Smoking Effect on Peripapillary and Macular Microvascular Structure in Inactive Graves' Ophthalmopathy

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Abstract

Objective

The aim of this study was to evaluate the smoking effect on peripapillary and macular microvascular structure in patients with inactive Graves' ophthalmopathy (GO) and to compare these structures with those of healthy control subjects.

Methods

A total of 34 healty participants (control group), 22 inactive GO patients with smoking (smoker group) and 19 inactive GO patients with nonsmoking (non-smoker group) were recruited in this prospective study. After detailed ophthalmological examination, vessel densities (VD) of the superficial capillary plexus (SCP), deep capillary plexus (DCP), retinal peripapillary capillary (RPC) and foveal avascular zone (FAZ) area, acircularity index (AI) of the FAZ were analyzed with optical coherence tomography angiography (OCTA) for each eye.

Results

Vessel density in the total peripapillary; superior and inferior sectors of RPC were significantly lower in inactive GO patients with smoking ($p<0.05$ for all sectors) compared to control group. Besides, the FAZ AI was significantly higher in smoker and non-smoker inactive GO groups compared to healthy subjects ($p=0.0001$, $p=0.0001$, respectively). No significant difference was found in the FAZ area, and all SCP, DCP macular measurements between groups ($p>0.05$ for all).

Conclusion

OCTA findings of lower peripapillary VD in the smoker group show smoking effect on the optic disc head microvasculature in inactive GO patients. These results could reflect early subclinical optic disc vasculature damage in smoker inactive GO subjects.

Introduction

Graves' ophthalmopathy (GO), is an autoimmune inflammatory disorder that mainly affects patients with Graves' disease [1]. The prevelance of GO in Graves' disease patients is 34–46% [2]. Smoking has been shown as a strongest modifiable risk factor in GO, increases the risk of development of severe forms of GO and decreases response to treatments for moderate-to-severe and active GO [3]. Knowledge of the hemodynamic effects of smoking on ophthalmic vasculature is limited. Role of smoking on retrobulbar blood flow was reported in Graves' disease by using colour Doppler imaging [4]. The authors declared decreased venous pressure of superior ophthalmic vein in smokers [4].

Optical coherence tomography angiography (OCTA) is a noninvasive technique that allows physicians to assess retinal microvasculature structure without dye injection (5). OCTA provides rapid, high-resolution

3D images and reliable quantitative data from the retinal and choroidal vasculature [6]. The effects of smoking on optic nerve and macular microvascular changes in inactive GO has not been shown using OCTA, until now. The aim of this prospective study was to investigate the effect of smoking on the peripapillary and macular microvascular structure changes in inactive GO by using OCTA.

Methods And Patients

Patients with inactive GO who visited the outpatient clinic of University of Health Sciences, Ulucanlar Eye Education and Research Hospital were recruited for this prospective, cross-sectional study. Also, age and sex-matched healthy subjects were enrolled simultaneously from the same hospital.

The study was performed in accordance with the tenets of the Declaration of Helsinki and also adhered to the requirements of the ethics committee.
All participants provided informed consent to participate in the study.

A total of 34 healty participants (control group; age and sex-matched healthy non-smoker volunteers), 22 GO patients with smoking (smoker group) and 19 GO patients with nonsmoking (non-smoker group) were included in the study. The inclusion criteria for GO patients were following: 1) age of > 18 years, 2) euthyroid state with normal ranges of thyroid hormones and thyroid autoantibody at least 3 months, 3) the clinical activity score (CAS) < 3 for at least 3 months prior the OCTA analysis, 4) no history of treatment with glucocorticoid and radioactive iodine, 5) mild GO, 6) OCTA images with Quality score > 7.

The exlusion criteria for all patients were following: 1) refractive spherical and cylindrical error > 2D, 2) presence of any ocular disease (cataract, glaucoma, significant media opacity, retinal disease, disthyroidoptic neuropaty or any optic neuropathy).

