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Dry eye disease and retinal nerve fiber layer changes in chronic smokers

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Purpose: To study the effect of smoking on tear film parameters and retinal nerve fiber layer thickness (RNFL) in chronic smokers. **Methods:** This was a cross-sectional study, which included 60 (120 eyes) smokers who have smoked at least 10 pack-year and an equal number of healthy subjects as a control for comparison. In addition to history, a detailed slit-lamp examination was done to evaluate the anterior and posterior segments. All patients underwent Schirmer's I test (SIT) with Whatman-41 filter paper, tear meniscus height (TMH), and RNFL with a Fourier-domain optical coherence tomography (OCT) and tear film breakup time (TBUT) with 2% fluorescein and cobalt blue filter using slit-lamp biomicroscopy. **Results:** The (mean ± SD) age of the participants was 56.48 ± 10.38 years. There was a statistically significant reduction in tear film parameters in smokers compared to nonsmokers (P = 0.000). The incidence of MGD was found to be higher in smokers when compared to nonsmokers with a P value of 0.000. RNFL in all four quadrants was also significantly reduced in smokers compared to nonsmokers (P = 0.00). **Conclusion:** This study shows that chronic smoking leads to an increased incidence of dry eye disease and is associated with RNFL thinning. Smoking can result in cumulative RNFL loss in patients with ocular neurodegenerative disorder and OCT of these patients may have to be interpreted keeping this in mind.

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Worldwide, every year 7 million people die due to tobacco use, making it the leading single preventable cause of death.[1] Smoking affects the eyes also, the toxins associated with smoking decrease blood flow and initiate clot formation within ocular capillaries, resulting in deprivation of vital nutrients that are essential for the eye.[2] In smokers, both erythrocytes and leucocytes levels are found in larger proportions along with activated platelets as compared to the nonsmokers. This contributes to the hyperviscosity and higher risk of thrombus formation within the vessels. All these factors lead to an increased risk of ocular ischemia, impairment of normal functioning of the cells, and hence, is responsible for multiple ocular diseases. Dry eye disease (DED) is a multifactorial disease characterized by abnormal tear film, itching, redness, light hypersensitivity, and blurred vision. Environmental factors, lifestyle, age, sex, drugs, and systemic disease are known factors for the DED; among which smoking has been postulated as one of the important risk factors leading to peroxidation of the outermost layer of the pre-corneal tear film.[3] Studies suggesting smoking-related damage to retinal vasculature detected by optical coherence tomography (OCT) are inconsistent and the relationship between smoking and ocular damage has not been well established yet. Henceforth, the purpose of the present study is to evaluate DED and retinal nerve fiber layer (RNFL) in chronic smokers.

Methods

Subjects

This was a prospective cross-sectional study done at a tertiary care center in north India for 1 year from November 2017 to November 2018. Patients attending the Ophthalmology and Pulmonology services were recruited in the study. In total 60 (120 eyes) smokers and 60 healthy (120 eyes) subjects as controls who were matched for age and sex agreed to participate in the study. All the study participants gave consent and a prior clearance was obtained from the institutional ethical committee for the study in reference. The study was conducted following the tenets of the Declaration of Helsinki.

Patients with age ranging between 22–78 years and who smoked at least 10 pack-years were included (pack-year was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked).[4] Patients with a history of ocular surface disease affecting the production, secretion of tears like Sjogren's syndrome, Stevens-Johnson disease, conjunctivitis (infectious and allergic), blepharitis, chronic contact lens use, gross lid abnormalities, or an established case of DED were excluded. Patients with preexisting glaucoma, retinal diseases, optic nerve pathology, significant use of visual display unit, history of ocular trauma or chemical burn, previous eye surgery in the last 3 months were also excluded.

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History of the duration of smoking and number of cigarettes smoked per day were taken. The ophthalmological examination included uncorrected and best spectacle-corrected visual acuity with a self-illuminated Snellen chart at 6 m distance under ambient lighting. Anterior segment examination with slit-lamp biomicroscope and fundus evaluation with a double aspheric +90 D fundus lens was carried out.

