# Diabetic Retinopathy Choroidal Density Maps

*Passant Sayed Saif[1], Ahmed Tamer Sayed Saif[2]*


## ABSTRACT

**Purpose:** Early detection of diabetic retinopathy (DR) is a sight-saving procedure. Fundus fluorescein angiography is one of the leading tools for the early detection of DR, however it is an invasive procedure. OCTA has been nominated as a non-invasive tool for the early detection of DR.

Optical Coherence Tomography(OCT) and Optical Coherence Tomography Angiography (OCTA) for the quantitative assessment of choroidal vascular density map correlated with choroidal thickness in normal individuals and in diabetic patients with and without diabetic retinopathy (DR).

**Patients and Methods:** This study included 64 eyes. The diabetic and control groups were recruited from an internal medicine clinic at Misr University for Science and Technology Hospital and asked to participate in this study. This study was designed as an observational and cross-sectional study in the period from 12/2017 to 12/2019.

**Results:** There was a decrease in choroidal thickness and vascular density in patients with diabetes.

**Conclusion:** Our study suggests that OCTA can identify preclinical DR prior to the manifestation of clinically apparent retinopathy. Our findings highlight the potential role of OCT-A in the monitoring and quantification of choroidal vascular alterations in diabetes.


**Keywords:** Diabetic retinopathy, Optical coherence tomography angiography

## INTRODUCTION

Diabetic retinopathy (DR) is the common leading cause of vision loss, due to macular edema or vitreous hemorrhage.[1]

The greater the duration of diabetes, the greater the risk of developing DR.[2]

Microvascular changes, including capillary remodeling, regression, and decreased density , have been proven to be the cause of DR changes through histopathological and imaging studies.[3]

Non-invasive dye-free OCT angiography (OCTA) facilitates the visualization of both choroidal and retinal vasculature, thus allowing the detection of angiographic features of DR. OCTA can detect areas of non-perfusion in both the superficial and deep plexuses, and microaneurysms have been outlined clearly.[4]

OCTA delineates pathogenic changes in foveal microvascular networks and precisely quantifies the superficial retinal capillary plexus.[5]

OCTA has been used in recent studies on macular vessel density quantification.[6]

Longer wavelength Swept-source -OCT allows deeper and clearer penetration up to the sclero-choroidal interface. In addition, it has a high scanning speed.[7]

## AIM OF THE WORK

Optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) were used to assess choroidal vascular density maps and choroidal thickness in normal individuals and diabetic patients with and without diabetic retinopathy (DR).

1- Fayoum, Ophthalmology, Department of Ophthalmology, Misr University for Science and Technology, Cairo, Egypt

2- Department of Ophthalmology, Faculty of Medicine Fayoum University, Cairo, Egypt

**Received:** 12.04. 2020
**Accepted:** 20.01.2022

*Ret-Vit 2022; 31: 198-205*

DOİ:10.37845/ret.vit.2022.31.35

**Correspondence Adress:**
Ahmed Tamer Saif
Fayoum, Ophthalmology, Department of Ophthalmology, Misr University for Science and Technology, Cairo, Egypt

**Phone:** +20 100 669 9288

**E-mail:** ats00@fayoum.edu.eg

## PATIENTS AND METHODS

This study included 64 eyes. The diabetic and control groups were recruited from an internal medicine clinic at Misr University for Science and Technology Hospital were asked to participate in this study.

This study was designed as an observational and cross-sectional study in the period from 4/2018 to 12/2019.

This study was performed in accordance with the ethical standards of the Declaration of Helsinki in 1964. The study was approved by the local IRB and ophthalmology council.

**Study Population**: **Eyes were divided into 4 groups:**

- ***Group1*** consisted of 16 eyes of normal healthy individuals (control group).
- ***Group 2*** consisted of 16 eyes with a clinical diagnosis of non-diabetic retinopathy,
- ***Group3*** consisted of 16 eyes with a clinical diagnosis of non-proliferative diabetic retinopathy.
- ***Group 4*** consisted of 16 eyes with a clinical diagnosis of proliferative diabetic retinopathy.

**Inclusion criteria:** Both sexes (male and female). Best-corrected visual acuity (BCVA) greater than 0.5 logMAR in the study eye at baseline examination (to ensure proper execution of examination). Age 30-60years old

**The exclusion criteria were as follows:** IOP > 21 mmHg. High Myopia. Media opacity in study eyes

**Study design:** All subjects who participated in the study were asked to sign consent before inclusion. They were then subjected to full medical and family histories. Careful ocular examination and OCT.

**The ocular examination included: a-** Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) using a Snellen chart and converted to log MAR. **b-** Intraocular pressure by Goldman applanation tonometer. **c-** Anterior and posterior segment examination by slit-lamp biomicroscopy. **d-** Dilated fundus examination with both slit-lamp biomicroscopy with a 90D lens and indirect ophthalmoscopy.