Detailed ophthalmic examination including eyelid width, proptosis, pupillary responses, refraction, colour vision test, visual acuity, intraocular pressure measurement, slit lamp examination, anterior and posterior segment examination were performed for all participitant. The demographic information including age, sex, smoking status, duration of GO, and therapy method were recorded. Also, laboratory bimarkers such as free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), and TSH-receptor autoantibody (TRAb) were recorded in the patients with GO. Smoking package year was calculated by multiplying the number of packs of cigarettes smoked per day by the number of the years. The CAS system was used to estimate GO disease activity status for each patient [7], and severity classification were made using the European Group on Graves' ophthalmopathy (EUGOGO) criteria [8].

OCTA was performed by the researcher (SD) who was blind to the patients using the XR Avanti AngioVue OCTA (Optovue, Fremont, California, USA) (Version 2017.1.0.151). This system uses a split-spectrum amplitude decorrelation angiography (SSADA) algorithm and operates at 70.000 A-scans per second to acquire OCTA volumes consisting of 400 x400 B-scans. A 6 × 6 mm macular scan was used to measure retinal capillary plexuses. The angio-retina scans automatically inserted three fovea-centered circles on the macula to detect the superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel

densities (VD). Foveal zone vessel density was defined as the area of the small circle, with a diameter of 1 mm. The parafoveal zone VD was defined as the areas of the middle circle, with a diameter of 3 mm. The following recorded parameters were; the foveal avascular zone (FAZ) area (mm^2) and acircularity index (AI) of the FAZ (AI, the rate of the perimeter of FAZ and the perimeter of a circle with equal area).

For optic nerve OCT-A, a 4.5 × 4.5 mm rectangle scan centered on the optic disc was employed. In optic nerve head (ONH) scan, the software automatically calculated the retinal peripapillary capillary (RPC) VD (total, superior and inferior hemi).

All the scans were performed for all participants in the same time frame from 1 to 2 pm to avoid possible diurnal variations. All OCTA images were reviewed by another researcher (KSC). In GO group, the affected eye was was selected in unilateral disease and the selection of the measurement was made randomly in bilateral disesase. In control group, the data from the right eye were used for selection.

Statistiscal analyses were performed with Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illionis, USA) version 22.0. The data were presented as the mean ± standart deviation. For categorical variables, the Chi-square test was used. The normality of the data was confirmed using the Kolmogorov-Smirnov test. Kruskall wallis test was used for variables that did not show normal distribution. The Games-Howell post-hoc test was used to analyse the difference OCTA parameteres. A p-value < 0.05 was considered statistically significant.

Results

A total of 75 participants was enrolled in this prospective study, with 34 (45.3%) healty control, 22 (29.4%) inactive GO patients with smoking and 19 (25.3%) inactive GO patients with nonsmoking. There was no significant difference among the groups in terms of age (p = 0.27), sex distribution (p = 0.39), spherical equivalent (p = 0.40) and intraocular pressure (p = 0.32). The mean duration of the GO was 16.04 ± 14.5 months in smoker patients and 25.4 ± 18.1 months in non-smoker patients (p = 0.73). All patients of GO were inactive stage (CAS < 3) and there was no difference in CAS between smokers and non-smokers (p = 0.28). In terms of laboratory values, there were no significant differences in the FT3, FT4, TSH and TRAb between smokers and non-smokers in GO group (p = 0.10, p = 0.79, p = 0.29, p = 0.65, respectively). The mean package smoking year was 19.4 (range:5–40) in GO with smoking group. There was no significant difference between package smoking year and OCTA measurements in smokers (p > 0.05, for all). Table 1 shows demographic and clinical characteristics of the inactive GO patients and control group.

