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Impacts of smoking & ocular activity on Behcet disease & normal control by optical coherence tomography angiography (OCTA) in Upper Egypt

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***Abstract*---**Retinal vasculitis and vein occlusions are common causes of serious visual loss in Behcet's disease. The aim of the current work was the comparison of the OCTA results of BU cases, BD without uveitis cases &normal control was further subdivided to smokers &non-smokers to permit us to recognize retinal micro-circulation variations at the macular level in BU cases even in the nonattendance of preceding angiographic diagnosing of vasculitis & impact of smoking on BD clinical results of Behcet uveitis(BU), Behcet disease with no uveitis cases &normal control by the following parameters; Vessel density of macular area (VD) & foveal Avascular zone (FAZ) using OCTA. The conclusion of this study shows reduction of vessel density of macular area in Behcet uveitis (BU) rather than Behcet disease without uveitis &normal control & Enlarged FAZ in BU rather than BD without uveitis & normal control. The study results revealed areas of hypoperfusion of macular area even in BD without clinical signifacnce. Hazards of smoking on uveitis cases. There is a need to larger samples & lack of stable treatment protocols.

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***Keywords*---**Behcet disease, Optical coherence tomography angiography, Vasculitis, Uveitis, Retinal vein occlusion, smoking.

Introduction

Behçet's disease (BD) is a systemic vasculitis including veins and arteries of all sizes, marked by recurrent aggravations and re-missions (1). The spectrum of the disease is heterogeneous and involves muco-cutaneous lesions, arthritis, neurologic involvements, ocular inflammation, and others less frequently diagnosed (2). BD is a chronic disorder marked by recurrent incidents of severe inflammations that can lead to significant ocular damages causing non-reversible changes and significant vision losing (3). Chief reasons of serious vision losing in Behçet's uveitis involve optic nerve atrophy, macular damages, and retinal vascular occlusions causing ischemic retinopathy with vitreous hemorrhage, or neo-vascularization, neo-vascular glaucoma (4).

Smoking is the most extensive habit of men. In the cigarette, there are more than 4,000 toxic constituents that influence the vascular and immune system by including vasospasm and platelet aggregation and lessening the anti-oxidants in the blood (5). Smoking is as well accompanyed with several ocular disorders, like dry eye, Graves ophthalmopathy, cataract, cystoid macular edema (CME), age-linked macular degenerations, and uveitis (6).

New researches revealed that, contrary to the pro-inflammatory impact of some constituents in the cigarette, nicotine has an antiinflammatory consequence by lessening the cytokine productions and variation of nitric-oxide (NO) (7). Furthermore, it was concluded that smoking can lead to signs of Behçet diseae(BD), principally on muco-cutaneous ulcers. In contrast, it was previously described that smoking can have a promising consequence on signs of BD, while discontinuing smoking can activate or worsen the disorder, particularly muco-cutaneous lesions (8). These results focus the requirement for study of the impact of smoking on BU.

Optical coherence tomography angiography (OCTA) is a new noninvasive device to investigate the morphology of the micro-vasculature of the central retina, but with no possibility of delivering beneficial data on the retinal vessel penetrability that can settle and count the degree of vasculitis and existence of macular edema (9). OCTA was confirmed as an advantageous method to visualize retinal capillary nonperfusion, equivalent to those realized on fluorescein angiography (FA), and changes of deep capillary plexus (DCP) and superficial capillary plexus (SCP) (10).

Cases & Methods

- Type of the study: This is a cross sectional study.
- Site of the study: Participants were selected conveniently from regularly visited cases of immunology clinic, internal medicine department in Beni-suef university hospital(population of upper Egypt)
- Period of the study: The study was at period between first of September 2019 to end of March 2021.

- Study population and Sample size: sample size was determined via the following formula: $n=z^2\times PQ/D^2$
  Where:
  n= required sample size.
  Z= Confidence level at 95% (Standard value of 1.96)
  P= estimated prevalence of BD based on a recent study P=3.20 %
  $Q=1-P$
  D= margin of error i.e 0.05
  n= $(1.96)^2(0.032)(1-0.032)/(0.05)^2=60$
  So participants were divided into 6 groups: Group 1: smoker BU cases (10 cases) ,Group 2: non-smoker BU cases (10 cases) , Group 3: smoker BD cases without uveitis (10 cases) , Group 4: non-smoker BD without uveitis cases (10 cases), Group 4: smoker normal control (10 cases) &Group 6 : non smoker normal control (10 cases),

- Data collection Methods and Tools:
  Each Participant experienced a full ophthalmic investigation including the following evaluations: visual acuity using Landolt C chart expressed by Decimel and refractive error with autorefractometer, IOP measurement with a Goldman applanation tonometer, anterior segment examinations by slit-lamp bio-microscopy, fundus examinations and ONH assessment with a 90-diopter lens and OCT angiography (Macula).

