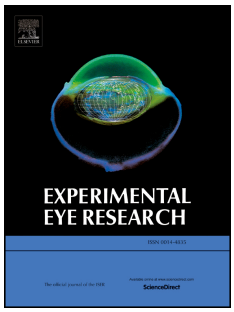

The effect of active smoking, passive smoking, and e-cigarettes on the tear film: An updated comprehensive review

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TITLE:

The effect of active smoking, passive smoking, and e-cigarettes on the tear film: an updated comprehensive review

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Abstract

Active tobacco smoking, passive smoking, and e-cigarette smoking have been associated with different systemic and ocular diseases. The precorneal tear film plays an important role in eye health and its analysis can provide useful information on ocular status. This review investigates the effects of different types of smoking on the precorneal tear film, by analyzing the peer-reviewed literature on this topic. Specifically, tear evaporation rate, stability, volume, ferning, osmolarity, and physical composition (lipids and proteins) of tear film are detailed. Most of the reported works show that cigarette smoking reduces tear film stability and quality by affecting its components. This review highlights that smoking severely affects the tear film, but a single test is not sufficient to determine these effects because smoking can impact different parts of the eye.

1. Introduction

Active tobacco smoking has been associated with different systemic (United States Surgeon General, 2014) and ocular conditions. In terms of ocular disease, smoking has been associated with cataract (Kelly et al., 2005), age-related macular degeneration (Khan, 2006), and ocular ischemia (Solberg et al., 1998) for example. Tobacco smoke contains many toxic elements, such as carbon monoxide, methanol,

aldehydes, nitrosamines, hydrocarbons, and heavy metals (Smith and Hansch, 2000). These compounds can cause damage to the ocular tissues due to ischemic and oxidative effects (Solberg et al., 1998; Cheng et al., 2000). Active tobacco smoking of cigarettes has been shown to be irritative for the ocular surface (Moss, 2000), and damage of the corneal epithelial cells has also been recently reported (Ağın et al., 2020). Concerning dry eye disease (DED), active tobacco smoking has been suggested as a potential risk factor (Yoon et al., 2005). However, the Epidemiology Report subcommittee of the TFOS DEWS II stated that there was inconclusive evidence that smoking could be a risk factor of DED (Stapleton et al., 2017).

Passive smoking, also known as environmental tobacco smoking (ETS), may also affect the eye. Indeed, due to its exposure to the environment, the eye is particularly susceptible to air pollutants (Gupta and Muthukumar, 2018). ETS has been reported to be the most common indoor air pollutant in developed countries (Lois et al., 2008). This type of smoking has several implications on the eye. For example, it is considered to be a risk factor for dry eye syndrome in children (El-Shazly et al., 2012) and responsible for a hypermetropic shift in the refraction of children exposed to ETS in the early years of life or with expectant mothers smoking during gestation (Stone, 2006).

Recent years have seen an increase in the use of electronic cigarettes (ECs), also referred to as e-cigarettes (Bertholon et al., 2013; Chatham-Stephens et al., 2016; Isa et al., 2019). ECs are handheld devices usually composed of a battery, a flow sensor, an atomizer, and a coil with the active liquid in it (Brown and Cheng, 2014). The liquid is made of water with propylene glycol, vegetable glycerin, nicotine (optional) and flavoring (Kosmider et al., 2014; Tayyarah and Long, 2014). Despite having fewer toxins than tobacco cigarettes (Margham et al., 2016), EC vapors also contain a significant amount of free radicals (Goel et al., 2015). The free radical load depends on the glycol propylene and glycerin ratio, the flavoring and the device temperature (Bitzer et al., 2018). In 2016 there were an estimated 10 million EC users worldwide (Margham et al., 2016) and there are reports of eye irritation by some users (Chatham-Stephens et al., 2016; Unger et al., 2016).