Table 1
Demographic and clinical data of all enrolled subjects

	Control group (n:34)	Inactive GO Smokers (n:22)	Inactive GO Non-smoker (n:19)	P value
Age (years)	41.6 ± 8.2	44.3 ± 6.7	40.2 ± 9.0	0.27*
Sex (male/female)	13/21	6/16	4/15	0.39¶
Spherical equivalent (D)	0.6 ± 0.2	0.6 ± 0.2	0.5 ± 0.2	0.40*
Duration of GO (months)	NA	16.04 ± 14.5	25,4 ± 18.1	0.73*
CAS	-	0.3 ± 0.68	0.18 ± 0.39	0.28*
Package smoking year	-	19.4 (range 5–40)	-	-
FT3, pg/ml	-	3.4 ± 0.9	2.9 ± 0.8	0.10*
FT4, ng/dl	-	0.89 ± 1.9	0.61 ± 0.2	0.79*
TSH, µIU/ml	-	1.7 ± 1.0	2.1 ± 1.25	0.29*
TRAb, IU/L	-	3.35 ± 1.9	3.03 ± 1.9	0.65*
Values are means ± standart deviations for all subjects in each group.				
¶ Pearson chi-square test, *t test,				
GO: Graves'orbitopathy,CAS:clinical activity score				
FT3: free triiodothyronine; FT4: freethroxine; TSH:thryoid-stimulatinghormone; TRAb:TSH-receptor autoantibody; NA: not applicable; -: not performed				

Macular and ONH vessel density parameters across groups were listed in Table 2. There were no significant differences among groups with regard to FAZ area ,VD of SCP and DCP ($p > 0.05$, for all). In Kruskal Wallis analysis, statistically significant differences were found in AI ($p < 0.0001$, for all). After Post-hoc analyses, compared to healthy controls, smokers and non-smoker patients in inactive GO group had significantly higher AI ($p < 0.0001$, for all). There was no significant difference in any macular VD parameteres between smoker and non-smoker patients in inactive GO group.

Table 2
Comparison OCTA parameters between groups

		GO			Post-HOC analysis¶ P values		
Variables	Control group	Smoker	Non-smoker	P value*	Control vs smoker GO	Control vs nonsmoker GO	Smoker vs nonsmoker GO
FAZ area (mm^2)	0.23 ± 0.1	0.26 ± 0.91	0.31 ± 0.16	0.19	0.05	0.20	0.18
AI	1.1 ± 0.03	2.01 ± 0.41	2.01 ± 0.31	0.0001	0.0001	0.0001	1.0
VD of SCP (%)							
Whole	50.8 ± 3.8	49.7 ± 2.9	50.04 ± 3.5	0.442	0.59	0.84	0.98
Fovea	20.3 ± 3.9	23.1 ± 5.4	19.3 ± 5.6	0.141	0.14	0.79	0.095
Parafovea	52.4 ± 4.6	52.3 ± 3.7	51.8 ± 5.8	0.899	0.99	0.93	0.95
VD of DCP (%)							
Whole	49.6 ± 5.5	50.3 ± 5.7	51.08 ± 4.5	0.766	0.90	0.61	0.88
Fovea	40.2 ± 5.1	38.7 ± 5.7	36.2 ± 5.3	0.086	0.63	0.04	0.32
Parafovea	55.5 ± 3.4	54.8 ± 4.3	55.4 ± 3.4	0.917	0.85	0.99	0.88
VD of RPC (%)							
Peripapillary	54.2 ± 3.02	52.1 ± 2.03	53.6 ± 2.7	0.013	0.009	0.831	0.224

Values are means ± standart deviations unless otherwise indicated.

GO: Graves'ophthalmoparthy, FAZ:foveal avascular zone, AI: acircularity index VD: vesseldensity, SCP: superficial capillary plexus, DCP: deep capillary plexus, RPC: Retinal peripapillary capillary

*Comparison was performed using Kruskal-Wallis test for continous variables.