Scans were done via the AngioPlex OCTA package on a Zeiss Cirrus HD-OCT (AngioPlex, CIRRUS HDOCT model 5000; Carl Zeiss Meditec, Inc., Dublin, OH), which utilizes a mean value projecting to give en face scans (11). Every case was scanned 2 times per eye by the same specialist and device at every visit. Cases weren't moved at the headrest amid scans and an break of 30 sec to 1 min was taken amid successive images in one visit. Every image was assessed for horizontal motion artifacts and signal intensities (12).

Fig. (1) ZEISS HD-OCT Model 5000 instrument with Angioplex TM OCTA capability.

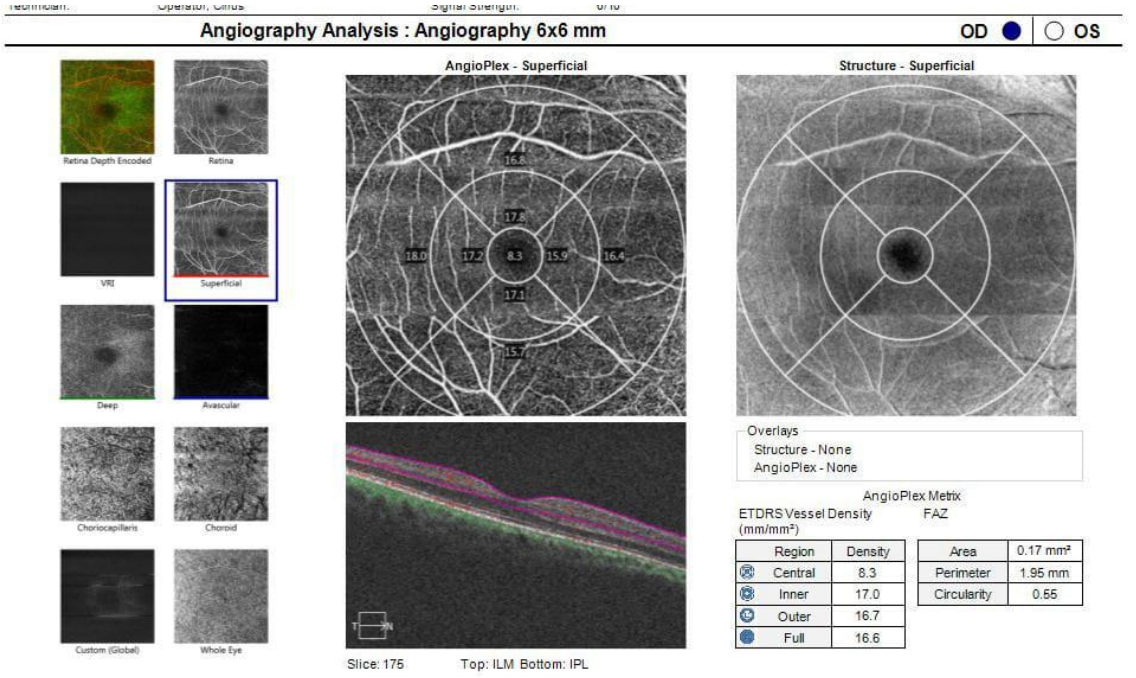

Fig. (2) OCTA printout of normal control.