In addition to these comprehensive assessments, the ocular surface assessment was carried out. Schirmer's I test (SIT) and tear film breakup time (TBUT) was performed according to the preset standardized protocol described in the literature.[5] Tear meniscus height (TMH, mm) was done using Fourier-domain OCT (Optovue RT100, Fremont, CA) as described by Eroglu *et al*. [Fig. 1].[6] All the precautions were taken to avoid any artifact during the examination. The presence or absence of meibomian gland dysfunction (MGD) and its assessment was done according to the protocol set by Wang *et al*.[7]

Measurement of RNFL thickness

RNFL thickness was measured using the Optic nerve head (ONH) protocol on Fourier-domain OCT (Optovue RT100, Fremont, CA) in all the subjects according to the standardized method. RNFL was recorded in four quadrants (superior, inferior, temporal, and nasal) wherein each quadrant was further divided as superotemporal (ST), superonasal (SN), inferotemporal (IT), inferonasal (IN), temporal-upper (TU), temporal-lower (TL), nasal-lower (NL), and nasal-upper (NU).[8]

Statistical analysis

All statistical analysis was done by using statistical software Statistical Package for Social Sciences, 22.0 version (SPSS version 22). All continuous variables were described as mean ± standard deviation (mean ± SD). Statistical analysis of the continuous variable was done using an independent *t*-test.

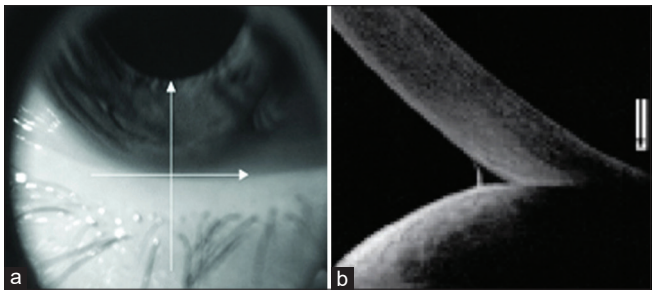

Figure 1: Tear meniscus height by optical coherence tomography; (a) A cross-line at 6'O clock hour with a horizontal line on the lower lid margin and vertical line on the inferior cornea (b) Cross-section of the tear meniscus as visualized by optical coherence tomography

A *P* value <0.05 was considered significant. A *P* value of <0.05 was considered significant. Pearson's correlation was used to analyze the correlation between different parameters.

Results

The present study included 120 eyes of chronic smokers (subject) and 120 eyes of nonsmokers (control). The demographic indices are described in Table 1. Subsequent Tables 2 and 3 shows the comparison of tear film parameter among smokers and nonsmokers and Table 4 describes the comparison of RNFL thickness.

The (mean ± SD) age of the participants was 56.48 ± 10.38 years and the maximum participants were found to be men (81.6%). The value of tear film parameters in smokers and nonsmokers was within the normal limit. However, there was a significant reduction in tear film parameters in smokers with a *P* value of 0.00 when compared to nonsmokers. In the present study, the incidence of MGD was found to be higher in smokers when compared to nonsmokers with a *P* value of 0.000.

RNFL thickness was observed to be reduced significantly in all four quadrants in smokers with a *P* value of 0.00, 0.00, 0.00, 0.00 in superior, inferior, nasal, and temporal quadrant, respectively, when compared with nonsmokers [Fig. 2].

To rule out confounding factors tear film parameters were correlated with age in smokers. A negative correlation was seen between tear film parameters like SIT and TBUT with an R-value of -0.99 and -0.97, respectively with increasing age in smokers. However, there was no statistically significant correlation between advancing age and tear film parameters in nonsmokers.

It was also observed that there is no significant correlation between age and RNFL thickness in smokers and nonsmokers.

Discussion

Smoking causes several harmful changes in the human body including the eye resulting in increased morbidity and premature deaths. In the eye, apart from diseases like thyroid ophthalmopathy, cataract, primary open-angle glaucoma, age-related macular degeneration, retinal venous occlusion, anterior ischemic optic neuropathy, it is also known to affect the blood flow, tear film, and the RNF thickness.[9] Very few studies, especially in India have focused on the effect smoking has on various parts of the eye. Those already done in the past have focused mainly on the tear film abnormalities. Studies on RNFL thickness have shown inconsistent results. This study assessed the tear film and RNFL in smokers and controls.

