# The effect of cigarette smoking on choroidal vasculature measured by Optical Coherence Tomography Angiography (OCTA)

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## Abstract

**Background**: Cigarette smoking has been associated with low blood velocity of ophthalmic artery, while systolic blood pressure has been positively correlated with velocities in the ophthalmic artery and the central retinal artery. These effects are the result of interaction of nicotine-induced peripheral vasoconstriction and vasodilation caused by carbon monoxide in smokers. OCTA is a novel, noninvasive scanning technology which allow visualizing of the retinal and choroidal circulation. It permits assessing the retinal vasculature layer by layer and allows physicians to take images of the deep capillary plexus with no dye injection.

**Methods:** retrospective case control study included 100 participants (50 smokers and 50 healthy nonsmokers) recruited from Ophthalmology Department in Beni -Suef University Hospital. Participants were equally divided into two groups: **Group (1):** Included 50 smokers otherwise healthy. Group **(2):** Included 50 normal subjects (nonsmokers) used as control. Both groups underwent OCTA study.

**Results:** A highly significant statistical difference between both groups regarding smoking duration, while age and gender were of no significant. No statistical difference between both groups regarding perfusion within retinal layers between both groups as recorded in whole image. Age, IOP and neovascularization were positively, correlated with duration of smoking, perfusion and choroidal thicknesses in all areas were negatively correlated with duration of smoking.

**Conclusion:** We did not find a significant difference in choroidal blood flow, vessel density, or choroidal thickness measurements between the study and control groups in a chronic period. We also noticed that OCTA is a good new noninvasive procedure for imaging choroidal circulation.

## Keywords

Choroidal circulation ,OCTA, smoking effect, Optical coherence tomography angiography

## 1. Introduction

The choroid is responsible for vascular support of the outer retina. Structurally and functionally normal choroidal vasculature is essential for retinal function: abnormal choroidal blood volume and/or compromised flow can result in photoreceptor dysfunction and death**(1)**.

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Whereas retinal circulation supplies oxygen and nutrients to the internal layers of retina, choroidal circulation is nourishing the external retinal layers. Choroidal vasculature, the major source of the blood supply to the posterior segment of eye, is also accountable for transporting waste metabolites from the retinal pigment epithelium (RPE), so it plays a main role in normal retinal function**(2).**

Choroidal circulation is associated with various retinal diseases for example age-related macular degeneration (AMD) and diabetic retinopathy (DR), which are considered major reasons for visual loss or impairment. Consequently, visualizing the microvasculature and blood flow in the choriocapillaris and the capillary layer of the choroid, is of great interest**(3).**

Tobacco smoking is a risk factor for atherosclerosis of coronary, aortic, and cerebral circulations , also it causes numerous changes in the blood circulation of some organs by the local metabolic and vascular effects of systemically absorbed products of cigarette smoking **(4).**

The relationship of tobacco smoking with macrovascular and peripheral vascular disease is well documented in the literature. Though the hemodynamic effects of nicotine are well documented, the pathogenesis of ocular blood flow changes with tobacco is not fully cleared**(5).**

Various hypotheses have been advanced to explain this causal relationship; some of these theories are proved with verified evidence, whereas others require extra investigation. When researchers make studies proposals to clarify the effect of a single factor, large sample are hard to avoid because of the complexity of the etiologies of these diseases, which involve many interactive genetic and external factors**(6).**

The higher risk of ischemic disease in smokers can be explained by several mechanisms. Both erythrocyte and leukocyte concentrations are raised up in smokers, also thrombocytes are activated in the blood of long-standing smokers. The previous factors may lead to increased viscosity and a higher risk of thrombosis. There is also an increase in the clotting potential of the blood, as individuals who smoke have elevated levels of plasma fibrinogen. Nicotine, a prime component of tobacco, leads to activation of α - adrenergic receptors, causing vasoconstriction**(7).**

Up till now, clinical imagining of retinal vessels has been restricted to indocyanine green angiography and fluorescein angiography, that need injection of a contrast dye. In spite of

the clinical importance of these techniques, they have some disadvantages as being invasive, take long time, and depend on skill of photographer. Injection of dye may also lead to side effects as nausea, vomiting, and rarely, anaphylactic shock that can cause death **(8).**

In recent times, there is a great interest with a new OCT imaging procedure called OCT angiography (OCTA). Optical Coherence Tomography Angiography separates microvascular circulation from data of OCT image data using highly specific accession and processing procedures. This helps visualizing retinal blood flow with no need for injecting intravenous contrast dye **(9).**

**2: Purpose:**

To study the effect of cigarette smoking on choroidal circulation by using OCTA by comparing the choroidal vasculature, choroidal thickness and choroidal vessels density in smokers with nonsmokers.

**3: Patients and methods**

This is study was carried out on 100 participants at the Ophthalmology Department in Beni Suef University Hospital. participants were equally divided into two groups: **Group (1):** Included 50 smokers otherwise healthy individuals. (40 men, 10 women)

**Group (2):** Included 50 normal subjects (non-smokers) used as control. (45 men, 5 women) Informed consent will be obtained from all of the study participants

**3.1 Inclusion criteria:**

Cigarette smokers (Nicotine amount in each cigarette 1 mg to 2 mg.) with at least 10 years smoking history, Aged 25-45 years

**3.2 Exclusion criteria:**

Ocular and systemic diseases affect the eye, alcohol consumption in the smoking group, any systemic vascular abnormalities (e.g. cardiac, diabetes mellitus or hypertension).