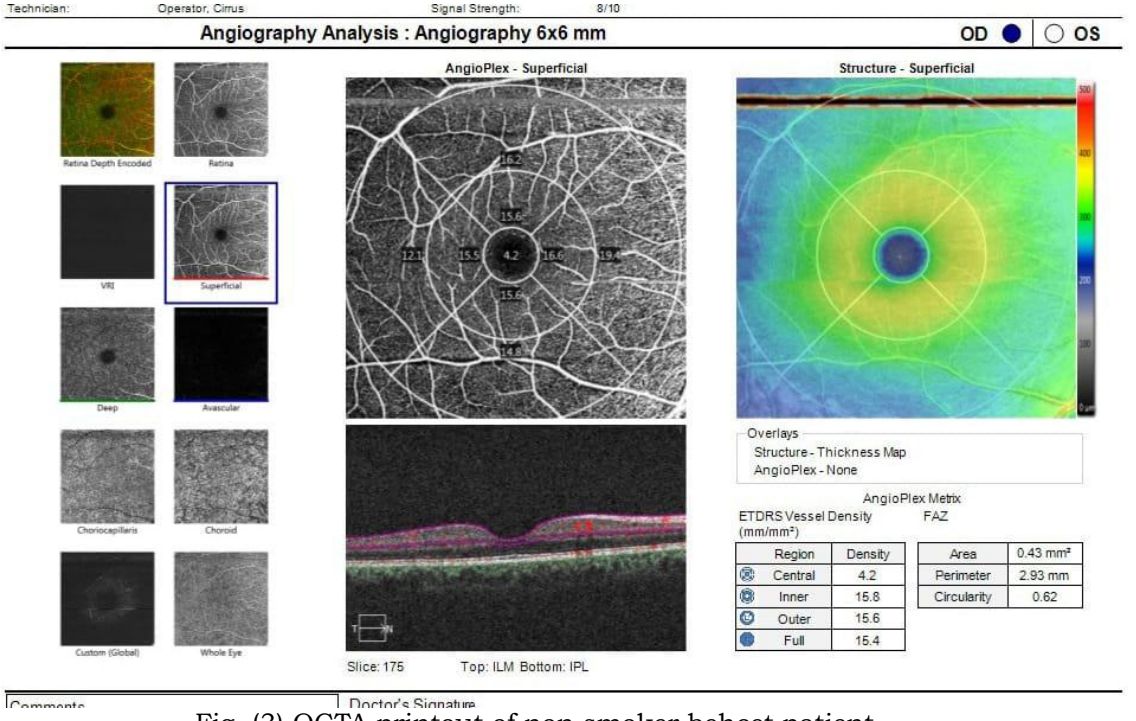

Fig. (3) OCTA printout of non smoker behcet patient.

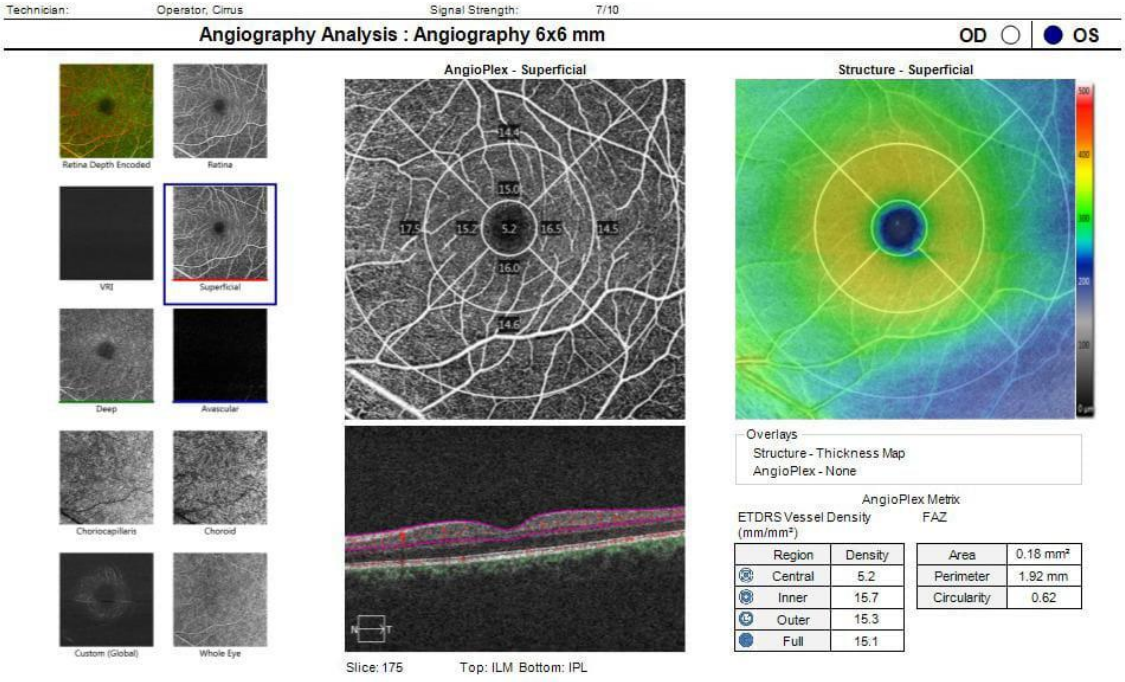

Fig. (4) OCTA printout of smoker behcet patient.

Cases were selected conveniently according to the following Inclusion and Exclusion criteria

a) Inclusion criteria:

- Behcet pateints (Smokers &non Smokers)
- Normal control (Smokers &non Smokers)

b) Exclusion criteria

- Eyes with coexisting vascular retinal pathologies.
- Eyes with glaucoma.
- Eyes with media opacities, which can influence the quality of the OCT image.