Diabetes was defined according to World Health Organization guidelines as fasting plasma glucose≥126 mg/dL or 2-h plasma glucose≥200 mg/dL or being on antidiabetic medication. The controls (group N) had normal glycaemic values.[8,9]

**Prepare the patient:** Insure the fasting of the patients for at least 4 hours prior to photography to avoid fluctuations of choroidal thickness.

**Optical coherence tomography (OCT):** SS-OCT and OCT angiography image acquisition. During the same visit, all study subjects underwent swept-source (SS)-OCT examination (DRI Triton, Topcon, Tokyo, Japan) to acquire choroidal thickness measurements.

A six-line radial pattern scan (1,024 A-scans) centered on the fovea of each eye was obtained. Choroidal thickness was measured as the vertical distance between the posterior edge of the hyper-reflective retinal pigment epithelium and the choroid/sclera junction. The choroidal thickness was manually measured using a built-in caliper in the OCT software (nasal, temporal, superior, and inferior) at 2 mm from the fovea.

OCT Angiography was done: To study the choroidal vessel density map in the (4.5x4.5 mm scan) (measured manually by the operator by applying a superior line at the level of Bruch's membrane and an inferior line that descended according to choroidal thickness at their different quadrants (nasal, temporal, superior , and inferior thickness).

Only OCT good-quality images with a signal strength index >60 were used , and poor quality image scans were excluded. Scans were excluded if they were: (1) weak local signal or poor clarity (2),weak patient fixation leading to unsolved motion artifacts, (3) macular edema, and (4) macular segmentation errors.[10, 11]

### Statistical Analysis

**Data Management and Analysis:** The collected data were revised and tabulated into an Excel 2013 and statistical analysis by SPSS version 24.

**P-value: Level of significance:** P>0.05: non-significant (NS). P<0.05: significant (S). P<0.01: highly significant (HS)

## RESULTS

This study included 4 groups: Group1 (control group of normal individuals), Group2 (diabetic patients with no evidence of diabetic retinopathy changes), Group3 (diabetic patients with non-proliferative diabetic retinopathy), and Group 4 (diabetic patients with proliferative diabetic retinopathy). There were 45.3% female versus 54.7%, ranging in age from 35 to 51 years included in this study.

The mean age of the control group was 38.31%, while the mean age of group II was 42.19%, the non-proliferative DR group was 49.38% and the mean age of the proliferative DR group was 50.75% as shown in Figure 1.

OCT showed a highly significant decrease in choroidal thickness (Figure 2) in the superior, inferior, and nasal

