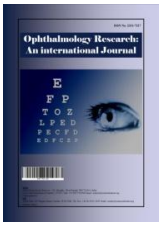

Ophthalmology Research: An International Journal

14(4): 1-7, 2021; Article no.OR.71750
ISSN: 2321-7227

Association between Diabetic Macular Edema and Capillary Non Perfusion; An Optical Coherence Tomography Angiography Study

Mostafa A. Waly[1*], Hammouda Hamdi Ghoraba[2], Mohamed Hosni El-Bradey[2] and Mostafa Abd El Latif Abo El Einen[2]

[1]Department of Ophthalmology, Faculty of Medicine, Kafr-Elsheikh University, Kafr-Elsheikh, Egypt.
[2]Department of Ophthalmology, Faculty of Medicine, Tanta University, Tanta, Egypt.

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 HG and ME managed the analyses of the study. Author HE managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/OR/2021/v14i430197
Editor(s):
(1) Dr. Tatsuya Mimura, Tokyo Women's Medical University, Japan.
Reviewers:
(1) Uma Narayanamurthy, Mahatma Gandhi Medical College and Research Institute, India.
(2) Hayder Abdul-Amir Makki Al-Hindy, University of Babylon, Iraq.
Complete Peer review History: https://www.sdiarticle4.com/review-history/71750

Original Research Article

Received 25 May 2021
Accepted 31 July 2021
Published 02 August 2021

ABSTRACT

Aims: The aim is to use of OCTA to describe the retinal structural damages observed in DME and the relationship between the edema and the capillary non perfusion and to quantify VD and the FAZ area.
Study Design: prospective, cross sectional, observational study
Place and Duration of Study: University Hospitals in the period between March 2018 to March 2020.
Methodology: OCTA images were obtained using the AngioVue (Optovue Inc., CA, USA). For quantitative analysis of the VD and the FAZ area with the help of the manufacturer's automated software.
Results: The study included included 160 eyes of 135 diabetic patients, 61 (45%) females and 74 (55%) males and 20 eyes from 20 age-matched healthy individuals (12 males and 8 females). A significantly worse visual acuity was found in diabetic eyes with CME (mean ($\overline{x}$) ± SD LogMAR 0.61

**Corresponding author: E-mail: mostwaly@gmail.com;*

± 0.33), than NPDR eyes without macular edema (0.25 ± 0.19), and controls (Mean ± SD LogMAR 0.02 ± 0.05),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 and non-flow area) aided in the objective quantification of macular perfusion and accurate measurement of the FAZ area in diabetic eyes with and without macular edema. Both parameters were significantly correlated with visual function in treatment-naive diabetic eyes with macular edema.

Keywords: FAZ area; vessel density; cystoid macular edema; optical coherence tomography angiography.

ABBREVIATIONS

FAZ : foveal avascular zone
DCP : deep capillary plexus
SCP : superficial capillary plexus
VD : vessel density, NPDR: non poliferative diabetic retinopath
VEGF : vascular endothelial growth facto
DR : diabetic retinopathy

1. 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 840 nm, and the second one is the swept-source OCT (SS-OCT), with a longer wavelength approximately 1050 nm.

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].

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 describe the retinal structural damages observed in DME and the relationship between DME and the capillary non perfusion and to quantify vascular capillary density and the foveal avascular zone area.

2. MATERIALS AND METHODS

This cross sectional, observational study was conducted on 160 eyes from 135 diabetic patients and 20 eyes from 20 healthy age matched individuals in the period from March 2018 to March 2020.

The study was performed according to principles of the Declaration of Helsinki. All subjects

provided written informed consent to get involved in this study.

2.1 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).
5. Group V : 20 healthy eyes of age matched subjects as control group (Control Group)

2.2 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.

2.3 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 AngioAnalytics, an automatic quantification tool that measured flow area, non flow area, and flow area density [10]. AngioAnalytics evaluated and then reported the relative density of flow as a percentage of the total evaluated area [11]. With AngioAnalytics 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 (mm2) [14].

3. RESULTS

Statistical analyses were performed using SPSS Statistics version 20 (IBM, Armonk, NY). Chi-square test ($\chi 2$) 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 and 20 eyes from 20 age-matched healthy individuals (12 males and 8 females).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.

A significantly worse visual acuity was found in diabetic eyes with cystoids macular edema (mean ($\bar{x}$) ± SD LogMAR 0.61 ± 0.33), than NPDR eyes without macular edema (0.25 ± 0.19), and controls (Mean ± SD LogMAR 0.02 ± 0.05).