OCT Angiography parameters including macular Vessel density& FAZ parameters were obtained in all subjects.

- Ethical considerations: including explaining the study to participants, informed consent from participants and approval of the ethical committee fulfilled.
- Statistical Analysis:
  The most suitable statistical methods to summarize and infere the findings and tests of significance were used.

Results

This current study was a crosssectional study conducted on a population of sixty BU cases &normal control divided into six equal groups (10 cases in each

group) to assess the OCTA results of smokers & non-smokers of BU cases, BD without uveitis cases & normal control. Table (1) demonstrate the baseline data of the studied population. The age distribution was similar in all groups without a significant change (p-value=0.632). While regarding gender, males were significantly predominant in the smoker Behçet disease without uveitis cases &normal control. Visual acuity is lowest in BU non-smoker cases & to lesser extent BU smokers cases but with a significant difference (p=0.001). IOP is highest in BU non-smoker cases & to lesser extent BU smokers cases but with a significant difference (<0.0001).
The mean duration (months) of Behçet diseaewas higher in BD without uveitis smoker cases, however this difference has statistically significant meaning (p-value= <0.0001).

Table 1
Baseline data of the studied cases One-Way ANOVA test for quantitative data between the three groups Chi square test (if less than 20% of cells have expected count less than 5) or Fisher's Exact test (if more than 20% of cells have expected count less than 5) for qualitative data between groups Significant level at P value < 0.05

Characteristic	Normal control N= 20		Behcet uveitis BU-cases N= 20		Behcet disease without uveitis BU-cases N= 20		*p-value*
	Non-Smokers N= 10	Smokers N= 10	Non-Smokers N= 10	Smokers N= 10	Non-Smokers N= 10	Smokers N= 10	
Age; (years) Mean ±SD	45.80 ± **14.37**	45.00 ± **20.02**	36.40 ± **10.72**	43.80 ± **12.35**	38.20 ± **16.92**	44.40 ± **13.74**	0.632
Gender Male Female	4(40.0%) 6(60.0%)	10(100.0%) 0(00.0%)	2(20.0%) 8(80.0%)	8(80.0%) 2(20.0%)	2(20.0%) 8(80.0%)	10(100.0%) 0(00.0%)	<0.0001*
VA Mean ±SD	0.76 ± **0.33**	0.84 ± **0.18**	0.36 ±**0.30**	0.51 ± **0.33**	0.71 ± **0.24**	0.82 ± **0.16**	0.001*
IOP Mean ±SD	12.80 ± **1.03**	12.30 ± **1.57**	18.80 ± **2.99**	17.40 ± **2.72**	15.60 ± **1.58**	13.60 ± **1.58**	<0.0001*
Duration; (months) Mean ±SD	0.00	0.00	158.20 ± **113.46**	244.80 ± **144.58**	156.00 ± **183.48**	252.40 ± **170.93**	<0.0001*

Table (2) demonstrates a comparison of the capillary vessel densities in cases with Behcet uveitis,Behcet diseaewith no uveitis cases &normal control according to smoking status as examined by OCT-A. Although all the OCT-A parameters obtained in the current study regarding Behçet uveitis cases were less than BD without uveitis & normal control with a significant change (P-values <0.0001)*.

Table 2: Comparison of the capillary vessel densities among studied cases according to smoking status as examined by OCT-AOne-Way ANOVA test for quantitative data between the three groups Significant level at P value < 0.05

Characteristic	Normal N= 20		Behcet uveitis BU-cases N= 20		Behcet disease without uveitis BU-cases N= 20		*p-value*
	Non-Smokers N= 10	Smokers N= 10	Non-Smokers N= 10	Smokers N= 10	Non-Smokers N= 10	Smokers N= 10	
VD of fovea Mean ±SD	1.98 ± 0.55	2.45 ± 0.32	5.47 ± 0.75	0.47 ± 0.13	6.20 ± 3.51	4.66 ± 0.55	<0.0001*
VD of superior parafoveal Mean ±SD	11.19 ± 2.89	9.35 ± 0.89	11.07 ± 4.31	6.46 ±2.23	12.27 ± 5.72	14.96 ± 0.55	<0.0001*
VD of inferior parafoveal Mean ±SD	10.49 ± 4.57	9.58 ± 0.22	10.32 ± 4.08	6.28 ± 1.92	12.29 ± 6.01	15.56 ± 0.52	<0.0001*
VD of nasal parafoveal Mean ±SD	10.98 ± 4.09	9.00 ± 0.47	12.53 ± 4.72	5.94 ± 1.83	11.90 ± 5.64	15.16 ± 0.78	<0.0001*
VD of temporal parafoveal Mean ±SD	11.15 ± 4.22	10.09 ± 1.74	9.96 ± 3.17	5.95 ± 2.45	12.02 ± 5.96	15.48 ± 0.69	<0.0001*
VD of superior perifoveal Mean ±SD	11.44 ± 4.13	11.05 ± 0.87	8.10 ± 5.31	8.64 ± 2.47	12.89 ± 4.59	15.06 ± 0.68	<0.0001*
VD of inferior perifoveal Mean ±SD	14.07 ± 5.19	12.30 ± 1.01	7.84 ± 4.99	8.86 ± 3.47	12.14 ± 5.02	14.72 ± 0.38	0.001*
VD of nasal perifoveal	9.52 ± 4.30	11.44 ± 1.74	9.50 ± 7.12	12.23 ± 5.57	13.81 ± 4.88	18.37 ± 0.79	0.001*