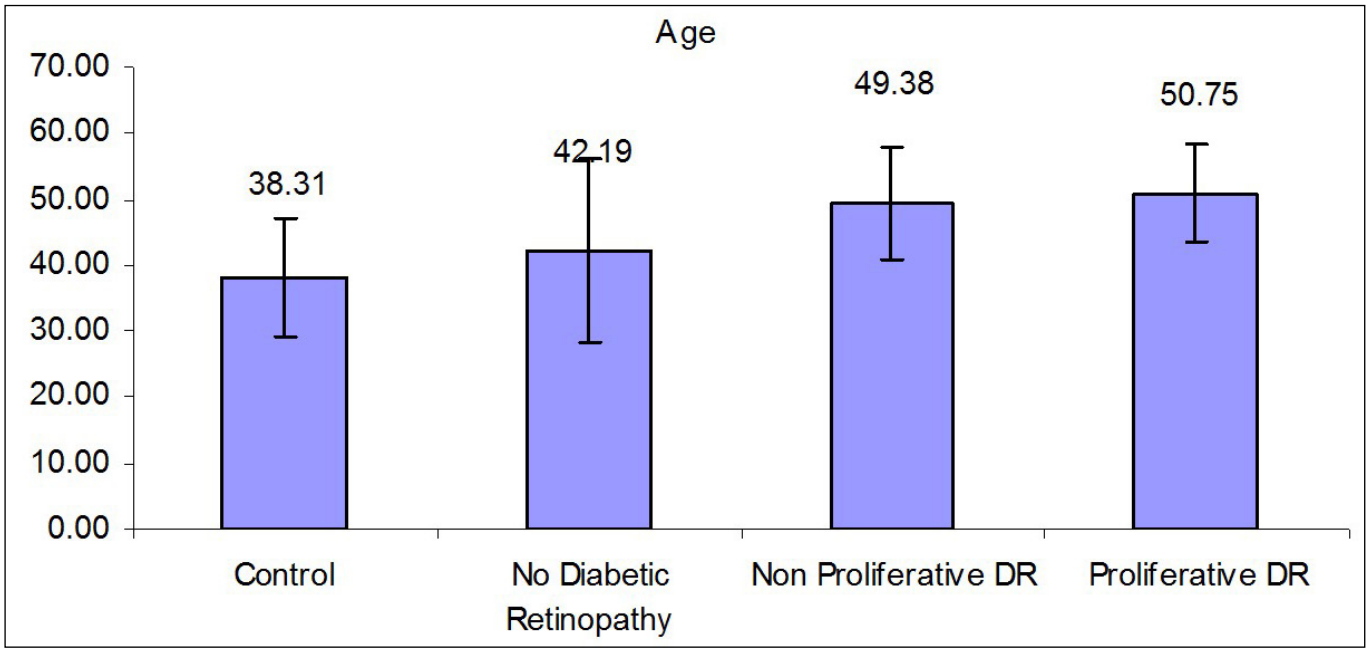


**Figure 1:** *The mean age of different groups.*

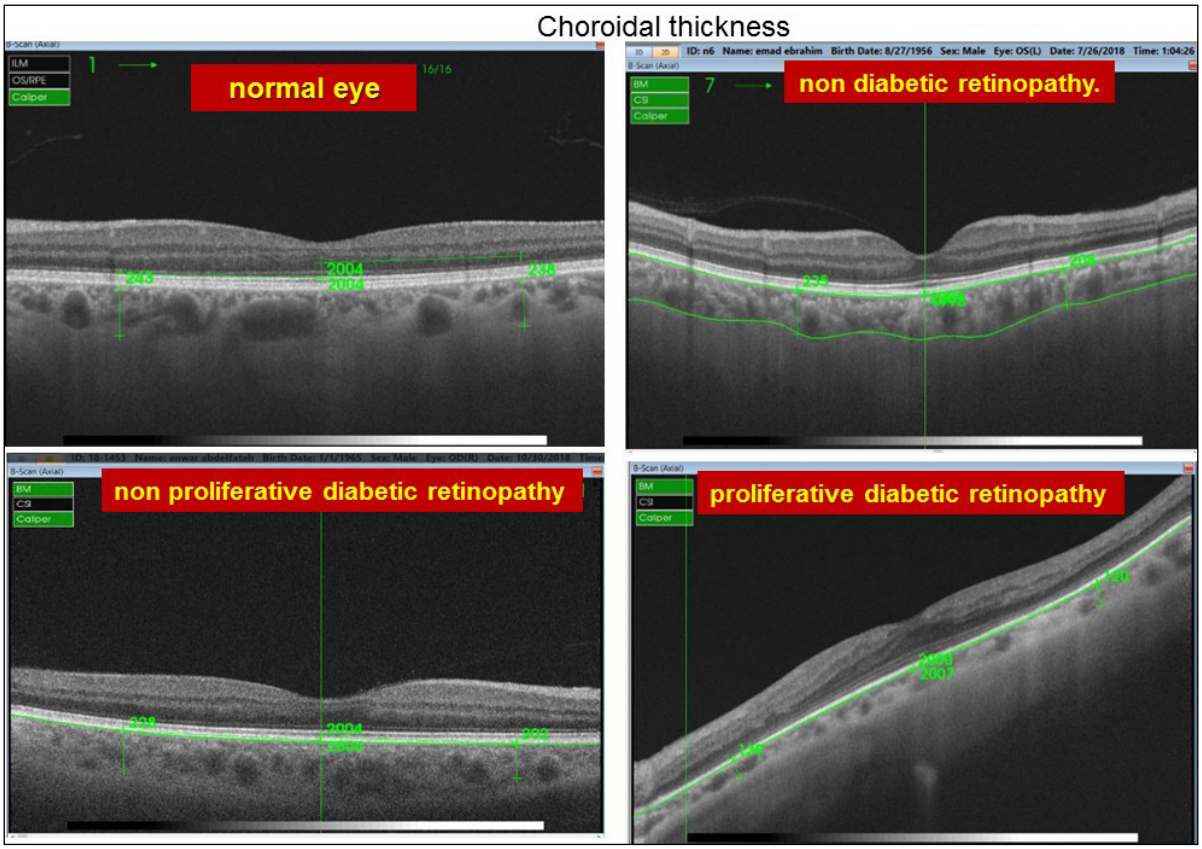


**Figure 2:** *Sample of choroidal thickness in different study groups.*

quadrants and a significant decrease in the temporal choroidal thickness quadrant, as shown in Table 1.

On measuring the choroidal (Figure 3) vessel density maps showed a highly significant decrease in vessel density in all groups compared to the control group, as shown in Table 2.

On comparing the control group to the no evidence of DR group (P1), the choroidal vessel density maps showed a high statistically significant decrease in choroidal vessel density in the inferior, nasal, and temporal vessel density maps and an only statistically significant decrease in the superior quadrant. But there was a highly statistically