**3.3 All patients were subjected to:**

All participants underwent:

**-full history taking**

**-ophthalmological examination.**

- vision assessment and BCVA using the Snellen chart
- Anterior segment examination using a slit lamp
- Fundus examination using Slit-lamp biomicroscopy with +90 D volk lens, and indirect ophthalmoscopy
- Intraocular pressure

**-Investigations included**

OCTA (optovue type, software version:2016.0.0.52)

Assessment of:

- Choroidal circulation
- Choroidal vessel density
- Choroidal Thickness (CT)

**Statistical methodology**

The collected data were organized, tabulated and statistically analyzed using SPSS (ver. 25.0; IBM, Chicago, IL, USA). Quantitative data was displayed in the form of mean ± standard deviation (SD). Qualitative data was demonstrated through figures of frequency and percentage. Charts of different types were used to illustrate data and relations where appropriate. A probability value (P value) less than 0.05 was considered significant.

This study is a case control study included 100 participants (50 smokers and 50 healthy nonsmokers) recruited from Ophthalmology Department in Beni -Suef University Hospital with exclusion the patients with: Ocular disease preventing the examination of the cornea, having any ocular surgery, history of chronic ocular disease (e.g. glaucoma, cataract, and uveitis), history of smoking or alcohol consumption in the control group, History of alcohol consumption in the smoking group, history of any systemic vascular disease (e.g. cardiac, diabetes mellitus or hypertension), and history of taking any medication within the past 3 months to this study, including systemic vasoactive drugs.

**4: Results**

**Table 1 Demographic data of the study groups**

| Demographics Data | Smokers N=50 | Non smokers N=50 | Test value | P-value |
|---|---|---|---|---|
| **Age** Mean±SD | **33.16±7** | **31.02±3.8** | **1.89** | **0.062**[1] |
| **Gender** | | | | |
| Female | **10(20%)** | **5(10%)** | **1.96** | **0.161**[2] |
| Male | **40(80%)** | **45(95%)** | | |

1. Mann Whitney U test;
2. Chi square test

*statistically significant at $p< 0.05$.

Table 1 shows the demographic data in the study The range of age group among participants was (25-45) years with mean age of non-smokers was 31.02 ± 3.8 years, while the mean age of smoker was 33.16±7 years.

Regarding gender, most of participants were males in both groups with no statistical significant difference (p=0.161).

**Table 2 shows smoking index:**

| | Smokers N=50 | Non smokers N=50 | Test value | P-value |
|---|---|---|---|---|
| **Smoking duration** Mean±SD | **14.4±4.5** | **0** | **98** | **0.0001**[1*] |
| **Cigarettes / day** Mean±SD | **25.86±5.47** | **0** | | |
| **Smoking index** Mean±SD | **379.92±164.39** | **0** | | |

The mean duration of smoking among smokers was 14.4±4.5 years, while the mean smoking index was 379.92±164.39

**Table 3 Perfusion within retinal layers among groups.**

| Perfusion | Smokers N=50 | | Non smokers N=50 | | Test value | P-value |
|---|---|---|---|---|---|---|
| | Normal perfusion | Decreased Perfusion | Normal perfusion | Decreased Perfusion | | |
| Superficial layer | 50(100%) | 0(0%) | 50(100%) | 0(0%) | 0.00 | 1.00[1] |
| Deep layer | 50(100%) | 0(0%) | 50(100%) | 0(0%) | 0.00 | 1.00[1] |
| Outer retina | 50(100%) | 0(0%) | 50(100%) | 0(0%) | 0.00 | 1.00[1] |
| Choriocapillaris layer | 50(100%) | 0(0%) | 50(100%) | 0(0%) | 0.00 | 1.00[1] |
| Neovascularization | 0(0%) | | 0(0%) | | 0.00 | 1.00[1] |

Table 3 shows no statistical difference between both groups regarding perfusion within retinal layers.

