (Median (IQR))		.268 (.184 - .302)	.317 (.174-.371)	1.08	.277

Table 3: Differences in Superficial and Deep Vessel Density Based on the Type of Diabetic Macular Edema

Variable N.=21		**Superficial vessel density (%) Mean**	**SD**	**Student t-test**	**P value**
Type of ocular edema	Non center involved DME	48.59	3.24	2.170	**.037 (S)**
	Center involved DME	45.72	3.85		
Variable N.=21		**Deep vessel density (%) Mean**	**SD**	**Student t-test**	**P value**
Type of ocular edema	Non center edema	45.3000	6.66798	.035	.972
	Center edema	45.2333	4.74658		

S: Significant: p <.05; SD: standard deviation

Table 4: Spearman correlation between the studied patients' superficial vessel density and different variables.

Superficial vessel density (%)	**Spearman Correlation Coefficient**	***P* value**
Age (years)	.044	.849
Best corrected visual acuity	-.318	.052
FAZ(mm^2)	-.135	.421
RPC density (%)	.087	.604
Peripapillary RNFL thickness (µm)	.205	.217
Deep vessel density (%)	.463	**.003 (HS)**
DM duration (years)	.219	.341
Hypertension duration(years)	-.029	.922

HS: Significant: p<.01

Discussion:

In this research, we assessed the changes on the foveal avascular zone and the vessels density in diabetic cases with center and non-center involved diabetic macular edema through using optical coherence tomography angiography. Moreover, we evaluated these changes according to variable factors such as patients' sex, age, duration of the disease. This study was performed on 38 eyes of 21 diabetic cases, 27 eyes with center involved diabetic macular edema and 11 eyes with non-center included diabetic macular edema, scanned using the OptoVue OCT angiography. In our study, the mean of the age of the patients was 57.3±9.69 while the mean of the duration of D.M. was 10±10.16 years.

In our study we found that, the mean of FAZ, SVD, and DVD are 0.2745±0.085, 46.5±3.87 and 45.2±5.27 respectively. A greatly significant positive association has been observed among superficial and deep vessel density (p-value below 0.005). According to type of diabetic macular edema and its relation to other variables we found that, superficial vessel density was statistically significant higher in non-center involved DME (p-value below 0.05). Otherwise, a statistically insignificant relationship has been observed between type of

diabetic macular edema with Age, sex, duration of D.M. and FAZ.

Mastropasqua et al.,2017 [10] have done a study designed to calculate reproducibility of foveal avascular zone region measurement, include sixty eyes of sixty diabetic cases (thirty-five men and twenty-five women; mean age 65.6±5.7 year, range 54-72 year) have been enrolled for the research. Diabetic cases have been graded regarding the Clinical Diabetic Retinopathy Scale. There were fifteen eyes without any sign of diabetic retinopathy, fifteen eyes with mild NPDR, fifteen eyes with severe or moderate NPDR, fifteen eyes with PDR. A control group of twenty healthy age-matched cases (eight women and twelve men; mean age 64.5±7.6 year, range 54-73 year) has been chosen for statistical comparisons. Mastropasqua et al., [10] reported an enlargement of the FAZ of diabetic cases with various stages of diabetic retinopathy (60 eyes) and decrease in the vessel density in both SVD and DVD. Mean foveal avascular zone region was 0.285±0.128 millimeters square in the healthy group (20 subjects) and 0.235±0.055 millimeters square in diabetic cases without diabetic retinopathy. For the diabetic retinopathy patients, FAZ area showed more enlargement especially with severe NPDR and PDR (p-value below 0.001). Furthermore, the mean of SVD in the normal group was 32.27±8.38 and 26.92±3.94 in cases with non-proliferative diabetic retinopathy and 21.95±6.80 in proliferative diabetic retinopathy cases (p-value equal to 0.006). On the other hand, the mean of DVD in the normal group was 49.54±11.01 and 44.97±8.10 in mild NPDR. The mean of DVD was more decreasing in advanced DR stages. They concluded that, diabetic retinopathy led to an enlargement of the FAZ in different measure regarding the stage of diabetic retinopathy. In addition, there is a decrease in both SVD and DVD and the rate of decrease depends on the stage of DR. Our results are consistent with Mastropasqua et al. [10] results regarding mean of DVD but differs regarding mean of FAZ and SVD. The reason may be that our study was done on a lesser scale; most of our patients were in stage of mild NPDR with less duration of disease than Mastropasqua et al., [10] study. A fresh research, that involved cases with anti- vascular endothelial growth factor and PRP management, showed that the reduced deep capillary plexus vessel density was mainly present in early diabetic retinopathy, while in eyes with progressed DR, the change of vessel density was chiefly observed in the superficial layer. A combined model of superficial capillary plexus foveal avascular zone area, deep capillary plexus vessel density and a circularity has been utilized to differentiate eyes with various severity of diabetic retinopathy with a great ROC value (Ashraf M. et al., 2020) [11]. In our research, we observed that, superficial vessel density was statistically significant higher in non-center involved DME (p value< 0.05). Unfortunately, we could not found any studies in the literature, which illustrate the relation between type of DME and different measurements of OCTA.

Conclusion:

Our statistical analysis showed that superficial vessel density was significant higher in non-center involved DME (p-value below 0.05), a greatly significant positive association has been observed among superficial and deep vessel density (p value< 0.005). In addition, our results are consistent with the convention that the reduced deep capillary plexus vessel density was mainly present in early diabetic retinopathy. In the meantime, our statistical

analysis showed that there is no relation between type of macular edema and age, sex, duration of D.M. or FAZ.

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