The precorneal tear film is a layer of fluid that covers the ocular surface and plays a fundamental role both in eye health and in vision, since it is the first refractive surface of the eye (Willcox et al., 2017). The tear fluid is formed by layers of different composition. The mucous layer is produced by both the goblet cells and the corneal and conjunctival epithelia. It is composed mainly by transmembrane mucins, immunoglobulins, salts, urea, enzymes, glucose, and leukocytes. It affects the stability of the upper layers, while protecting the eye surface from the adherence of pathogens (Stahl et al., 2012). The aqueous layer is produced both by the main lacrimal gland and by the accessory lacrimal glands of Krause and Wolfring. It consists mainly of water, electrolytes, proteins and vitamins. These components ensure an anti-microbial activity as well as a nutritional supply for the cornea (Stahl et al., 2012). The outer lipid layer is secreted mainly by the meibomian glands and in part also by the glands of Moll and Zeiss. The main function of the lipid layer is to reduce evaporation of the underlying aqueous phase in the open eye

(Georgiev et al., 2017). Generally, the structure of the tear film is described as three-layered, with an internal mucous layer in contact with the epithelium, an aqueous intermediate layer forming the bulk of the tear volume, and a lipid outer layer that prevents evaporation of the tears. However, a two-layer structure of the tear film has been also proposed, with a superficial lipidic layer and an inner mucin/aqueous glycocalyx gel (Cher, 2008; Willcox et al., 2017).

This systematic review focuses on the effects of active smoking, ETS and ECs on the properties of the tears.

2. Method

For the purposes of this review a search of the peer-reviewed literature was carried out using PubMed in June 2020. The terms used in the search were: *smoking* OR *passive smoking OR nicotine OR electronic cigarettes* AND *tear film*. Other relevant papers were identified from the references cited by the papers revealed from the original search terms.

3. Tear evaporation rate

The tear evaporation rate (TER) indirectly quantifies the evaporation of the aqueous layer of the tear film and is an important factor in tear dynamics (Goto et al., 2003; Tomlinson and Khanal, 2005; Wong et al., 2018). This measurement is performed on the exposed ocular surface by employing temperature and humidity sensors integrated within goggles worn over the eyes. The goggles can be either closed-chamber or open-chamber. Furthermore, some devices provide a ventilation system that adds air, at a known relative humidity and at a specific flow rate (Wong et al., 2018). Despite the increasing relevance of TER measurements, there is still a lack of a standardized method to measure and report results. In the literature, there are only a few studies that compare this value in smokers and non-smokers, but the results are in agreement. Matsumoto and coworkers employed a ventilated closed-chamber evaporimeter device and measured a significantly higher values in smokers ($7.7 \pm 0.2 \times 10^{-7}$ g cm^{-2} s^{-1}) than in a non-smoking control group ($2.5 \pm 0.9 \times 10^{-7}$ g cm^{-2} s^{-1}) (Matsumoto et al., 2008). Similar results were found in a more recent study (Alanazi et al., 2019), using an unventilated closed-chamber evaporimeter. The average TER was significantly higher ($p<0.05$) in the smoking group (median = 37.7 g m^{-2} h^{-1} corresponding to 10.5×10^{-7} g cm^{-2} s^{-1}, interquartile range = 59.3 g m^{-2} h^{-1}) than in the control group (median = 15.4 g m^{-2} h^{-1} corresponding to 4.3×10^{-7} g cm^{-2} s^{-1}, interquartile range = 13.1 g m^{-2} h^{-1}). These studies used different evaporimeters so the values cannot be directly compared, but the order of magnitude is similar and the ratio between the data found for smokers and non-smokers suggests a reasonable agreement between them.

Aside from studies on active smokers, a few experiments have been performed exposing non-smokers to cigarette smoke in order to evaluate TER with a tear evaporimeter from KAO Corporation (KAO Corporation, Tokyo, JP) (Rummenie et al., 2008; Ward et al., 2010). Rummenie and coworkers reported a

significant increase ($p< 0.05$) in TER values 5 minutes after smoking exposure (1.84 ± 1.19 vs 3.34 ± 2.04 x 10^{-7} g cm^{-2} s^{-1}, respectively) and a significant decrease ($p< 0.05$) comparing 5-minute and 24-hour pause after exposure (3.34 ± 2.04 vs 2.13 ± 0.91 x 10^{-7} g cm^{-2} s^{-1}, respectively) (Rummenie et al., 2008). Similar results were found in a more recent study where a significant increase ($p< 0.05$) between the TER before and after a 2-hour break after smoking exposure in non-smokers and non-CL wearers were reported (2.2 (0.1-3.7) and 2.7 (0.4-6.5) 10^{-7} g cm^{-2} s^{-1}, respectively) (Ward et al., 2010).