**Table 1:** *Comparison Group1 (Normal individuals), Group2 (Diabetic patients without diabetic retinopathy), Group3 (diabetic patients with non-proliferative diabetic retinopathy) and Group 4 (diabetic patients with proliferative diabetic retinopathy) with regard to choroidal thickness (µm).*

| Variables | Diagnosis | | | | | | | | ANOVA | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control (2) | | Non Diabetic Retinopathy (3) | | Non Proliferative DR (1) | | Proliferative DR (4) | | | |
| | Mean | ± SD | Mean | ± SD | Mean | ± SD | Mean | ± SD | | |
| **Superior Choroidal thickness (µm)** | 265.50 | 14.65 | 229.50 | 2.10 | 225.31 | 1.70 | 196.56 | 21.65 | 74.063 | 0.000 |
| **Inferior Choroidal thickness (µm)** | 266.81 | 40.45 | 236.31 | 26.56 | 234.25 | 2.91 | 173.88 | 13.92 | 38.102 | 0.000 |
| **Nasal Choroidal thickness** | 255.00 | 23.74 | 226.31 | 3.34 | 218.88 | 3.34 | 186.56 | 31.21 | 32.447 | 0.000 |
| **Tempo Choroidal thickness (µm)** | 251.06 | 50.10 | 234.13 | 35.92 | 231.88 | 73.54 | 191.31 | 70.43 | 2.901 | 0.042 |

| Post hoc analysis | | | | | | |
|---|---|---|---|---|---|---|
| | P1 | P2 | P3 | P4 | P5 | P6 |
| Sup choroidal thickness | 0.000** | 0.000** | 0.000** | 0.371 | 0.000** | 0.000** |
| Inf choroidal thickness | 0.001** | 0.001** | 0.000** | 0.818 | 0.000** | 0.000** |
| Nasal choroidal thickness | 0.000** | 0.000** | 0.000** | 0.291 | 0.000** | 0.000** |
| Temporal choroidal thickness | 0.424 | 0.366 | 0.006** | 0.915 | 0.046* | 0.059 |