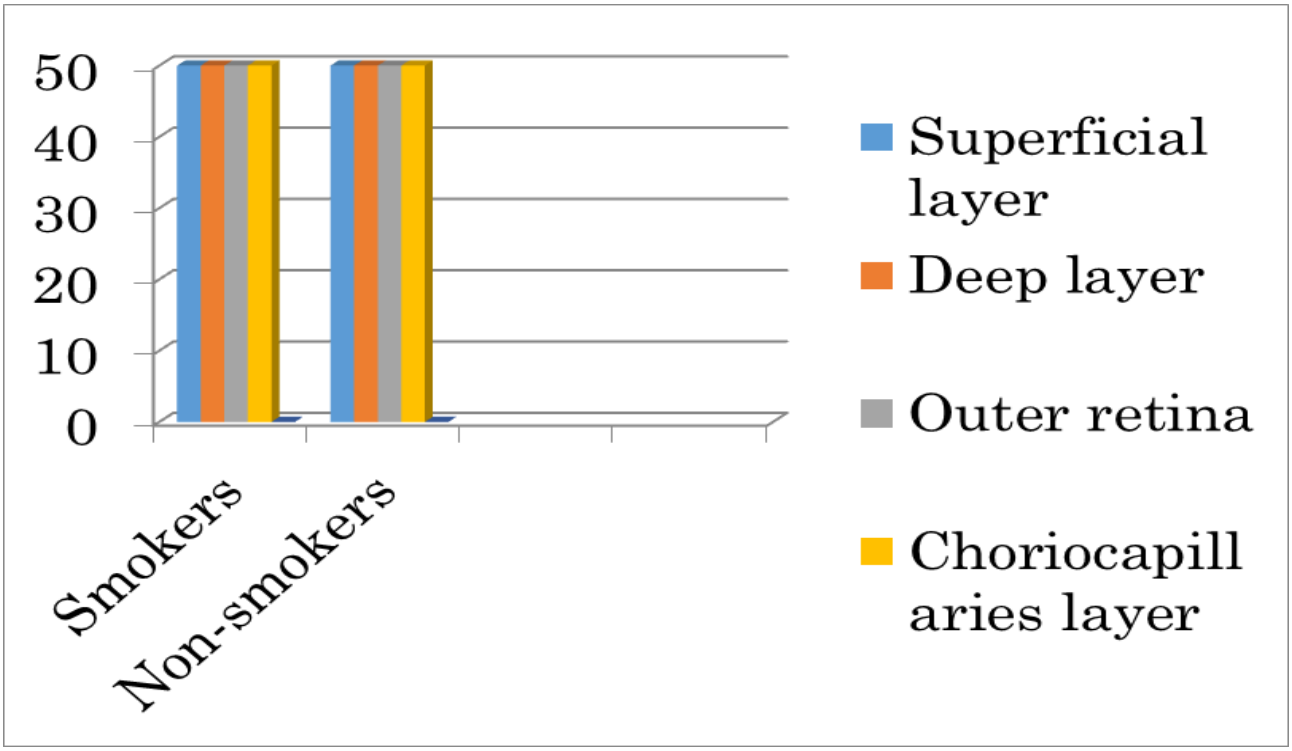



**Figure 1 Perfusion within retinal layers among groups.**

**Table 4 Choroidal Thickness (CT) data in both groups**

| | Smokers N=50 | Non smokers N=50 | Test value | P-value |
|---|---|---|---|---|
| **Whole Image** | | | | |
| Superior hemi. | 288 ±8.6 | 288.3±8.6 | 0.00 | 0.994[1] |
| Inferior hemi. | 284.7±11.2 | 284.8±11.4 | | |
| **Fovea** | 251.5±16.1 | 251.6±16.3 | 0.00 | 1.00[1] |
| **Parafovea** | | | | |
| Superior | 321.0 ±20.2 | 321.1 ±20.3 | 0.00 | 1.00[1] |
| Inferior | 314.3 ±21.4 | 314.5 ±21.6 | 0.00 | 1.00[1] |
| Temporal | 316.1 ±19.7 | 316.3 ±19.9 | 0.00 | 1.00[1] |
| Nasal | 315.0 ±21.1 | 315.0 ±21.3 | 0.00 | 1.00[1] |
| **Perifovea** | | | | |
| Superior | 292.1 ±11.6 | 292.3 ±11.9 | 0.00 | 1.00[1] |
| Inferior | 280.0 ±10.4 | 280.0 ±10.7 | 0.00 | 1.00[1] |
| Temporal | 258.1 ±11.0 | 258.3 ±11.1 | 0.00 | 1.00[1] |
| Nasal | 234.5 ±20.6 | 234.6 ±20.7 | 0.00 | 1.00[1] |

Table 4 shows no statistical significant between both groups as recorded in whole image, foveal, parafoveal and perifoveal areas 2(nasal, temporal, superior, and inferior quadrants)

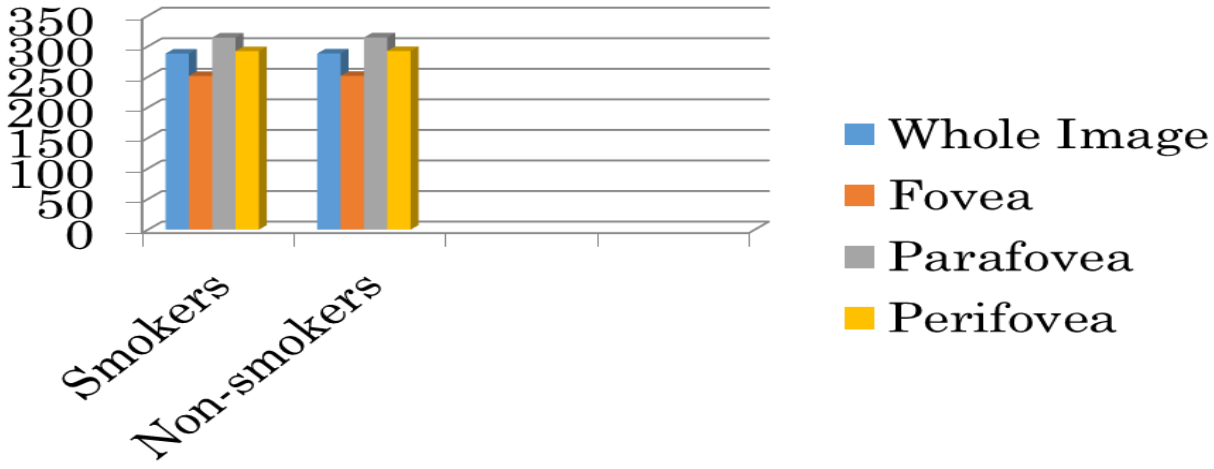



**Figure (2) Choroidal Thickness (CT) in both groups**

**Table 5 Choroidal vessel density (%) percentage data in both groups:**

| | Smokers N=50 | Non smokers N=50 | Test value | P-value |
|---|---|---|---|---|
| **Whole Image** | | | | |
| Superior hemi. | 49.0±1.3 | 49.02±1.4 | | |
| Inferior hemi. | 47.6±.97 | 47.8±0.98 | 0.00 | 0.994[1] |
| **Fovea** | 25.3±1.8 | 25.4±1.9 | 0.00 | 1.00[1] |
| **Parafovea** | | | | |
| Superior | 52.0 ±1.08 | 52.1 ±1.08 | 0.00 | 1.00[1] |
| Inferior | 52±1.5 | 52 ±1.6 | 0.00 | 1.00[1] |
| Temporal | 51.8 ±1.6 | 51.9 ±1.7 | 0.00 | 1.00[1] |
| Nasal | 50 ±.97 | 50.1 ±0.98 | 0.00 | 1.00[1] |
| **Perifovea** | | | | |
| Superior | 49.1 ±1.8 | 49.2 ±1.9 | 0.00 | 1.00[1] |
| Inferior | 48.08±1.0 | 48.09 ±1.1 | 0.00 | 1.00[1] |
| Temporal | 47.3 ±1.2 | 47.4 ±1.3 | 0.00 | 1.00[1] |
| Nasal | 51.1 ±.8 | 51.2 ±0.9 | 0.00 | 1.00[1] |

Table 5 shows choroidal vessel density (%) percentage in both groups as recorded in whole image, foveal, parafoveal and perifoveal areas 2(nasal, temporal, superior, and inferior quadrants). The differences in percentages of vessels thickness in all areas and all quadrants weren't statistically significant among two groups.