4. Stability of tear film

Tear break-up time (TBUT) is used to evaluate the stability of the tear film and its measurement represents one of the major clinical tests in DED diagnosis (Wolffsohn et al., 2017). This test can evaluate the simultaneous contributions of the principal elements in the precorneal tear film, i.e., water, lipids, and mucins. Traditionally, to measure TBUT, topical fluorescein is instilled into the inferior fornix of the conjunctiva. Then, the patient is asked to blink three times and to look straight ahead without blinking. Using a slit-lamp biomicroscope with the cobalt blue filter in place, the operator measures the interval between the last blink and the appearance of the first dry spot, seen as a dark patch, that indicates a breaking of the tear film in that area. Typically, the measurement is repeated three times because of its poor repeatability (Vanley et al., 1977; Cho, 1991). Poor repeatability, reproducibility, and accuracy represent the main criticisms of this approach, mainly as a consequence of the current impossibility of standardization of the instilled fluorescein volume and concentration (Savini, 2008). Usually, TBUT is measured in seconds and a value of less than 10 seconds is considered abnormal (Mengher et al., 1985), although lower values have been suggested as the cut-off between normal tears and tears suggestive of DED (Paugh et al., 2020).

Exposure to cigarette smoking has been associated with a statistically significant reduction of TBUT, as reported by different authors (Satici et al., 2003; Altinors et al., 2006; Matsumoto et al., 2008; Thomas, 2012; Sayin et al., 2014; Aktaş et al., 2017; Acar et al., 2017; Mohidin and Jaafar, 2020). Only two studies reported similar values in smokers and in non-smokers (Table 1) (Ağın et al., 2020; Muhafiz et al., 2019).

Further studies have been performed to investigate the correlation between the number of cigarettes smoked per day and the reduction of TBUT values. Few works (Yoon et al., 2005; Aktaş et al., 2017; Khalil et al., 2018) found an inverse correlation between the amount of smoked cigarettes and TBUT. This correlation may also explain the variability of the mean TBUT values of smokers reported in the different studies as described in Table 1.

Only one study has been conducted looking at TBUT amongst ECs users (“vapers”), where a reduction in TBUT scores compared to the non-smoking group was seen (Isa et al., 2019).

With regard to passive smoking, studies are in good agreement with those conducted on active smokers (both of tobacco and ECs). In fact, there is a significant decrease in the TBUT values in subjects exposed to smoking, as reported in Table 2 (Rummenie et al., 2008; Ward et al., 2010).

Table 1. Summary of TBUT values for active smokers and non-smokers.

TBUT (s)			
Study	**Smokers**	**Non-smokers**	**Significant difference**
(Satici et al., 2003)	11.9 ± 5.8	14.9 ± 5.5	Yes (p<0.05)
(Altinors et al., 2006)	5.4 (1-10)	11.2	Yes (p<0.05)
(Matsumoto et al., 2008)	3.2 ± 0.7	14.2 ± 2.4	Yes (p<0.001)
(Thomas, 2012)	7.26 ± 1.86	11.28 ± 1.27	Yes (p<0.001)
(Sayin et al., 2014)	8.24 ± 2.39	11.15 ± 1.94	Yes (p=0.000)
(Aktaş et al., 2017)	8.14 ± 3.49	13.67 ± 4.69	Yes (p<0.001)
(Acar et al., 2017)	5.17 ± 2.85	10.03 ± 3.44	Yes (p<0.001)
(Khalil et al., 2018)	11.9 ± 5.8	14.9 ± 5.5	Yes (p<0.05)
(Muhafiz et al., 2019)	9.65 ± 6.14	11.23 ± 5.94	No
(Ağın et al., 2020)	10.96 ± 3.64	10.52 ± 2.25	No
(Mohidin and Jaafar, 2020)	3.24 ± 1.05	5.51 ± 1.44	Yes (p=0.0001)
Study	**Vapers**	**Non-smokers**	**Significant difference**
(Isa et al., 2019)	2.68 (2.33-3.18)	4.12 (3.56-5.07)	Yes (p<0.0001)

Table 2. Summary of TBUT values for non-smokers after and before exposure.