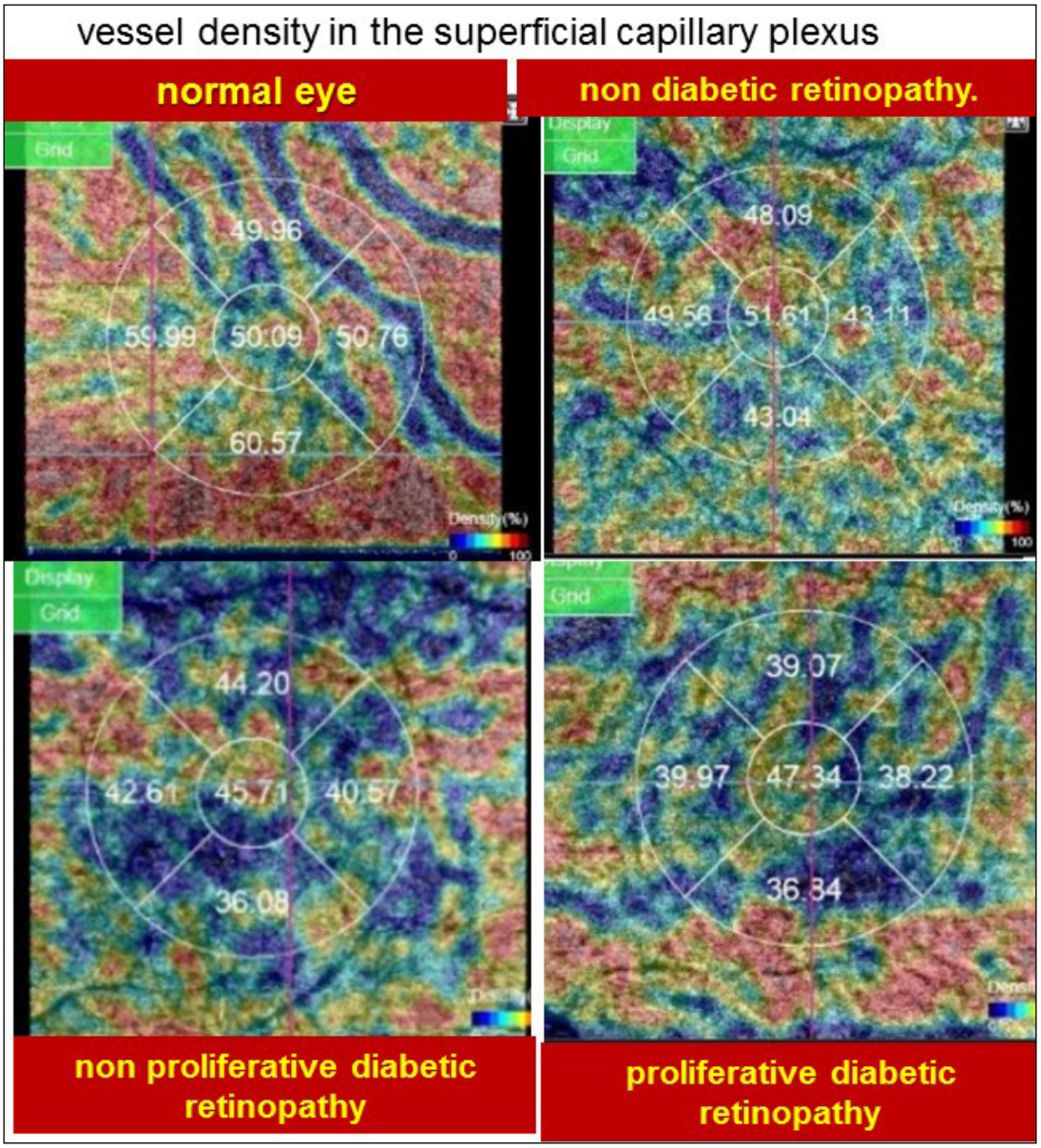


**Figure 3:** *Choroidal density map in the Superficial Capillary plexus of different groups.*

**Table 2:** Comparison Group1 (normal individuals), Group2 (diabetic patients without diabetic retinopathy), Group3 (diabetic patients with non-proliferative diabetic retinopathy) and Group 4 (diabetic patients with proliferative diabetic retinopathy) with regard to choroidal density in Superior, Inferior, Nasal & Temporal quadrants.

| Variables | Diagnosis | | | | | | | | ANOVA | P-value |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control (2) | | Non Diabetic Retinopathy (3) | | Non Proliferative DR (1) | | Proliferative DR (4) | | | |
| | Mean | ± SD | Mean | ± SD | Mean | ± SD | Mean | ± SD | | |
| **Choroidal density sup** | 50.68 | 0.68 | 48.23 | 2.32 | 44.19 | 2.34 | 40.28 | 5.60 | 31.412 | 0.000** |
| **Choroidal inf.** | 53.77 | 4.16 | 49.18 | 0.93 | 46.58 | 0.80 | 38.35 | 4.20 | 73.576 | 0.000** |
| **Choroidal nasal** | 49.46 | 4.57 | 45.73 | 2.41 | 45.04 | 2.04 | 42.31 | 1.08 | 17.334 | 0.000** |
| **Choroidal density** | 57.43 | 5.88 | 47.35 | 1.79 | 44.46 | 2.91 | 40.67 | 3.13 | 58.863 | 0.000** |

significant decrease in all quadrants when the control group was compared to the nonproliferative and proliferative groups (P2and P3), as shown in Table 3.

There was a statistically significant decrease in superficial vessel density in the inferior and temporal quadrants in comparing the non-DR group to the nonproliferative DR group, this comparison also showed no statistically significant decrease in the nasal quadrant but a highly significant decrease in the superior quadrant. (P4).

Table 3 also demonstrates the high significant decrease in the choroidal vessel density map comparing the non-DR group to the proliferative DR group in all quadrants (P5). as well as on comparing the nonproliferative DR group to the proliferative DR group (P6).

There was no statistically significant difference between choroidal thickness and choroidal vessel density, as shown in Table 4.

## DISCUSSION

DR is a progressive microvascular disease. OCTA can advance our understanding of DR by providing high-resolution images of retinal and choroidal microvasculature blood flow and structure [4].

Previous studies[9] have shown that many factors may affect the retina and choroid like diabetes mellitus (DM), especially in the proliferative stage of diabetic retinopathy. There is a metabolic and vascular factor, or yet unknown factors that affect the thickness and morphology of the retina and choroid.

**Table 3:** Post Hoc test displaying multiple comparisons within groups regarding Choroidal density maps in superior, inferior, nasal, and temporal quadrants.

| | Post hoc analysis | | | | | |
|---|---|---|---|---|---|---|
| | P1 | P2 | P3 | P4 | P5 | P6 |
| **Choroidal density sup** | .038* | .000** | .000** | .001** | .000** | .001** |
| **Choroidal inf.** | .000** | .000** | .000** | .018* | .000** | .000** |
| **Choroidal nasal** | .000** | .000** | .000** | .494 | .001** | .008** |
| **Choroidal density** | .000** | .000** | .000** | .033* | .000** | .006** |

P1: Control group vs. non-DR group
P2: Control group vs. non-proliferative DR group
P3: Control group vs. proliferative DR group
P4: Non-DR group vs. non-proliferative DR group
P5: Non-DR group vs. proliferative DR group
P6: Non-proliferative DR group vs. proliferative DR group

**Table 4:** Correlation between choroidal thickness and choroidal density maps in the superior, inferior, nasal, and temporal quadrants.

| | Superior choroidal thickness | | Inferior choroidal thickness | | Nasal choroidal thickness | | Tempochoroidal thickness | |
|---|---|---|---|---|---|---|---|---|
| | r | P-value | r | P-value | R | P-value | r | P-value |
| Choroidal density sup | 0.207 | 0.157 | 0.017 | 0.909 | -0.144 | 0.328 | -0.034 | 0.818 |
| Choroidal inf | -0.145 | 0.325 | -0.002 | 0.991 | 0.031 | 0.832 | 0.164 | 0.264 |
| Choroidal nasal | -0.113 | 0.443 | 0.16 | 0.276 | 0.118 | 0.423 | 0.243 | 0.096 |
| Choroidal density temporal | -0.236 | 0.106 | -0.055 | 0.71 | -0.004 | 0.978 | 0.193 | 0.189 |