Table 1: Demographic indices

Age (Years)	Male *n* (%)		Female *n* (%)		Total *n* (%)
	Smokers	Nonsmokers	Smokers	Nonsmokers	
≤40	3 (2.5)	3 (2.5)	0 (0)	0 (0)	6 (5)
41-50	12 (10)	12 (10)	5 (4.2)	5 (4.2)	34 (28.3)
51-60	14 (11.6)	14 (11.6)	5 (4.2)	5 (4.2)	38 (31.6)
61-70	15 (12.5)	15 (12.5)	1 (0.8)	1 (0.8)	32 (26.6)
71-78	5 (4.2)	5 (4.2)	0 (0)	0 (0)	10 (8.3)
Total	49 (40.1)	49 (40.8)	11 (9.2)	11 (9.2)	120

Table 2: Comparison of tear film parameters between smokers and nonsmokers

Eye	Smokers (*n*=120)	Nonsmokers (*n*=120)	*P*
SIT[$] (mm)	17.81±9.97	25.82±5.55	0.000**
TMH[#] (μm)	192.74±41.23	234.23±46.16	0.000**
TBUT[¶] (s)	10.15±8.78	17.75±5.51	0.000**

[$]Schirmer's I test. [#]Tear meniscus height. [¶]Tear film breakup time

Table 3: Presence or absence of MGD in smokers and nonsmokers

Eye	MGD[§]	Smokers (*n*=120) *n* (%)	Nonsmokers (*n*=120) *n* (%)	*P*
	Present	42 (35)	22 (17)	0.000
	Absent	78 (65)	98 (83)	0.000

[§]Meibomian gland dysfunction

The mean age of patients in our study was 56.48 ± 10.38 years with a male preponderance (81.6%). In another study from India, the mean age of the participants was lesser and was found to be 35.14 ± 14.5 years in smokers and 36.4 ± 12.3 years in nonsmokers, with all male participants.[3] The reason for male preponderance in Indian studies may be because India is a country with numerous social stigmas where male smoker's acceptance is more likely as compared to female acceptance. Studies from the West have also reported a younger mean age in smokers compared to India. The reason may be the early smoking culture in the western world.

As it is a well-known fact that SIT measures both the basal as well as reflex tear secretion, and smoking damages the pre-corneal tear film via lipid peroxidation. Thus, on measuring the SIT values in smokers and comparing it with those of nonsmokers, we found that although the value was within normal limits in smokers, it was significantly reduced when compared to that in nonsmokers. Studies conducted in Korea

Table 4: Comparison of RNFL thickness between smokers and nonsmokers

Parameters	Smokers (*n*=120)	Nonsmokers (*n*=120)	*P*
Superior	112.08±23.77	128.36±17.38	0.000**
Superonasal	106.75±25.06	123.66±22.91	0.000**
Superotemporal	117.07±25.90	131.96±16.20	0.000**
Inferior	121.91±24.39	138.54±15.78	0.000**
Inferonasal	117.88±27.95	136.99±22.31	0.000**
Inferotemporal	125.94±20.83	140.09±9.25	0.001**
Nasal	74.72±12.58	85.91±11.64	0.000**
Nasal-upper	77±13.24	90.1±13.66	0.000**
Nasal-lower	72.12±13.58	81.56±11.24	0.000**
Temporal	72.44±11.43	81.86±11.01	0.000**
Temporal-upper	74.68±1 2.40	82.20±10.73	0.001**
Temporal-lower	71.13±10.86	80.11±9.55	0.000**