TBUT (s)					
Study	**Before smoking exposure**	**5 min after exposure**	**Significant difference (before vs 5 min after)**	**24 h after exposure**	**Significant difference (before vs 24 h after)**
(Rummenie et al., 2008)	9.30 ± 3.34	5.90 ± 2.94	Yes (p<0.05)	7.21 ± 3.39	Yes (p<0.05)
Study	**Before smoking exposure**	**2 h after exposure**	**Significant difference (before vs 2 h after)**		
(Ward et al., 2010)	10 (3-17)	6.0 (2-13)	(p<0.05)		

5. Volume of tear film

The volume of tear film is assessed by several tests such as Schirmer's test or similar, tear meniscus height, and phenol red thread test (McGinnigle et al., 2012; Wolffsohn et al., 2017). Schirmer's test is a quantitative test used to evaluate the amount of the aqueous component of tear film (i.e., basal tear secretion). The test can be performed with or without local anesthesia with both approaches able to detect variations in the basal tear secretion, but the use of local anesthesia seems to assure a more reliable result since reflex tearing is removed (Li et al., 2012). Schirmer's test results, either with or without the addition of an anesthetic, remain in general highly variable and poorly reproducible (Clinch, 1983; Cho and Yap, 1993).

When applied to smokers, research involving Schirmer's tests is contradictory. Some studies reported that Schirmer's test results were significantly lower in the smoking group (Yoon et al., 2005; Sayin et al., 2014; Khalil et al., 2018), whereas other works reported no significant difference between smoking and non-smoking groups (Altinors et al., 2006; Matsumoto et al., 2008; Thomas, 2012; Aktaş et al., 2017; Acar et al., 2017; Muhafiz et al., 2019; Ağın et al., 2020). On the other hand, Satici and coworkers, who performed the test without local anesthesia, reported a significant increase of Schirmer's test values for smokers (Satici et al., 2003). The higher result in smokers compared to non-smokers in this study conducted with no anesthesia (Satici et al., 2003) may suggest an increase in reflex tear secretion. In another study (Aktaş et al., 2017), the mean value was found to be higher in smokers, but the difference was not statistically significant. Only one study has been conducted on vapers and non-smokers, performing Schirmer's test with topical anesthesia (Isa et al., 2019). The results showed a significant increase in tear production in vapers compared to non-smokers.

When non-smokers were exposed to smoking, no significant difference was found in the mean Schirmer's test value before and after the exposure (Rummenie et al., 2008; Ward et al., 2010), as reported in Table 4.

Table 3. Summary of Schirmer's test results for active smokers and non-smokers. with or without anesthesia.

Schirmer's test (mm of moisture on the filter paper in 5 minutes)				
Study	**Anesthesia**	**Smokers**	**Non-smokers**	**Significant difference**
(Satici et al., 2003)	No	30.3 ± 16.7	23.8 ± 12.4	Yes (p<0.05)
(Yoon et al., 2005)	Yes	6.29 ± 2.85	10.04 ± 3.87	Yes (p<0.05)
(Altinors et al., 2006)	Yes	10.23	10.63	No
(Sayin et al., 2014)	Yes	13.30 ± 4.63	15.45 ± 4.11	Yes (p<0.05)
(Acar et al., 2017)	Yes	14.25 ± 5.94	15.48 ± 7.01	No

(Aktaş et al., 2017)	No	25.88 ± 8.88	24.22 ± 8.92	No
(Ağın et al., 2020)	Yes	13.12 ± 3.76	13.08 ± 2.65	No
(Matsumoto et al., 2008)	No	13.3 ± 2.1	17.1 ± 2.6	No
(Thomas, 2012)	Yes	20.21 ± 6.62	19.12 ± 5.93	No
(Khalil et al., 2018)	Yes	13.91 ± 6.81	16.58 ± 7.41	Yes (p<0.05)
(Muhafiz et al., 2019)	Yes	8.90 ± 4.95	13.08 ± 8.61	No
	Anesthesia	**Vapers**	**Non-smokers**	**Significant difference**
(Isa et al., 2019)	Yes	14.5 (12.0-17.0)	8.0 (7.0-11.0)	Yes (p=0.001)

Table 4. Summary of Schirmer's test results for non-smokers after and before exposure.