The control group and 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) and significantly lower than the control group (P <0.001). The SCP VD of the spongy group was not significantly different from the CME group (P = 0.175), but was significantly lower than the control group (P <0.001) (Table 1).

The control group and 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).The CME group had significantly larger Superficial Capillary Plexus (SCP) fovea FAZ area size than all the other groups (P <0.001 for any). Among all the other groups, there was no significant difference regarding the FAZ,The FAZ area was significantly larger in diabetic eyes without edema than the control eyes, at the level of DCP (P <0.001 for any). The CME group had significantly larger DCP foveal avascular zone size than the NO DR and the NPDR (P =0.032 and P =0.05 respectively).

4. DISCUSSION

We conducted a cross sectional study to evaluate the role of OCTA in describing the retinal structural damages observed in diabetic macular edema and the relationship between diabetic macular edema and the capillary non perfusion. Also we followed 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 3 mm Angio Retina scans (P = < 0.001) when compared to controls.

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

Table 1. Superficial capillary plexus vessel density values % in different grades of diabetic retinopathy

Groups	SCP VD (%) $\bar{x} \pm SD$	Median	Kk	P value	Post Hoc
No DR (Group I)	51.78 42.32	51.98	118.66	<0.001	P1 <0.001 P2 <0.001
NPDR (Group II)	42.31 +3.78	43.10			P3 <0.001 P4 0.365
Spongy (Group III	40.28 + 4.13	40.65			P5 0.22 P6 <0.001
CME (Group IV)	37.68 + 5.47	37.60			P7 <0.001 P8 0.175
Control (Group V)	53.07 + 3.57	52.62			P9 <0.001 P10 <0.001

P1: NO DR Vs NPDR, P2: No DR Vs Spongy, P3: No DR Vs CME, P4: No DR Vs Control, P5: NPDR vs Spongy, P6: NPDR Vs CME, P7: NPDR vs Control, P8: Spongy Vs CME, P9: Spongy Vs Control, P10: CME Vs Control

Table 2. Deep capillary plexus vessel density values % in different grades of diabetic retinopathy

Groups	DCP VD (%) $\bar{x} \pm SD$	Median	k	P value	Post Hoc
No DR (Group I)	58.93 £1.77	59.46	127.71	<0.001	P1 <0.001 P2 <0.001
NPDR (Group II	44.73 + 4.25	44.27			P3 <0.001 P4 0.395
Spongy (Group III	43.17+5.71	41.30			P5 0.846 P6 0.003
CME (Group IV)	40.95 + 4.70	40.45			P7 <0.001 P8 0.473
Control (Group V)	57.59 + 4.23	56.87			P9 <0.001 P10 <0.001

P1: NO DR Vs NPDR, P2: No DR Vs Spongy, P3: No DR Vs CME, P4: No DR Vs Control, P5: NPDR vs Spongy, P6: NPDR Vs CME, P7: NPDR vs Control, P8: Spongy Vs CME, P9: Spongy Vs Control, P10: CME Vs Control

the superficial (P = 0.365) and deep (P = 0.395) capillary plexuses in 3 x 3 mm Angio Retina scans when compared to controls. 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].

Howerver 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.

In the present study, diabetic eyes with cystoid macular edema presented with significantly reduced visual acuity when compared to diabetic eyes with spongy edema and eyes without DME including No DR and NPDR eyes as well as control eyes (P= < 0.001 for any. Samara et al. Used the 3 x 3 mm octa macular scan to study macular vascular density at both scp and dcp in diabetic (npdr and pdr) patients and to quantify diabetic macular ischemia. In all eyes, they found a statistically significant negative correlation between the logmar visual acuity and the vascular density in both the superficial ($r = -0.52$; $p < 0.001$) and deep ($r = -0.50$; $p < 0.001$) networks. A positive correlation was found between logmar visual acuity and faz area in both the superficial ($r = 0.29$; $p < 0.01$) and deep ($r = 0.48$; $p < 0.001$) networks. The authors concluded that using automated quantitative algorithms allow for objective assessment of retinal vascular changes in eyes with dr that are correlated to visual acuity [18].