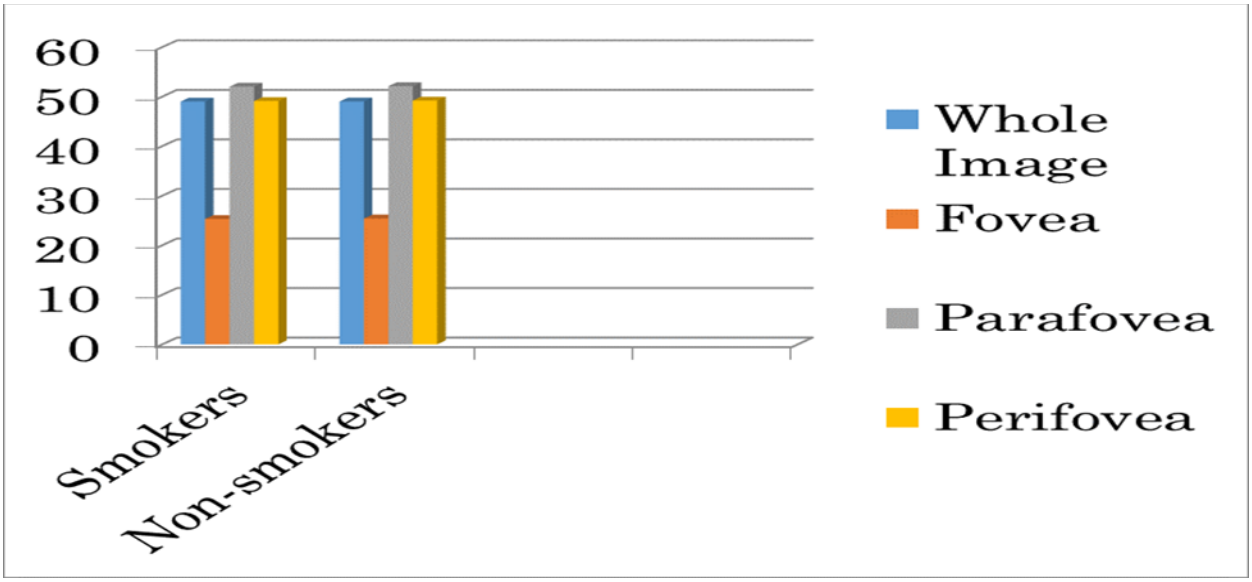



**Figure 3 Choroidal vessel density (%) percentage data in both groups.**

**Table 6 Correlations of duration of smoking with demographic characteristics and choroidal thicknesses parameters among smokers.**

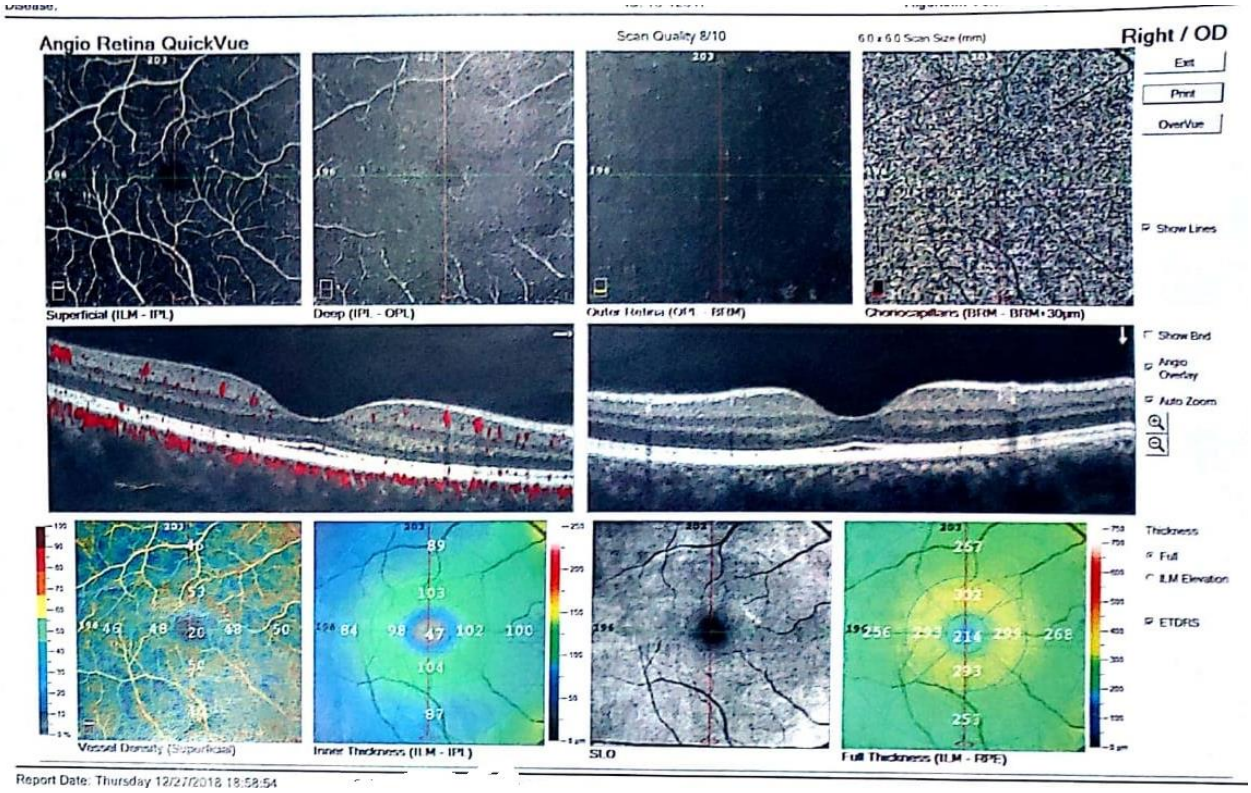
| | Duration of smoking | |
|---|---|---|
| | Spearman's coefficient | P-value |
| Age | 0.489 | 0.001* |
| Gender | 0.126 | 0.211 |
| Side | 0.098 | 0.241 |
| UCVA | 0.132 | 0.146 |
| IOP | 0.424 | 0.021* |
| Perfusion | -0.521 | 0.001* |
| Neovasularization | 0.453 | 0.002* |
| Whole Image CT | -.0782 | 0.001* |
| Fovea CT | -0.256 | 0.011* |
| Parafovea CT | -0.621 | 0.001* |
| Perifovea CT | -0.344 | 0.001* |