VD of temporal perifoveal Mean ±SD	9.89 ± 2.22	8.83 ± 0.36	8.28 ± 5.03	6.12 ± 1.41	12.63 ± 5.07	12.92 ± 1.07	<0.0001*
VD of inner retina	13.55 ± 2.57	11.62 ± 0.54	10.95 ± 3.91	5.83 ± 1.87	12.88 ± 5.87	15.17 ± 0.45	<0.0001*
VD of outer retina Mean ±SD	12.45 ± 2.66	10.69 ± 0.46	8.36 ± 5.51	8.95 ± 3.19	13.87 ± 5.20	14.89 ± 0.43	<0.0001*
VD of full retina Mean ±SD	0.09 ± 0.09	00.00 ± 00.00	11.22 ± 3.81	8.24 ± 2.92	13.07 ± 5.15	14.91 ± 0.36	<0.0001*

characteristic	Behcet uveitis (BU) N= 20		*p-value*
	Non-Smokers N= 10	Smokers N= 10	
VD of fovea Mean ±SD	5.47 ± 0.75	0.47 ± 0.13	<0.0001*
VD of superior parafoveal Mean ±SD	11.07 ± 4.31	6.46 ±2.23	<0.010*

Table 3
Comparison of the capillary vessel densities among Behçet uveitis cases according to smoking status as examined by OCT-A.

- Independent sample T-Test test for quantitative data between the groups
- Significant level at P value < 0.05Table (3)

VD of inferior parafoveal Mean ±SD	**10.32 ± 4.08**	**6.28 ± 1.92**	**<0.014***
VD of nasal parafoveal Mean ±SD	12.53 ± 4.72	5.94 ± 1.83	<0.002*
VD of temporal parafoveal Mean ±SD	9.96 ± 3.17	5.95 ± 2.45	<0.005*
VD of superior perifoveal Mean ±SD	8.10 ± 5.31	8.64 ± 2.47	0.774
VD of inferior perifoveal Mean ±SD	7.84 ± 4.99	8.86 ± 3.47	0.602
VD of nasal perifoveal	9.50 ± 7.12	12.23 ± 5.57	0.353
VD of temporal perifoveal Mean ±SD	8.28 ± 5.03	6.12 ± 1.41	0.220
VD of inner retina	10.95 ± 3.91	5.83 ± 1.87	0.003*
VD of outer retina Mean ±SD	8.36 ± 5.51	8.95 ± 3.19	.773
VD of full retina Mean ±SD	11.22 ± 3.81	8.24 ± 2.92	0.067

demonstrate a comparison of the capillary vessel densities in cases with Behçet uveitis according to smoking status as examined by OCT-A . Although all the OCT-A parameters obtained in the current study regarding Behçet uveitis smokers cases were less than non smokers ones with a significant change(P-values <0.0001) * within vessel density of the fovea &parafovea.

characteristic	Behcet disease without uveitis N= 40		p-value
	Non-Smokers N= 20	Smokers N= 20	
VD of fovea Mean ±SD	5.83 ± 2.99	2.56 ± 2.18	<0.0001*
VD of superior parafoveal Mean ±SD	11.67 ± 4.97	10.71 ± 4.64	0.531
VD of inferior parafoveal Mean ±SD	11.31 ± 5.10	10.92 ± 4.95	0.810
VD of nasal parafoveal Mean ±SD	12.21 ± 5.07	10.55 ± 4.92	0.299
VD of temporal parafoveal Mean ±SD	10.99 ± 4.77	10.72 ± 5.19	0.862
VD of superior perifoveal Mean ±SD	10.49 ± 5.42	11.85 ± 3.74	0.364
VD of inferior perifoveal Mean ±SD	9.99 ± 5.35	11.79 ± 3.85	0.230
VD of nasal perifoveal Mean ±SD	11.66 ± 6.35	15.30 ± 4.99	0.051
VD of temporal perifoveal Mean ±SD	10.46 ± 5.40	9.52 ± 3.69	0.527
VD of inner retina Mean ±SD	11.91 ± 4.96	10.50 ± 4.97	0.373
VD of outer retina Mean ±SD	11.11 ± 5.93	11.92 ± 3.77	0.612
VD of full retina Mean ±SD	12.14 ± 4.51	11.57 ± 3.98	0.674