**$P<0.01$ *$P<0.05$

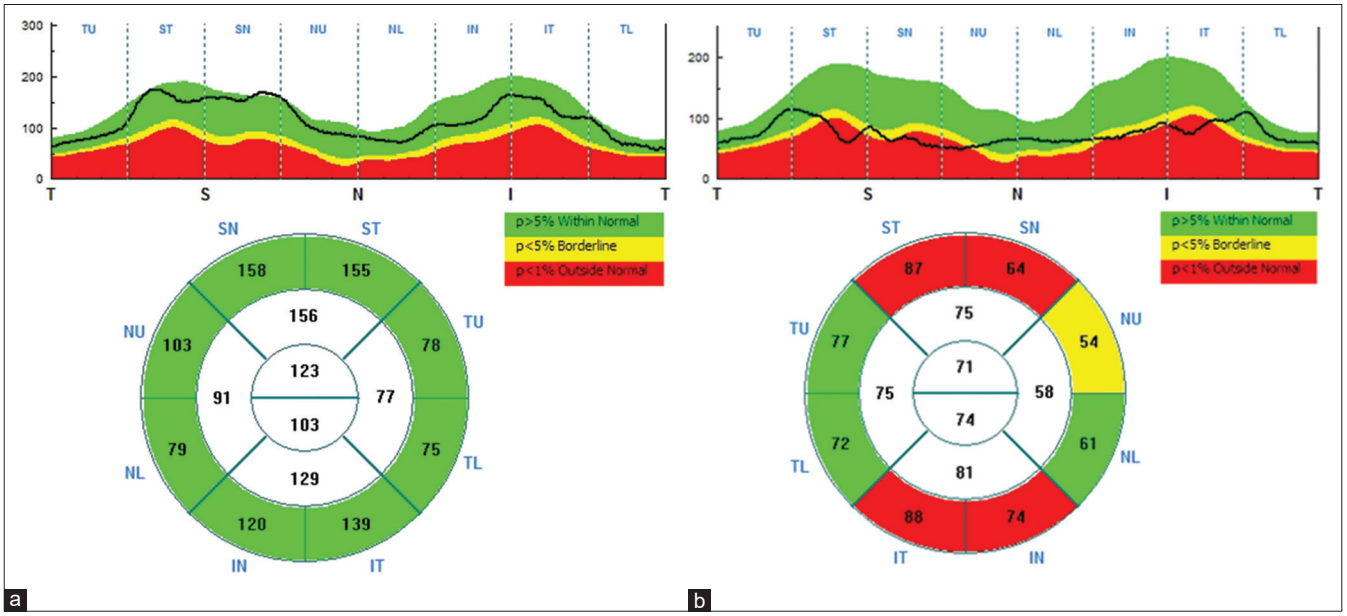

Figure 2: Retinal nerve fiber layer (RNFL) thickness using ONH protocol; (a) Normal RNFL thickness in a nonsmoker (b) RNFL thinning in a smoker

and Turkey also found Schirmer's test values to be reduced in smokers.[10,11] In the latter study it was reported that the values decreased further as the number of pack-years increased. On the other hand, in a study by Altinor *et al*. no significant difference was found between the SIT among the two groups.[12] Cigarette smoking changes the proteinaceous nature of tear film and causes a histological alteration in conjunctiva leading to low conjunctival and corneal sensitivity secondary to alteration in subbasal corneal nerve plexus and thus resulting in decreases basal tear secretion and resulting in reduced SIT value. Another mechanism may be due to inflammatory mediators as a result of smoking which may cause chronic inflammation of the ocular surface and consequent neurosecretory block leading to a reduction in reflex secretion.[13]

Similarly, we found a significant reduction in the value of TBUT in smokes as compared to nonsmokers. Similar findings were seen in the study conducted by Satici *et al*. and Aboud *et al*. where TBUT to be significantly reduced in smokers (11.9 ± 5.8) when compared to nonsmokers (14.9 ± 5.5).[2,14] The TBUT measures tear film stability which can be altered due to excessive evaporation or any mechanical damage. Tear film serves as a protective coat by resisting the deleterious effect from the external environment and preserve the integrity of underlying tissues. Smoking leads to the generation of a cascade of inflammatory mediators in absence of antioxidants leading to peroxidation of the lipid layer which acts as a barrier to prevent cellular damage, conjunctival goblet cells, and also loss of microvilli.[15] This changes the corneal homeostasis and thus compromise corneal transparency and leads to tearing film instability. On the other hand, the expression of interleukin 6 (IL-6) has been linked to disrupting the epithelial cell barrier. These cytokines result in hyperosmolarity leading to tearing film instability. Rummenie *et al*. found a 50% increase in the concentration of IL-6 exactly after 1 day of cigarette smoke exposure.[16]

TMH was also found to be decreased significantly in chronic smokers in the present study when compared to nonsmokers. TMH is one of the quantitative tests to analyze tear volume composed of tear meniscus and inferior tear meniscus correlates well with tear volume. A study by Mainstone *et al*. found that TMH has strong correlations with noninvasive breakup time and is one of the powerful predictors of DED.[17] To our knowledge and thorough search of the literature, no comparative study could be found that correlates TMH via OCT. In smokers, chronic inflammation leads to alteration of sensory and autonomic nerve fiber which is present on the ocular surface leading to neurogenic inflammation. This increases the release of two sensory neuropeptides, substance P, and calcitonin gene-related peptide (CGRP) in the tears of smokers. Substance P act on epithelial and immune cells by releasing cytokines and chemokines causing lacrimal gland and ocular surface inflammation. On other hand, CGRP dilates blood vessels and stimulates extravasation of leukocytes leading to intense inflammation.[18] All these factors lead to a reduction in TMH which is a known parameter for DED.