¶ Games-Howell post-hoc test was used to analyse the difference OCTA parameters

		GO			Post-HOC analysis¶ P values		
-Superiorhemi	54.8 ± 3.5	52.2 ± 2.3	53.8 ± 2.9	0.01	0.005	0.668	0.206
-Inferiorhemi	53.9 ± 2.5	52.07 ± 1.9	53.9 ± 2.8	0.038	0.008	1.00	0.093
Values are means ± standart deviations unless otherwise indicated.							
GO: Graves'ophthalmoparthy, FAZ:foveal avascular zone, AI: acircularity index VD: vesseldensity, SCP: superficial capillary plexus, DCP: deep capillary plexus, RPC: Retinal peripapillary capillary							
*Comparison was performed using Kruskal-Wallis test for continous variables.							
¶ Games-Howell post-hoc test was used to analyse the difference OCTA parameters							

VD of RPC in peripapillary, superior and inferior hemi sectors were significantly different among groups (p = 0.013, p = 0.01, p = 0.038, respectively). After post-hoc analysis, there was a significant difference between healthy controls and smoker GO patients for peripapillary, superior and inferior hemi sectors in RPC measurements (p = 0.009, p = 0.005, p = 0.008, respectively). There was no difference between smokers and non-smokers in inactive GO patients and also there was no significantly difference between healthy controls and non-smoker GO patients for RPC measurements.

Discussion

The most important extrathyroidal manifestation of Graves' disease is GO and it negatively affects the quality of life in these patients [9]. Smoking increases the risk of developing severe stage of GO, and reduces or delays the response to immun suppressive treatments used in the treatment of moderate-severe and active GO [3]. In previous studies, hemodynamic changes on ophthalmic vasculature have been shown to be vital in GO pathogenesis and currently, microvascular structures have begun to be evaluated with the help of OCTA. Studies have shown that retinal microvascular density can be affected by disease activity, TRAb levels, and severity of disease in Graves' disease [10–12]. However, it has not yet known whether smoking affects the microvascular structure in inactive GO. In this prospective study, we analyzed the effect of smoking on microvascular density of optic nerve and macula by excluding reported features associated with impaired microvascular density in GO in other studies. This is the first study evaluating the effects of smoking on peripapillary (RPC) and macular VD in inactive GO patients. We revealed that smoking may lead to reduction in peripapillary VD in this group patients. We also reported that AI was lower in the control group than inactive GO group, and there was no smoking effect on other macular measurements.

In healthy smokers, many studies have been conducted on the effects of smoking on ophthalmic vasculature [13–17]. In a study conducted with the help of the Laser Speckle method, it was reported that

smoking causes increased blood flow in the optic nerve head and choroid [13]. On the contrary, Morgado et al.[14] reported that smoking was associated with an increased retinal blood flow. Although there are different results among studies, it is obvious that smoking leads to vascular dysfunction in the ophthalmic vasculature. Recently, OCTA has been used to evaluate the effects of smoking on the retinal and ONH microvascular measurements [15–17]. One study showed that smoking causes a decrease in macular VD in the acute period in chronic smokers, however, this effect hasn't seen in the chronic period [15]. But there was no data about peripapillary vessel density. In contrast, Chiesielski et al. [16] reported that there was no immediate effect of smoking on macular and ONH VD parameteres in healthy habitual smokers. Another study compared the acute effect of smoking on macular and ONH VD in healthy non-smokers [17]. The authors reported that only one cigarette smoking significantly decreases the macular and ONH VD parameters at the acute period in non-smokers and that the increase in these parameters after one hour was slower when compared to non-smokers [17]. In the light of all these studies, it can be concluded that the effect of smoking on ophthalmic vasculature depends on the length of smoking history and smoking state, however, the reason for these contradicting results is unknown. In this study, we also reported that there was no significant difference between package smoking year (mean package smoking year was 19.4 (range 5–40)) and OCTA measurements in smokers.

It has long been known that smoking affects Graves' hyperthroidisim and especially on GO, however, the mechanism is not clear [18–19]. The effects of smoking on retrobulbar blood flow with Doppler ultrasonography were investigated in Graves' disease. It was reported that smoking significantly decreases venous pressure of superior ophthalmic vein Graves' disease [4].