Diabetes is a metabolic disease affecting the systemic vasculature. Although the principal changes in diabetic eyes occur in the retinal vasculature, additional changes are also observed in the choroidal layer, an important vascular tissue that supplies blood to the outer retina.[12] Histological studies of diabetic eyes show increased tortuosity, focal vascular dilation or narrowing, and the formation of sinus-like structures between the choroidal lobules and also, in some advanced cases, luminal narrowing of the capillaries, capillary dropout, and focal scarring.[13] Besides, studies using indocyanine green angiography show filling delay or defects in the choriocapillaris, saccular dilatations, microaneurysms in the choriocapillaris, and choroidal neovascularization.[14] Information regarding CT was based primarily on histologic examinations, which do not necessarily reflect the measurements of this dynamic tissue in vivo.[15]

**This study was conducted on 4 groups:** Group1 consisted of 16 eyes of normal healthy individuals (control group). Group 2 consisted of 16 eyes with a clinical diagnosis of non-diabetic retinopathy. Group 3 consisted of 16 eyes with a clinical diagnosis of non-proliferative diabetic retinopathy. Group 4 consisted of 16 eyes with a clinical diagnosis of proliferative diabetic retinopathy.

**Exclusion criteria include:** IOP more than 21 mmHg. High myopia. Media opacity in the study eye

OCT and OCTA measurement for choroidal thickness and choroidal density maps were performed. The same examiner performed all OCT examinations for all patients after 4 hours of fasting from smoking or drinking water, alcohol, or caffeine.

In our study, there was a decrease in choroidal thickness in diabetic patients.

In agreement with our study, *Querques et al*.[16] identified choroidal thinning despite the disease stage, even in diabetic patients without DR.

Also, *Sudhalkar et al*.[17] described a progressive thinning of CT with increasing severity of DR.

*Regatieri et al. (2012)*[18] *reported* that CT decreased in eyes with PDR.

Most studies report a progressively decreasing CT with increasing severity of retinopathy, similar to our report.[19]

A previous study by *Regatieri et al*.[18] stated that it is unclear whether choroidal thinning is primary or secondary to retinal ischemia. This study suggests that choroidal thinning precedes the onset of retinal pathology, and that thinning increases with progressive worsening of the retinopathy.

**In contrast to our study,**

A hospital-based study by *Kim et al.*[19] reported an increased CT in patients with increasing severity of DR, and while the exact mechanism as they state is unknown, there is conflicting evidence on the change in retinal blood flow and pulsatile ocular blood flow in subjects with diabetes.[20]

In our study , there was a decrease in choroidal vascular density.

In agreement with our study*, Nagaoka et al*.[20] demonstrated that there was a decrease in choroidal blood flow, even before visible DR was present.

Also, previous studies[21-25] have reported that choroidal circulation, estimated by color Doppler imaging of posterior ciliary arteries, is significantly decreased in patients with background DR.[26]

*Nagaoka et al.*[20] suggested that choroidal hypoperfusion might trigger the development of DR due to retinal tissue hypoxia and overexpression of VEGF.

*Schocket et al. in*[27] reported that choroidal volume and choroidal blood flow are significantly reduced in patients with PDR**.**

Feng Z, et al.[28] reported no significant changes between both sexes while there is decrease in age groups

**Other studies**[29-35] **also report the decrease in choroidal thickness in agreement with our studies**

**There were some limitations to our study**.

Approximately 16 eyes per diabetic group is a relatively small number.

Because we measured the choroidal thickness using the manual method, the results might contain slight errors, and this was the best clinical method currently available with the current OCT equipment, we tried to ameliorate this by taking 2 choroidal measurements for the same choroidal point.

Choroidal imaging was not performed at a specific time of the day; therefore, we cannot rule out the effect of diurnal variation on the CT, as reported previously[36-42]

However, choroidal thickness fluctuations were decreased by 4 h fasting to avoid the increase in choroidal thickness with water, alcohol, or caffeine intake and decreased thickness with smoking.

As is widely known, OCT angiography has issues regarding various artifacts, and artifacts appear more frequently in eyes with poor vision and retinal diseases.[43]

In this study, we excluded OCT angiography images with poor image quality or diabetic macular edema (DME) , which might introduce selection bias.[44]

## CONCLUSION

Our study suggests that OCTA can identify preclinical DR before the manifestation of clinically apparent retinopathy. Our findings highlight the potential role of OCT-A in monitoring diabetic patients, especially when fluorescein angiography is contraindicated.

### Compliance with Ethical Standards

In Compliance with Ethical Standards :

i) Informed consent was signed by all patients before enrollment in the study.

ii) The authors have no conflict of interest.

iii) IRB and Ophthalmology Council ethical approval was received.

iv) No funding was received for this study.