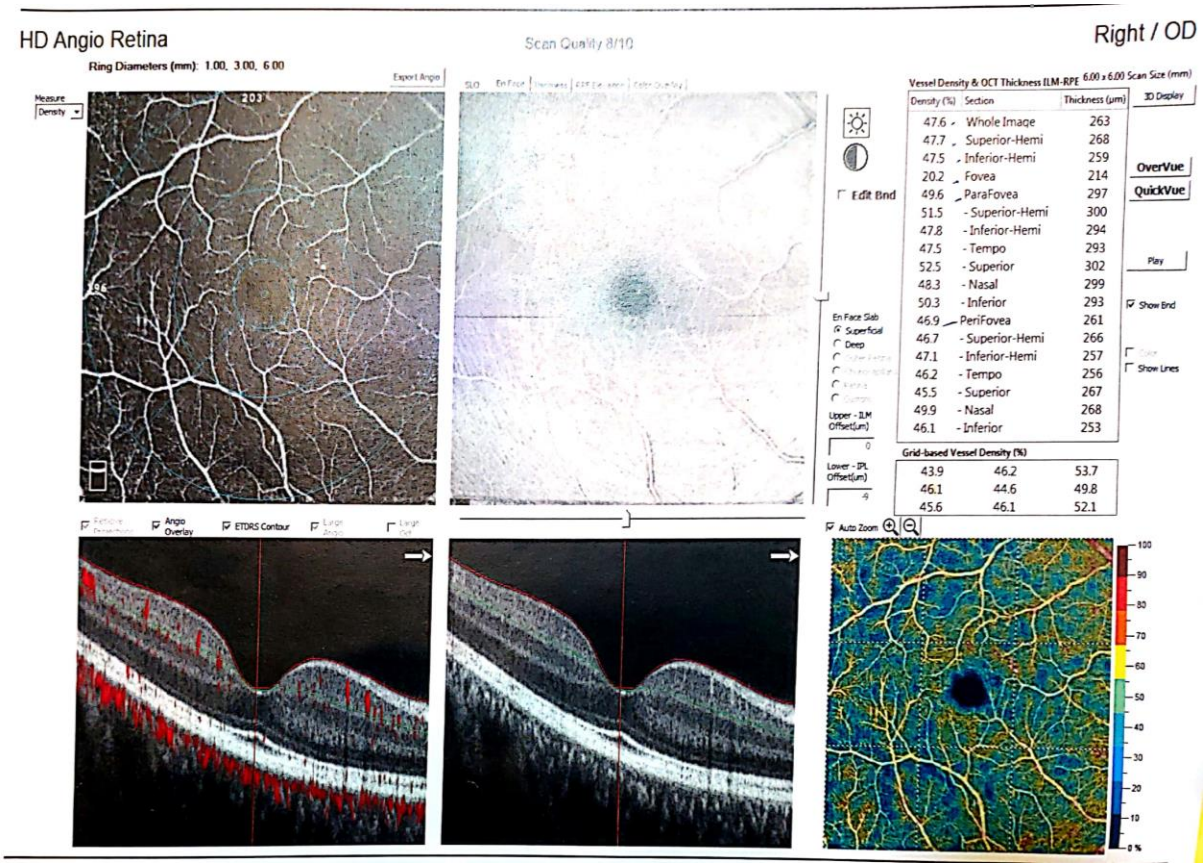
In this table, age, IOP and neovascularization were positively, correlated with duration of smoking. Moreover, perfusion and choroidal thicknesses in all areas were negatively correlated with duration of smoking. No statistically significant correlation was detected among gender, side, and UCVA and duration of smoking.