Table 4: Comparison of the capillary vessel densities among Behçet disease without uveitis according to smoking status as examined by OCT-A

- *Independent sample T-Test test for quantitative data between the groups*
- *Significant level at P value < 0.05*

Table (5) demonstrates a comparison of the foveal avascular area parameters among studied cases according to smoking status.Average avascular foveal zone area &circularity measured at the capillary plexus was larger in Behçet uveitis BU-cases &BD without uveitis than normal controls with a significant difference (P-values <0.0001*).Average FAZ perimeter was nearly similar among non smokers .However, average FAZ perimeter is larger in somkers BD without uveitis than smokers normal controls without a significant difference (p= 0.204).

characteristic	Normal N= 20		Behcet uveitis BU-cases N= 20		Behcet disease without uveitis BU-cases N= 20		p-value
	Non-Smokers N= 10	Smokers N= 10	Non-Smokers N= 10	Smokers N= 10	Non-Smokers N= 10	Smokers N= 10	
FAZ area Mean ±SD	0.07 ± 0.15	0.01 ± 0.01	1.10 ± 0.69	00.00 ± 00.00	0.06 ± 0.01	0.06 ± 0.14	<0.0001*
FAZ perimeter Mean ±SD	0.59 ± 1.24	0.07 ± 0.25	0.73 ± 0.10	0.00 ± 00.00	0.63 ± 1.02	0.48 ± 1.04	0.204
FAZ circularity Mean ±SD	0.10 ± 0.21	0.08 ± 0.25	00.00 ± 00.00	1.40 ± 0.52	0.15 ± 0.25	0.12 ± 0.26	<0.0001*

Table 5: Comparison of the foveal avascular area parameters among studied cases according to smoking status

- *One-Way ANOVA test for quantitative data between the three groups*
- *Significant level at P value < 0.05*

Table (6) demonstrate a Comparison of the foveal avascular area parameters among behcet uveitis (BU) patients according to smoking status.Average avascular foveal zone area ,perimeter &circularity measured at the capillary plexus was larger in behcet uveitis smokers than non smokers patients with a statistically significant difference.

characteristic	Behçet uveitis (BU) N= 20		p-value
	Non-Smokers N= 10	Smokers N= 10	
FAZ area Mean ±SD	1.10 ± 0.69	00.00 ± 00.00	0.001*
FAZ perimeter Mean ±SD	0.73 ± 0.10	00.00 ± 00.00	<0.0001*
FAZ circularity Mean ±SD	00.00 ± 00.00	1.40 ± 0.52	<0.0001*

Table 6: Comparison of the foveal avascular area parameters among Behçet uveitis cases according to smoking status

- *Independent sample T-Test test for quantitative data between the groups*
- *Significant level at P value < 0.05*

Table (7) demonstrate a Comparison of the foveal avascular area parameters among behcet disease patients according to smoking status.Average avascular foveal
zone area ,perimeter &circularity measured at the capillary plexus was larger in behcet disease smokers than non smokers patients with a statistically significant difference.

characteristic	Behcet patients N= 40		p-value
	Non-Smokers N= 20	Smokers N= 20	
FAZ area Mean ±SD	0.58 ±0.72	0.032 ± 0.078	0.003*
FAZ perimeter Mean ±SD	0.61 ± 0.74	0.32 ± 0.78	0.228
FAZ circularity Mean ±SD	0.062 ± 0.19	0.78 ± 0.75	<0.0001*

Table 7: Comparison of the foveal avascular area parameters among Behçet cases according to smoking status.