In the present study, FAZ area was measured using a non-flow AngioAnalytics tool. In agreement with the previously mentioned studies, we observed a progressive enlargement of the FAZ area as the DR progress. We found that in diabetic eyes with CME had significantly larger FAZ area size at the SCP level when compared to diabetic eyes without DME (no DR or NPDR eyes also when compared with the spongy edema eyes with (P = < 0.001) for any. Also CME group showed significantly enlarged FAZ area of the DCP level when compared to the no edema group (No DR and NPDR) (P = 0.032 and P = 0.05; respectively, also when compared to the control group (P = < 0.001). A previous report by Balaratnasingam et al. observed a significant correlation between FAZ area and VA in diabetic eyes with macular edema [19].

5. 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 OCTA parameters as vessel density (VD) and foveal avascular zone (FAZ) area as a potential biomarker for evaluating the risk of developing diabetic retinopathy in patients with diabetes without DR. Also the development of full-field OCTA fundus camera should be able to strengthen early diagnosis of DR and detection of pre clinical findings on a wider scale also to use also 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.

CONSENT

All patients were informed of the nature of the study and gave written informed consent before enrollment.

ETHICAL APPROVAL

The study was approved by the ethics committee of university.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Prog Retin Eye Res. 2018;64:1-55.
2. Borrelli E, Sarraf D, Freund KB, Sadda SR. OCT angiography and evaluation of the choroid and choroidal vascular disorders. Prog Retin Eye Res. 2018;67:30-55.
3. Tan PEZ, Yu PK, Balaratnasingam C, et al. Quantitative confocal imaging of the retinal microvasculature in the human retina. Invest Ophthalmol Vis Sci. 2012;53(9):5728-5736.
4. Jia Y, Tan O, Tokayer J, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Opt Express. 2012;20(4):4710-4725.
5. Zhang M, Hwang TS, Campbell JP, et al. Projection-resolved optical coherence tomographic angiography. Biomed Opt Express. 2016;7(3):816-828.
6. Spaide RF, Klancnik JMJ, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol. 2015;133(1):45-50.
7. De Carlo TE, Chin AT, Joseph T. Distinguishing diabetic macular edema from capillary nonperfusion using optical coherence tomography angiography. Ophthalmic Surg Lasers Imaging Retina 2016;47:108–114.
8. De Carlo TE, Chin AT, Bonini Filho MA, et al. Detection of microvascular changes in eyes of patients with diabetes but not clinical diabetic retinopathy using optical coherence tomography angiography. Retina. 2015;35:2229–2235.
9. Arevalo JF, Lasave AF, Arias JD, et al. Clinical applications of optical coherence tomography in the posterior pole: The 2011 José Manuel Espino Lecture - Part II. Clinical ophthalmology. 2013;7:2181–2206.
10. Spaide RF, Fujimoto JG, Waheed NK, et al. Optical coherence tomography angiography. Prog Retin Eye Res. 2018;64:1-55.
11. Kashani AH, Chen CL, Gahm JK, et al. Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. Progress in retinal and eye research, 2017;60:66–100.

12. Hagag Ahmed M, Gao Simon S, Jia Yali, et al. Optical coherence tomography angiography: Technical principles and clinical applications in ophthalmology. Taiwan journal of ophthalmology. 2017;115-129.
13. Hogan MJ, Alvarado JA, Weddell JE. Histology of the human eye. Philadelphia: Saunders. 1971;5,8,9,11.
14. Hendrickson AE, Youdelis C. The morphological development of the human fovea. Ophthalmology. 1984;91:603–612.
15. Mathilde M, Sikorav A, Semoun O, et al. Parafoveal OCT angiography features in diabetic patients without clinical diabetic retinopathy: A qualitative and quantitative analysis. Journal of ophthalmology. 2017;8676091.
16. Mané V, Dupas B, Gaudric A, et al. Correlation between cystoid spaces in chronic diabetic macular edema and capillary nonperfusion detected by optical coherence tomography angiography. Retina. 2016;36(Suppl 1):S102-S110.
17. Ishibazawa A, Nagaoka T, Takahashi A, et al. Optical coherence tomography angiography in diabetic retinopathy: A prospective pilot study. Am J Ophthalmol. 2015;160(1):35-44.e1.
18. Samara WA, Shahlaee A, Adam MK, et al. Quantification of diabetic macular ischemia using optical coherence tomography angiography and its relationship with visual acuity. Ophthalmology. 2017;124(2):235–244.
19. Balaratnasingam C, Inoue M, Ahn S, et al. Visual acuity is correlated with the area of the foveal avascular zone in diabetic retinopathy and retinal vein occlusion. Ophthalmology. 2016;123(11):2352–2367.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/71750