In the past, very few studies have studied the association of MGD with smoking. In the current study, MGD was more frequently seen in smokers (35%) as compared to nonsmokers (11%). A study from China also reported an increased incidence of MGD in smokers. The reason for this association may be that smoking releases various inflammatory mediators causing hyperviscosity of the meibum and also lead to hyperkeratinization of the meibomian gland system leading to decrease secretion of the meibum affecting the tear film stability.[7]

Besides, in the current study, RNFL thickness was found to be reduced in smokers in all the quadrants and was statistically significant. These findings were similar to a study conducted by Derviogullari *et al*. who concluded that there is a significant thinning of RNFL in inferior and superior quadrants.[15] Solberg *et al*. inferred that nicotine causes stimulation of α-adrenergic receptors which leads to vasoconstrictions of ocular capillaries and increases the carbon monoxide index in smokers, reducing oxygen-carrying capacity.[19] This has been seen to result in ischemia of retinal tissues leading to thinning of RNFL thickness. These changes might be due to toxins associated with smoking, which decreases the blood flow in the ophthalmic artery and also contribute to clot formation within ocular capillaries, thus cutting off the nutrients which are essential for RNFL physiology.[2] There is also an alteration of various substances like substances derived from the endothelium such as endothelin, nitric oxide, tissue plasminogen activator, and angiotensin-converting enzyme. Reduction in the hemodynamic response of retinal veins induced by flicker was found to be reduced in chronic smokers, supporting the hypothesis that the habit of chronic smoking leads to alteration of retinal vasculature. Garhofer *et al*. in his study reported that chronic smoking decreases nitric oxide synthase production which, in turn, decreases ocular blood flow in smokers leading to a reduction in RNFL.[20]

On studying the correlation between age and tear film parameters in smokers a negative weak correlation was established and it was observed that SIT, TBUT reduces with advancing age. This may be following lid laxity with older age which causes lacrimal pump failure and improper tear drainage. It also leads to unstable tear film and greater evaporation. This finding was similar to the study done by Uchino *et al*. who reported that aging may decrease tear secretion.[21] In a present study, a linear positive correlation was seen between TMH and increasing age. However, the correlation was not statistically significant. This may be due to an increase in reflex secretion while taking TMH via OCT as this method needs proper fixation by the participants. Moreover, most of the participants in this study belonged to the elderly group who may have senile ectropion giving rise to a false increased reading of TMH. However, TMH and TBUT showed a weak negative correlation with the advancing age of nonsmokers and a positive correlation with SIT. This confirms that age is one of the factors for dry eye but smoking adds to the morbidity.

Furthermore, a negative correlation between the advancing age of smokers and RNFL thickness was observed. The negative correlation was seen in most of the quadrants except the SN quadrant. However, in contrast to this, a positive weak correlation was observed between the advancing age of nonsmokers and RNFL thickness in all quadrants except temporal. These correlations seen were not significant statistically. This inference was as per the study conducted by Kanamori *et al*. who inferred that there is a 0.1–0.7% reduction in optic nerve fibers per year with increasing age.[22] Mansoori

et al. also inferred reduction in RNFL thickness with advancing age in most of the peripapillary RNFL except for the temporal quadrant and corresponding 7, 8, 9, and 10 0′ clock sector when measured via spectral OCT.[23] This difference in pattern loss may be due to different ethnic population or due to the use of different modality to measure RNFL thickness. Pieroth *et al*. in another study concluded similar findings and stated that there is approximately 10 μm thinning of RNFL per decade.[24]

To our knowledge, none of the studies in the past have studied the effect of smoking on tear film thickness on anterior segment-OST (AS-OCT). Besides, the current study includes age-matched controls unlike other studies, which is an advantage as age may itself cause changes in RNFL thickness.

The limitation of this study was a small number of patients and that it did not take into consideration the type of cigarette smoked and the occupation of an individual. Large multicentric studies are required to reach a consensus on the effect of smoking on RNFL thickness.

Conclusion

Chronic smoking increases the incidence of dry eye and is deleterious for the health of the retinal nerve fiber layer. Since the RNFL is already compromised in several ocular diseases such as glaucoma, diabetic retinopathy, smokers with the preexisting disease may result in having exacerbated degeneration of the optic nerve. The practice of methods to counsel all the smokers about lid hygiene should be included in day-to-day practice. Besides, an integrated approach between the ophthalmologist and tobacco prevention centers should be encouraged with adequate referrals from an ophthalmologist's end. This strategy may not only improve the ocular health but holistic health of patients in general.

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Conflict of interest

There are no conflicts of interest.

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