- *Independent sample T-Test test for quantitative data between the groups*
- *Significant level at P value < 0.05*

Table (8) demonstrate a Comparison of the foveal avascular area parameters among behcet disease without uveitis patients &normal controls according to smoking status. Average avascular foveal zone area

,perimeter &circularity measured at the capillary plexus were similar in Behçet disease without uveitis patients & normal control without a statistically significant difference.

characteristic	normal control N= 20		Behcet disease without uveitis N= 20		*p-value*
	Non-Smokers N= 10	Smokers N= 10	Non-Smokers N= 10	Smokers N= 10	
FAZ area Mean ±SD	0.07 ± 0.15	0.01 ± 0.01	0.06 ± 0.01	0.06 ± 0.14	0.549
FAZ perimeter Mean ±SD	0.59 ± 1.24	0.07 ± 0.25	0.63 ± 1.02	0.48 ± 1.04	0.568
FAZ circularity					

Table 8: Comparison of the foveal avascular area parameters among normal and Behçet disease without uveitis cases according to smoking status

- *One-Way ANOVA test for quantitative data between the groups*
- *Significant level at P value < 0.05*

Discussion

The present work was designed to study the impacts of smoking in Behçet disease by comparing the OCTA findings of smokers & non-smokers of Behçet uveitis BU-cases ,BD without uveitis & normal control. In the current study the number of males (36, 60%) were more than females (24, 40%) with a significant difference in sex between the two studied groups. Contrary to what is observed in the studied sample in our current study, the prevalence of BD wasn't revealed to be very different among males and females as reported in a large number of epidemiological researches (13), however each sign revealed a clear variance among the sexes (14). The prevalence of all ocular findings has been reported to be higher in females (15). This variance can be clarified by the fact that the current study focused on the impact of smoking, whose prevalence rate in Arab countries is naturally higher among males in comparison with females (16).

FA is more sensitive than clinical inspection in diagnosing the retinal vasculitis, viewing staining of the blood vessel wall and leak. Capillaritis, marked by capillary leakages and extents of capillary no perfusion, may be obvious only via FA (17). But, leakages of dye may limit our capability to assess adjacent capillaries perfusions. Furthermore, leakages may be existing because of formerly injured or ischemic capillaries beds in the nonattendance of active inflammations .OCTA isn't limited by leakages (or other reasons of hyper-fluorescence on FA like pooling and window fault), and may deliver micro-vascular morphological details and data concerning capillaries perfusions, with

quantitative ability, of both the surface and deep capillaries plexus (18)(19). Because of dye leakages, FFA doesn't permit foveal avascular zone (FAZ) measurements in the two eyes; consequently, the researchers have to select single eye. But, OCTA is a very advantageous device to assess and determine the FAZ. FAZ zones of the BU cases were concluded to be significantly larger than in healthy cases (20)(21).

Although all the vessel density as measured by OCT-A obtained in the current study regarding BU cases were less in BU cases, to lesser extent in BD cases without uveitis, than the normal population as reviewed, a comparison of the capillary vessel densities in cases with Behçet uveitis, BD cases without uveitis &normal control ,according to smoking status as examined by OCT-A reveled strong significant differences according to smoking status.

The results of the current study are in complete contrary with Biglin study conducted to study the association among smoking and prediction of ocular BD where they settled that smoking doesn't have a negative impact on the clinical results and prediction of uveitis in BD (22).

Ayhan Z &Hollo G studies were reported that increase the issues of the effect of smoking on retinal vascular factors determined by OCTA which in turn against our results. The findings gotten by Ayhan et al. revealed that smoking doesn't lead to significant fluctuations in the size of the FAZ area and the macular vessel densities in healthy habitual smoker(23). Holló G. proposes that macular and peripapillary vessel densities values in healthy middle-aged smokers aren't impacted by acute smoking (24).

Omae et al. claim that afterward smoking the retinal blood flowing and the blood speed significantly lessening with no any variations in vessels diameters, but they utilized other approaches to evaluate retinal circulations, which can be more sensitive to notice variations resulted from smoking than OCTA(25).

Rendering to Lin, et al. the strong association among smoking and uveitis doesn't mean that smoking leads to uveitis, nor exacerbates uveitis (26), but Galor A stated that smoking had a function in the activity, failing course and perpetuations of ocular inflammations, and the danger of inflammatory uveitis activity rises with growing cigarette number (27).

To summarize, smoking is significantly correlated with the increased probability of two-sided ocular inflammations, decreased vision on presentations and 17-27% elevated danger of inflammations relapsing in comparison to not smoking status (27), as well as with noninfectious uveitis activity causing elevated necessity for steroid eyedrops and raised occurrence of cataract and CME (28). All above motives and fact that previous/prior smokers have a clinical course of inflammations analogous to that of non-smokers (27). focus the necessity to encourage uveitis cases to stop or at minimum to decrease their smoking (28), professionals inspiring to stop smoking must be even a part of routine uveitis managing (27).

Inconsistently, Kaklamni VG &Ciancio G researches had concluded development or even full reversion of active, refractory muco-cutaneous lesions (oral aphthae) in cases with BD; among them were as well ex-smokers, afterward nicotine patch treatment for 6 months (29). however, nicotine patch has no influence on other Behcet's parameters, i.e. arthritis and uveitis (30).