## REFERENCES

1. Liu G, Xu D, Wang F (2018). New insights into diabetic retinopathy by OCT angiography. Diabetes Research and Clinical Practice.142:243-53.
2. Cho YH, Craig ME, Donaghue KC (2014): Puberty as an accelerator for diabetes complications. 15:18-26..
3. Matsunaga DR, Yi JJ, De Koo LO, et al. (2015): Optical coherence tomography angiography of diabetic retinopathy in human subjects. Ophthalmic Surg Lasers Imaging Retina, 46:796–805
4. Bandello F, Corbelli E, Carnevali A, et al. (2016): Optical coherence tomography angiography of diabetic retinopathy. Dev Ophthalmol., 56:107–12
5. Falavarjani KG, Sarraf D (2017): Optical coherence tomography angiography of the retina and choroid; current applications and future directions. J Current Ophthalmol., 29:1.
6. Hwang TS, Gao SS, Liu L, et al. (2016): Automated quantification of capillary nonperfusion using optical coherence tomography angiography in diabetic retinopathy. JAMA Ophthalmol., 134:367-73.
7. Zhang L, Buitendijk GH, Lee K, et al. (2015): Validity of automated choroidal segmentation in SS-OCT and SD-OCT. Invest Ophthalmol Vis Sci., 56: 3202–11.
8. Early Treatment Diabetic Retinopathy Study Research Group (1991): Grading diabetic retinopathy from stereoscopic color fundus photographs-an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology. 98:786-806.
9. Nassar, M., Saif, M., Saif, Aet al. 2016. Sensitivity and specificity of nassar color test in early detection of diabetic macular edema. retina vitreus, [online] 24, pp.109-119. Available at: <http://retinavitreus.com//index_pdf.php?l=tr&url=PDF_1620.pdf>.
10. Stanga PE, Tsamis E, Papayannis A, et al. (2016): Swept-source optical coherence tomography Angio™(Topcon Corp, Japan): a technology review. In OCT Angiography in Retinal and Macular Diseases, 56: 13-7.
11. Fenner BJ, Tan GS, Tan AC, et al. (2018): Identification of imaging features that determine quality and repeatability of retinal capillary plexus density measurements in OCT angiography. British Journal of Ophthalmology.; 102:509-14.
12. Nickla DL,Wallman J. (2010): The multifunctional choroid. Prog Retin Eye Res; 29: 144–68.
13. Shiragami C, Shiraga F, Matsuo T, et al. (2002): Risk factors for diabetic Choroidopathy in patients with diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol; 240: 436–42.
14. Weinberger D, Kramer M, Priel E, et al. (1998): Indocyanine green angiographic findings in nonproliferative diabetic retinopathy. Am J Ophthalmol; 126: 238–47.
15. Chen T, Cense B, Miller JW, et al. (2006): Histologic correlation of in vivo optical coherence tomography images of the human retina. Am J Ophthalmol; 141: 1165–8.
16. Querques G, Lattanzio R, Querques L, et al. (2012): Enhanced depth imaging optical coherence tomography in type 2 diabetes. Invest Ophthalmol Vis Sci. 53:6017–24.
17. Sudhalkar A, Chhablani JK, Venkata A, et al. (2015): Choroidal thickness in diabetic patients of Indian ethnicity. Indian journal of ophthalmology.; 63:912.
18. Regatieri CV, Branchini L, Carmody J, et al. (2012): Choroidal thickness in patients with diabetic retinopathy analyzed by spectral-domain optical coherence tomography. Retina. 32:563–8.
19. Kim JT, Lee DH, Joe SG, et al. (2013): Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients. Invest Ophthalmol Vis Sci; 54: 3378–84.
20. Nagaoka T, Kitaya N, Sugawara R, et al. (2004): Alteration of choroidal circulation in the foveal region in patients with type 2 diabetes. Br J Ophthalmol 88:1060–3.
21. de Carlo TE, Chin AT, Bonini Filho MA, et al. (2015): Detection of microvascular changes in eyes of patients with diabetes but not clinical diabetic retinopathy using optical coherence tomography angiography. Retina. 35:2364–70.
22. Scarinci F, Picconi F, Giorno P, et al. (2017): Deep capillary plexus impairment in patients with type 1 diabetes mellitus with no signs of diabetic retinopathy revealed using optical coherence tomography angiography. Acta Ophthalmol. 96(2):e264-e265 https://doi.org/10.1111/ aos.13510
23. Kim AY, Chu Z, Shahidzadeh A, et al. (2016): Quantifying microvascular density and morphology in diabetic retinopathy using spectral-domain optical coherence tomography angiography. Invest Ophthalmol Vis Sci. 57:362–70.

24. Agemy SA, Scripsema NK, Shah CM, et al. (2015): Retinal vascular perfusion density mapping using optical coherence tomography angiography in normals and diabetic retinopathy patients. Retina. 2015;35:2353–63.

25. Dimitrova G, Chihara E, Takahashi H, et al. (2017): Quantitative retinal optical coherence tomography angiography in patients with diabetes without diabetic retinopathy. Invest Ophthalmol Vis Sci 58(1):190–6.