## Cases examples

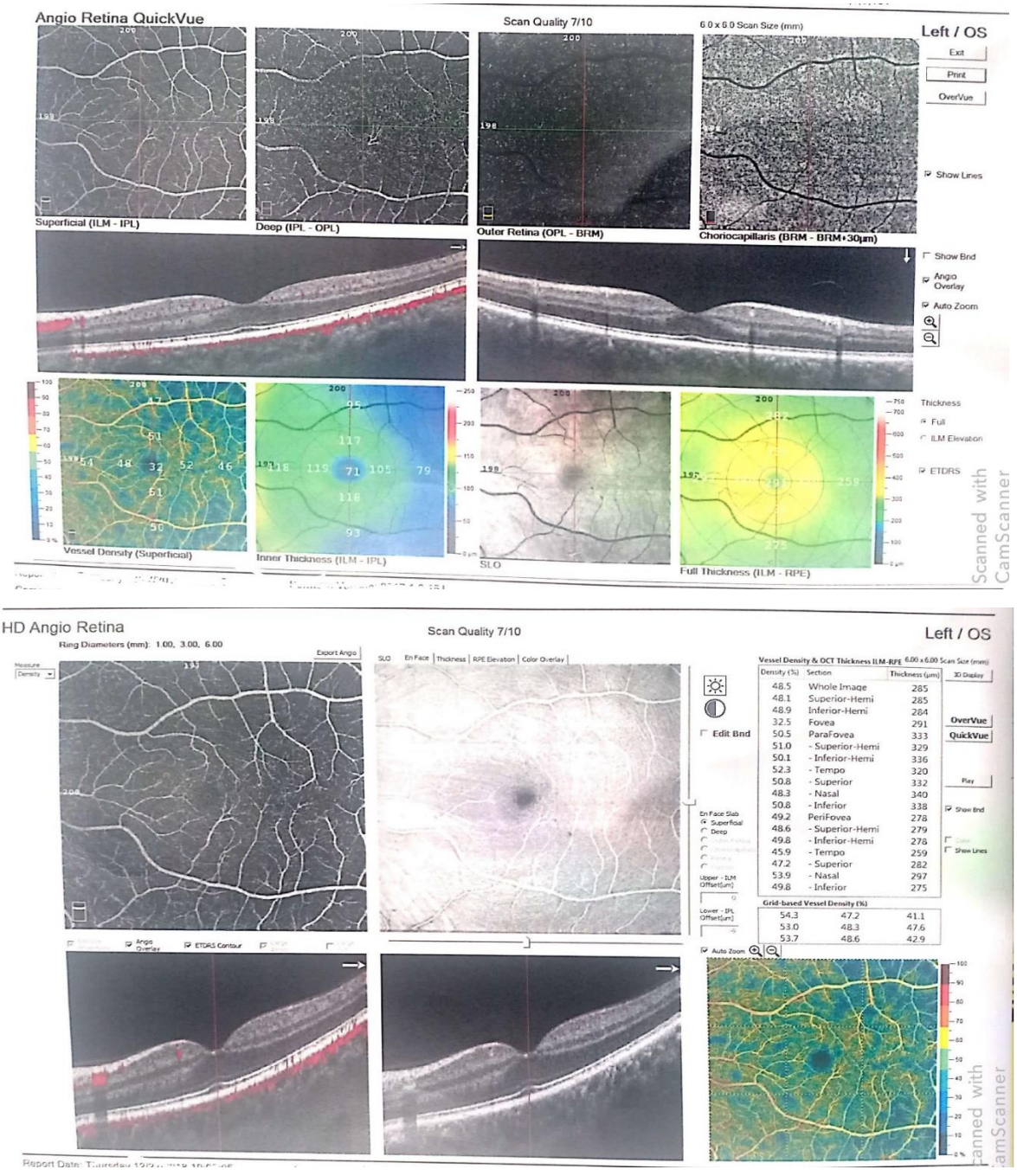
- **Figure 4 (below): OCT scan passing through the macular area in the right eye of 30 years old male smoker (about 10 years smoking duration), revealing the following:**
- **superficial capillary layer shows normal capillary perfusion**
- **Deep capillary layer shows normal capillary perfusion**
- **Outer retina shows normal perfusion**
- **Choriocapillary layer shows normal perfusion with no evidence of CNV formation with depositions**
- **vessel density analysis shows within normal macular density**

- **choroidal thickness shows within normal CT**



- **Figure 5: OCT scan passing through the macular area in the LEFT eye of 35 years old male healthy NON-smoker, revealing the following:**
- **superficial capillary layer shows normal capillary perfusion**
- **Deep capillary layer shows normal capillary perfusion**
- **Outer retina shows normal perfusion**
- **Choroicapillary layer shows normal perfusion with no evidence of CNV formation with depositions**
- **vessel density analysis shows within normal macular density**
- **choroidal thickness shows within normal CT**



**5: Discussion:**

Effects of cigarette smoking on the microcirculation involve cooperated endothelial-dependent vasorelaxation, aggregation of platelets, and dysfunction of endothelial cell. These effects cause vasodilatation or vasocontraction which lead to vascular blood flow changes **(10).** Harmful effects of cigarette smoking on the ocular microcirculation were studied in humans due to having dense microvascular bed readily measurable to noninvasive methods**(11).**

In this study, we aimed to study the effect of cigarette smoking on choroidal circulation by using OCTA by comparing the choroidal vasculature, choroidal thickness and choroidal vessels density in smokers with healthy. We found that smoking causes no significant difference in choroid blood flow, vessel density, or choroidal thickness measurements between the study and control groups. Moreover, we found that Optical Coherence Tomography Angiography (OCTA) is a good new noninvasive technique for studying choroidal circulation and diseases affecting it.

In 1993, ***Rojanapongpun and Drance*** (**12**) revealed a decrease of ophthalmic artery circulation after cigarette smoking by the mean of transcranial Doppler ultrasound**.** While, Morgado ***et al.*** (**13)** assessed the effect of smoking on retinal blood flow and autoregulation in smokers with and without DM by the mean of laser doppler velocimetry and retinal photography. They revealed that smoking decreases retinal blood flow and that the retinal vessels can autoregulate to hyperoxia; these results seem to be caused by the vasoconstrictive effect of nicotine, which result from stimulation of the sympathetic system , this was against our results because they used different technique in evaluation of retina blood flow (laser velocimetry and retinal photography).

**Robinson et al. (14)** evaluated the acute effect of smoking on macular capillary blood flow by the mean of a blue field simulation technique. Velocity of leukocyte flowing within their particular macular capillaries was measured in this technique. In contradiction of other studies, they revealed that cigarette smoking cause a significant rise in macular leukocyte velocity and blood flow .These results also are against ours that found that no difference in blood flow between smokers and healthy nonsmoking individuals because they used different technique in evaluation (blue field simulation technique).Similarly to ***Robinson et al. ,***(**14**) another study has confirmed amplification of blood velocity in observable surface vessels of the optic nerve head and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chorioretinal vessels in habitual smokers by the mean of laser speckle technology **(15).**

The difference among individuals in the response of blood flow to smoking may indicate variable levels of nicotine absorption and/or a variance in end-organ response to the mixture of chemicals in tobacco smoke**(16)**,and this might be an explanation for the difference between many studies' results. ***Yang et al.*** (**17**) have studied the effects of cigarette smoking on retinal and choroidal thickness and found no significant effect of tobacco smoking on retinal or choroidal thickness change was detected. However, smoking would influence the thickness of RNFL and GCL, these results are similar to our results except that we didn't study the RLNF and GCL.