Jain assumed that Smokers have a total 2.2-fold elevated odds of developing uveitis in comparison to those never smoked (31). Gonzalez have proposed a connotation amid smoking and elevated uveitic severity, uveitis is 1.8 fold more probable to have clinical activity in smokers, causing elevated frequencies of macular edema and cataracts (32).

In the original report performed by Spaide and Curciom, the examinations achieved by Heidelberg's OCT-A in 5 cases with retinal vasculitis of diverse etiology showed areas of micro-vascular flowing irregularity, capillary flowing loss and vascular re-modelling. In Spaide and Curciom research, wide areas of retinal capillary perfusions irregularities were detected in surface and deep plexuses (33). In contrast, Khairallah et al. have lately defined the results of OCT-A in 44 eyes of 25 cases with clinically active Behcet accompanying uveitis, which were investigated by OCT-A 3 × 3 mm with Topcon's DRI OCT Triton plus system, the same day FL.angiography (FA) was done (20). Khairallah et al. showed that marginal micro-vascular differences (disruption of the perifoveal capillary arcade, zones of capillary nonperfusion, irregularities in the perifoveal capillary network, and vascular re-modelling) were more frequently detected with OCT-A than with FA. They as well point out that capillary irregularities and architectural dis-organization of the capillary network were more common in the deep vascular plexus than in the surface plexus. Lastly, they revealed that the eyes with Behcet's disease had lower perifoveal capillaries densities and a foveal avascular area larger than the eyes of healthful persons (20).

Kim et al. (2016) done a quantitative OCTA analysis on eyes with macular edema to find out whether its existence was accompanying with differences in DCP density or morphology. In their cohort of uveitis cases, 16 eyes had macular edema. Analysis found significantly lower vessel densities in the deep plexus of uveitic persons with macular edema (34).

In the research by Bessette et al.(2016), only 56% of eyes that were active, with activity definite as leakages of the dye from the vessels on fluorescein angiography, showed irregularities on OCTA. On the other hand, 13 cases confirmed variations in the retinal micro-vasculature on OCTA that weren't recognized with FA (35).

Emre S. et al evaluated capillary vessel density CVD of these cases and in comparison, to controls. This device gives these CVDs as percentage rate. All factors were significantly lower in Behcet cases than in controls (36).

In the present results propose that Behçet uveitis cases may have micro-vascular changes at the macular level & to lesser extent BD deprived of uveitis illustrations changes at macular levels in the nonattendance of formerly

diagnosed retinal vasculitis in comparison with controls. The clinical significance of these changes is not evident.

Additionally, Khairallah et al. supposed that avascular foveal area was not significantly larger in Behçet cases than in the control group, either in the superficial or in the deep plexus (20). Ceylanglu et al. reported that cigarette smoking can cause enlargement of the FAZ area and decrease macular micro-vascular densities in healthy e-cigarette smokers (37).

In the present study, we found that Average avascular foveal zone area & Average avascular foveal zone circularity were measured at the superficial capillary plexus was larger in BU cases &BD without uveitis than normal control (p=<0.0001). Average FAZ perimeter was nearly similar among non smokers .However, average FAZ perimeter is larger in somkers BD without uveitis than smokers normal controls without a significant difference (p= 0.204).

The enlarged FAZ parameters may suggest the existence of macular ischemia in BU eyes (38), (39), (40). The larger FAZ parameters in smoker BU cases in the current study could be explained by the multiplier impact of both smoking and disorder.

In conclusion

the current study found that OCT-A allows us to identify retinal micro-circulation alterations at the macular level in Behçet uveitis cases even in the absence of previous angiographic diagnosis of vasculitis. The clinical significance of these alterations remains unclear, and further larger sample researches of a prospective nature are needed, where cases are clinically as-sessed with this exam and an analysis of the association between the degree of vascular alterations and the cases' disorder severity can then be conducted. However, our results imply that smoking has a significant influence on BD clinical results of uveitis. We believe bigger series are needed to corroborate our results with future follow-up.

Our study has some limitations:

1) Our overall sample size was modest; therefore, it is difficult to draw definitive conclusions from this study alone. Further researches are needed to verify our findings to prove or disprove the relationship between smoking and Behçet Uveitis.
2) The cross-sectional nature of our study and lack of stable treatment protocols that have an indirect impact on the severity of the disorder limits the strength of our conclusions.
3) All the researches about the impact of smoking on uveitis included uveitis types of different and variable etiologies. However,We included only the cases with Behçet disorder, and this may explain the contrary results about impact of smoking on prognosis and clinical findings of uveitis.

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