26. Dimitrova G, Kato S, Tamaki Y, et al. (2001): Choroidal circulation in diabetic patients. Eye (Lond). 15:602–7.

27. Schocket LS, Brucker AJ, Niknam RM, et al. (2004): Foveolar choroidal hemodynamics in proliferative diabetic retinopathy. Int Ophthalmol 25:89–94.

28. Feng Z, Wang G, Xia H, et al. Macular Vascular Geometry Changes With Sex and Age in Healthy Subjects: A Fundus Photography Study. Frontiers in Medicine [Internet]. 2021 Dec 15 [cited 2022 Jan 12];8. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.778346/full

29. Sousa DC, Leal I, Moreira S, et al. Retinal Vascular Reactivity in Type 1 Diabetes Patients Without Retinopathy Using Optical Coherence Tomography Angiography. Investigative Opthalmology & Visual Science [Internet]. 2020 Jun 23 [cited 2022 Jan 12];61(6):49. Available from: https://iovs.arvojournals.org/article.aspx?articleid=2770173

30. Dai Y, Zhou H, Chu Z, et al. Microvascular Changes in the Choriocapillaris of Diabetic Patients Without Retinopathy Investigated by Swept-Source OCT Angiography. Investigative Opthalmology & Visual Science [Internet]. 2020 Mar 30 [cited 2022 Jan 12];61(3):50. Available from: https://iovs.arvojournals.org/article.aspx?articleid=2764046

31. Abdelshafy M, Abdelshafy A. Correlations Between Optical Coherence Tomography Angiography Parameters and the Visual Acuity in Patients with Diabetic Retinopathy. Clinical Ophthalmology [Internet]. 2020 Apr [cited 2022 Jan 12];Volume 14:1107–15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7186882/

32. Orduna-Hospital E, Otero-Rodríguez J, Perdices L, et al. Microperimetry and Optical Coherence Tomography Changes in Type-1 Diabetes Mellitus without Retinopathy. Diagnostics [Internet]. 2021 Jan 16 [cited 2022 Jan 12];11(1):136. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7830999/

33. Huang X, Zhang P, Zou X, et al. Thinner Average Choroidal Thickness Is a Risk Factor for the Onset of Diabetic Retinopathy. Ophthalmic Research [Internet]. 2020 [cited 2022 Jan 12];63(3):259–70. Available from: https://www.karger.com/Article/Abstract/504756

34. Malik R, Khalil H, Samir A. (2021). OCT Angiographic changes in diabetic patients after cataract surgery. NILES journal for Geriatric and Gerontology, 4(Geriatric Ophthalmology), 40-52. doi: 10.21608/niles.2021.57099.1046

35. Saber E, Saif M, Saeed M. (2021). The effect of cigarette smoking on choroidal vasculature measured by Optical Coherence Tomography Angiography (OCTA). NILES journal for Geriatric and Gerontology, 4(Geriatric Ophthalmology), 1-18. doi: 10.21608/niles.2020.46466.1039

36. Di G, Weihong Y, Xiao Z, et al. (2016): A morphological study of the foveal avascular zone in patients with diabetes mellitus using optical coherence tomography angiography. Graefes Arch Clin Exp Ophthalmol. 254:873–9.

37. Garcia-Ramírez M, Hernández C, Villarroel M, et al. (2009): Interphotoreceptor retinoid-binding protein (IRBP) is downregulated at early stages of diabetic retinopathy. Diabetologia.; 52:2633–41.

38. Bogdanov P, Corraliza L, Villena JA, et al. (2014): The db/db mouse: a useful model for the study of diabetic retinal neurodegeneration. PLoS One.; 9:e97302.

39. Demir M, Oba E, Dirim B, et al. (2013): RETRACTED ARTICLE: Central macular thickness in patients with type 2 diabetes mellitus without clinical retinopathy. BMC ophthalmology. 13(1):11.

40. Thompson IA, Durrani AK, Patel S. (2019) . Optical coherence tomography angiography characteristics in diabetic patients without clinical diabetic retinopathy. Eye 33, 648–652 doi:10.1038/s41433-018-0286-x

41. Pires I, Santos AR, Nunes S, et al. (2013): Macular thickness measured by stratus optical coherence tomography in patients with diabetes type 2 and mild nonproliferative retinopathy without clinical evidence of macular edema. Ophthalmologica. 229:181-6.

42. Tan CS, Chan JC, Cheong KX, et al. (2015): Comparison of Retinal Thicknesses Measured Using Swept-Source and Spectral-Domain Optical Coherence Tomography Devices. Osli Retina. 46:172–9.

43. Say EA, Ferenczy S, Magrath GN, et al. (2017): Image quality and artifacts on optical coherence tomography angiography: comparison of pathologic and paired fellow eyes in 65 patients with unilateral choroidal melanoma treated with plaque radiotherapy. Retina. 37:1660-73.

44. Spaide RF, Fujimoto JG, Waheed NK (2015): Image artifacts in optical coherence angiography. Retina (Philadelphia, Pa.). 35:2163.