In addition, ophthalmic vasculature is affected by many factors such as hyperthyroidism, ocular inflammation and ocular hypertension in Graves' disease [20]. In these studies, old techniques were used to assess the degree of the disorder and it is impossible to evaluate microvascular structure anyway. Only a few studies can be found in the literature about microvascular structures with OCTA in inactive GO patients [10–12, 21]. But, these studies did not investigate the effect of smoking as a factor impairing microvascular perfusion in GO. It was reported that the activity status and TRAb associated with GO is the relevant factors for reduced retinal capillary density [10]. Tehrani et al. reported that there was no difference between peripapillary VD in inactive GO patients when compared to control group [11]. But, in this study they reported lower peripapillary and macular vessel density values in the active GO group. Zhang et al. reported that both peripapillary and macular vessel density had been decreased in patients without dysthyroid optic neuropathy (DON) versus healthy controls [12]. Also, they inferred that the decrease in peripapillary VD might be earliest detectable change in the course of DON development [12]. But there was no data about the CAS of the GO patients in Zang et al's study. Akpolat et al. reported that only parafoveal macular VD decreased in inactive GO, but they ignored the effects of thyroid hormone, antibody levels and smoking on retinal microvascular measurements in this study [21]. Unfortunately neither of aforementioned studies reported clearly the affects of the smoking on retina and optic disc microvascular perfusion in GO patients. Therefore, in this study, we included the patients without DON, euthyroid state with normal level of thyroid hormone and antibody in order to show only the effect of smoking on microvascular structure in inactive GO patients. We showed decreased density of RPC levels

in smoker inactive GO patients. According to us, the reduction of the peripapillary VD in inactive GO patients with smoking may be valuable to detect early optic nerve involvement in this group. Although no visual impairment was detected in our patients due to GO, other studies can light any correlation between visual acuity and effect of smoking in the future.

In this study we also found only higher AI values among all retinal OCTA parameters (FAZ area, VD of SCP, VD of DCP) in GO patients. The effect of smoking was not observed on FAZ AI. AI is a FAZ parameter showing regularity of FAZ boundaries. The pathophysiological mechanisms underlying the irregularities at the FAZ boundaries are multifactorial, including capillary occlusion, vascular remodeling, and hemodynamic disturbances. Previous studies related diabetic retinopaty (DR) have qualitatively shown alterations in AI and have suggested that the FAZ becomes more acircular in DR, with a greater impact on the FAZ shape of the FAZ than on its area [22]. We think that in our study higher AI levels develops as a result of the deterioration and reduction of blood flow through the effect Grave's disease in our inactive GO patients. Besides, the increase in AI can be considered as early onset of foveal non-perfusion in these patients.

To the best our knowledge, this is the first study evaluating the smoking effect on ocular microvascular parameteres by OCTA which is a quick and non-invasive technique in inactive GO patients. But, it should be noted that the study had some limitations. Unfortunately, retinal vessel velocity and flow rate can't be evaluated in the studies conducted with OCTA, differences between groups could have been observed if other techniques were used in these patients. So, it is impossible to compare the effects of smoking on OCTA with the Doppler velocity technique. Furthermore, with the help of the OCTA, we can only measure 4.5 x 4.5 mm ONH and 6.0 x 6.0 mm macular area. Microvascular changes on these small areas do not indicate that smoking effects same on all vessels in GO patients.

In conclusion, our study showed that chronic smoking may negatively effect peripapillary VD (RPC) in inactive GO. These results could reflect early subclinical optic disc vasculature damage in smoker inactive GO subjects. Larger studies that investigate the longterm effects of smoking on optic disc vasculature may help explain the role of smoking as an accelerating risk factor on optic disc microcirculation in inactive GO patients. Also, AI of inactive GO patients was significantly increased compared to healthy controls. The AI can be considered as an useful OCTA parameter to onset of early foveal non-perfusion in inactive GO patients.

Declarations

Funding No funding was received for this research.

Compliance with ethical standarts

Conflict of interest The authors declare that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication We obtained consent for publication from each patient.

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