***Wei et al.*** **(18)** have studied the choroidal structural changes in smokers by using choroidal vascularity index (CVI) and found that tobacco smoking accompanied with reduced choroidal vascularity in healthy individuals, and this association seems to be dose dependent as CVI reduced by 0.12% with each unit rise in smoking assessed by pack-year (P = 0.0009). In subgroup analysis, individuals smoking 8:12 and more than 12 pack-years had significantly lesser CVI in comparable to non-smokers (both P < 0.05) .These results differ from ours as they used a different technique and smokers were compared according to exposure to different doses of nicotine. This also can explain the difference. ***Sogawa et al*** (**19**) studied the subfoveal choroidal thickness by the mean of EDI-OCT and assessed the choroidal circulation through measuring the pulsatile ocular blood flow and choroidal blood flow and revealed that there is no correlation between subfoveal choroidal thickness and the choroidal circulation in young healthy individuals**,** and these results are correlated with our study results.

Impacts of smoking and nicotine on choroidal thickness were revealed by the mean of EDI OCT in many previous studies**(20).** ***Ulas et al.*** (**21**) found that smoking produced acute, significant rise in choroidal thickness that went back to baseline levels following 1 h. There was non-significant difference in choroidal and retinal thicknesses among the healthy young smokers and non-smokers**.** These results are similar to our results. ***Sizmaz et al.*** **(22)** demonstrated that cigarette smoking significantly and acutely decreased choroidal thickness, as assessed for the first time by Fourier domain OCT. The investigators commented that the decrease was most likely associated with decreased blood flow to the choroid after smoking**.** These results differ from ours due to using different


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technique for assessment (Fourier domain OCT) and measuring at different times following smoking (scanning at baseline, and 1 and 3 h following smoking one standard cigarette).

***Zengin et al.*** (**20**) studied the effect of nicotine on choroidal thickness by the mean of EDI OCT. They revealed that nicotine result in a significant reduction in choroidal thickness after oral consumption and clarified this acute reduction as a result of decreased ocular blood flow because of the vasoconstrictive effect of nicotine**.**These results are different from ours because they gave 4 mg nicotine gum for the smoking group before scanning and this is higher dose of nicotine than that in the standard cigarette (1-2 mg of nicotine).

***Moschos et al.*** **(23)** investigated The impact of tobacco smoking on retinal and choroidal thickness in Greek population and found that **t**obacco smoking seems to result in thinner choroid and retina compared to nonsmokers**.** This was different from our results because they assessed only the group of more than 25-year cigarette smoking which is a longer duration of smoking than we considered (14 ± 4), also they tested smoking group with mean age of (57.8 ± 4.5 years) which is older than we studied (33 ± 7 years) mean age.

***Teberik,*** (**24**) has compared the thickness of the macula, choroid, and peripapillary RNFL in smokers with those of healthy, nonsmoking persons by the mean of SD-OCT and revealed that RNFL thickness is reduced in healthy highly cigarette smokers, whereas CT is not affected. RNFL changes may be related to endothelial dysfunction and retinal vascular reactivity resulted from smoking**.** These results are similar to our results in that choroidal thickness is not affected by smoking. ***Tayyab et al***.(**25**) have studied the effect of chronic smoking on choroidal thickness and found that CT measurements did not differ among smokers and non-smokers when evaluated bt swept source OCT .These results agree with our study results. While, Holló**.,** ***(26)*** has studied the acute effect of smoking on peripapillary and superficial parafoveal vessel density (VD) in healthy smokers and revealed that values of vessel density in healthy middle-aged smokers are not affected neither by acute smoking a cigarette nor by the time passed for the recent cigarette. This shows that in continuing investigations for glaucomatous VD progression, we don't have to control smoking, at least in the normal control group**, and** this is exactly what our study results revealed While, Ciesielski ***et al.*** (**27**) study's displays no acute impacts of one-cigarette smoking in healthy


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habitual smokers on FAZ, macular VD in the central 3*3 mm area and peripapillary vessel density in the area of 4.5*4.5mm gained by specific OCTA machine**.** This is also agreeing with our study.

***Ayhan et al***. (**16**) have studied the acute and chronic impacts of smoking on macular microvascular vasculature by the mean of OCTA and revealed that, in spite of a significant reduction of macular blood flow at the acute stage of smoking, there wasn't any significant change in macular blood flow, VD, or FAZ measurements among the study and control groups in a chronic stage. These results confirmed that smoking causes hypoxia at macula at the acute stage **.**This study outcomes are similar to our results during chronic stage of smoking.

## 6: CONCLUSION

In conclusion, we evaluated the effects of smoking on choroidal microvascular structure by using OCTA. We did not recognize a significant variance in choroidal circulation, VD, or choroidal thickness measurements between the study and control groups.

We also noticed that OCTA is a good new non invasing procedure for imaging choroidal circulation.

## 7: Conflict of interest

We declare that we have no conflict of interest.

## 8: Summary:

Tobacco smoking has no effect on choroidal circulation and choroidal thickness during chronic stage, also the impact of smoking on choroid may vary according to many factors .

## 8. References:

1. Branchini LA, Adhi M, Regatieri CV, Nandakumar N, Liu JJ, Laver N, Fujimoto JG and Duker JS: **Analysis of choroidal morphologic features and vasculature in healthy eyes using spectral-domain optical coherence tomography**. *Ophthalmology* 2013,**120**(9):1901-1908
2. Sezer T, Altınışık M, Koytak İA and Özdemir MH: **The choroid and optical coherence tomography**. *Turkish journal of ophthalmology* 2016, **46**(1):30
3. Lutty GA, Hasegawa T, Baba T, Grebe R, Bhutto I and McLeod DS: **Development of the human choriocapillaris**. *Eye* 2010, **24**:408.
4. Messner B and Bernhard D: **Smoking and Cardiovascular Disease**. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2014, **34**(3):509-515
5. Wimpissinger B, Resch H, Berisha F, Weigert G,

Schmetterer L and Polak K: Response of choroidal blood flow to carbogen breathing in smokers and non-smokers. The British journal of ophthalmology 2004, 88:776-781

6. Cheng ACK, Pang C, Leung ATS, Chua JKH, Fan D and Lam DSC: **The association between cigarette smoking and ocular diseases**. *Hong Kong medical journal = Xianggang yi xue za zhi / Hong Kong Academy of Medicine* 2000, **6**:195-202
7. Inoue T: **Cigarette smoking as a risk factor of coronary artery disease and its effects on platelet function**. *Tobacco induced diseases* 2004, **2**(1):33-27
8. Bennett TJ, Quillen DA and Rolly Coronica D: **Fundamentals of fluorescein angiography**. *Curr Concepts Ophthalmology* 2001, 9(3):43-49
9. Onishi AC and Fawzi AA: **An overview of optical coherence tomography angiography and the posterior pole**. *Therapeutic advances in ophthalmology* 2019, **11**:2515841419840249-2515841419840249
10. Barua RS, Ambrose JA, Eales-Reynolds L-J, DeVoe MC, Zervas JG and Saha DC: **Dysfunctional endothelial nitric oxide biosynthesis in healthy smokers with impaired endothelium-dependent vasodilatation**. In: *Circulation. Volume 104*, edn.; 2001: 1905-1910
11. Omae T, Nagaoka T and Yoshida A: **Effects of Habitual Cigarette Smoking on Retinal Circulation in Patients With Type 2 Diabetes**. *Investigative ophthalmology & visual science* 2016, **57**(3):1345-1351
12. Rojanapongpun P and Drance SM: **The effects of nicotine on the blood flow of the ophthalmic artery and the finger circulation**. *Graefe's archive for clinical experimental ophthalmology* 1993, **231**(7):371-374.
13. Morgado P, Chen H, Patel V, Herbert L and Kohner E: **The acute effect of smoking on retinal blood flow in subjects with an without diabetes**. *Ophthalmology* 1994, **101**(7):1220-1226
14. Robinson F, Petrig B and Riva CE: **The acute effect of cigarette smoking on macular capillary blood flow in humans**. *Investigative ophthalmology visual science* 1985, **26**(5):609-613
15. Tamaki Y, Araie M, Nagahara M and Tomita K: **Acute effects of cigarette smoking on tissue**

**circulation in human optic nerve head and choroid-retina**. *Ophthalmology* 1999, **106**(3):564-569

16. Ayhan Z, Kaya M, Ozturk T, Karti O and Hakan Oner F: **Evaluation of Macular Perfusion in Healthy Smokers by Using Optical Coherence Tomography Angiography**. *Ophthalmic Surg Lasers Imaging Retina* 2017, **48**(8):617-622
17. Yang T-K, Huang X-GandYao J-Y: **Effects of Cigarette Smoking on Retinal and Choroidal Thickness**: A Systematic Review and Meta-Analysis Journal of Ophthalmology 2019, 2019:8
18. Wei X, Kumar S, Ding J, Khandelwal N, Agarwal M and Agrawal R: **Choroidal Structural Changes in Smokers Measured Using Choroidal Vascularity Index**. *Invest Ophthalmol Vis Sci* 2019, **60**(5):1316-1320
19. Sogawa K, Nagaoka T, Takahashi A, Tanano I, Tani T, Ishibazawa A and Yoshida A: **Relationship between choroidal thickness and choroidal circulation in healthy young subjects**. *American Journal of Ophthalmology* 2012, **153**(6):1129-1132. e1121
20. Zengin MO, Cinar E and Kucukerdonmez C: **The effect of nicotine on choroidal thickness**. *British Journal of Ophthalmology* 2014, **98**(2):233-237
21. Ulaş F, Çelik F, Doğan Ü and Çelebi S: **Effect of smoking on choroidal thickness in healthy smokers**. *Current Eye Research* 2014, **39**(5):504-511
22. Sızmaz S, Küçükerdönmez C, Pınarcı EY, Karalezli A, Canan H and Yılmaz G: **The effect of smoking on choroidal thickness measured by optical coherence tomography**. *British Journal of Ophthalmology* 2013, **97**(5):601-604
23. Moschos MM, Nitoda E, Laios K, Ladas DS and Chatziralli IP: **The Impact of Chronic Tobacco Smoking on Retinal and Choroidal Thickness in Greek Population**. *Oxid Med Cell Longev* 2016, **2016**:2905789-2905789.
24. Teberik K: **The Effect of Smoking on Macular, Choroidal, and Retina Nerve Fiber Layer Thickness**. *Turkish journal of ophthalmology* 2019, **49**(1):20-24
25. Tayyab H, Jahangir S and Kishi S: **Effect of Chronic Smoking on Choroidal Thickness as Measured by Swept Source**

**OCT When Compared to Non Smokers**. *Pakistan Journal of Ophthalmology* 2015, **3**(4).

26. Hollo G: **No Acute Effect of Smoking on Peripapillary and Macular Vessel Density in Healthy Middle-aged Smokers**. *J Glaucoma* 2019, **28**(5): e86-e88
27. Ciesielski M, Rakowicz P and Stopa M: **Immediate effects of smoking on optic nerve and macular perfusion measured by optical coherence tomography angiography**. *Scientific Reports* 2019, **9**(1):10161