Schirmer's test (mm of moisture on the filter paper in 5 minutes)						
Study	**Anesthesia**	**Before smoking exposure**	**5 min after exposure**	**Significant difference (before vs 5 min after)**	**24 h after exposure**	**Significant difference (before vs 24 h after)**
(Rummenie et al., 2008)	No	19.25 ± 12.03	19.35 ± 10.71	No (p>0.05)	18.95 ± 9.28	No (p>0.05)
Study	**Anesthesia**	**Before smoking exposure**	**2 h after exposure**	**Significant difference (before vs 2 h after)**		
(Ward et al., 2010)	No	12.2 ± 2.2	12.5 ± 3.5	No (p>0.05)		

Tear film volume can also be evaluated by measuring the tear meniscus height. Only one study has employed this test to compare tear volume in non-smokers and vapers (Isa et al., 2019). The results showed a significant (p= 0.002) decrease in tear meniscus height in vapers (vaper group: 235.0 (210.0–253.50) µm; non-smoking group: 203.0 (193.0–225.5) µm), suggesting that EC smoking reduces the tear volume by increasing evaporation of the tear reservoir (Golding et al., 1997).

6. Tear osmolarity

In 2008, the US Food and Drug administration approved a TearLab osmometer (TearLab, San Diego, CA, US) (Tashbayev et al., 2020), making tear osmolarity measurement available for clinical purposes. Since then, osmolarity measurement has become a fast and straightforward diagnostic test, and other devices have entered the market (Willcox et al., 2017). Tear film dysfunction and DED lead to an increase in tear

osmolarity values, mainly due to a higher concentration of sodium ions (Pflugfelder, 2011). Hyperosmolarity has been suggested to play a key role in DED pathogenesis (Craig et al., 2017) and it is considered the best current objective biomarker clue for a correct diagnosis (McGinnigle et al., 2012). This parameter is directly correlated with tear evaporation and flow rate, whereas it has an inverse behavior when compared to goblet cell density and granulocyte survival (Holland et al., 2013). A meta-analysis provided a reference value of tear osmolarity in normal subjects, which corresponds to 302.0 ± 9.7 mOsm/L (Tomlinson et al., 2006). An osmolarity above 308 mOsm/L has been defined to be a potential diagnostic biomarker for DED (Lemp et al., 2011; Craig et al., 2017). A recent study focused on the effect of smoking on the tear film osmolarity (Aktaş et al., 2017). The reported values for the non-smoking control group (301.14 ± 7.04 mOsm/L) were found to be in good agreement with the reference values reported in the literature. In contrast, the smoking group displayed a significant hyperosmolarity (305.38 ± 9.81 mOsm/L, $p<0.05$). Based on a previous study on tear osmolarity (Li et al., 2004), the authors suggested that this result is caused by tear film instability (Aktaş et al., 2017).

7. Tear film ferning

Tear ferning (TF) test is based on characteristic crystallization patterns generated by drying a small volume of tear sample (Masmali et al., 2014). A microscope is used to observe the TF patterns and they are assigned a grade from a five-point grading scale (Masmali et al., 2015). A study performed on control and DED patients evidenced that grades above 2 correspond to abnormal patterns (Masmali et al., 2015). The same approach was employed to investigate the effect of smoking on the tear film, reporting TF grades significantly higher in the smoking group (0.96 ± 0.54) than in non-smoking controls (0.41 ± 0.38) (Masmali et al., 2016).

8. Tear Lipids

The ocular surface is constantly exposed to oxidative stress caused by ultraviolet light and atmospheric oxygen, enhancing the formation of reactive oxygen species (ROS) (Hammond et al., 2014), and a decreasing presence of molecules with an antioxidant function, such as cysteine, glutathione, urate, and tyrosine (Choy et al., 2001).

Cigarette smoking has strong effects on inflammation and oxidative stress, as demonstrated on humans, animals, and *in-vitro* models (van der Vaart, 2004). It has been reported that each smoke puff carries a large amount of free radicals (in tar and gas phase) and of oxidizing molecules that cause an enormous oxidative stress at the eye level in smokers (Pryor, 1987; Duthie et al., 1993; Kirkham et al., 2004). Lipids can be affected by oxidative attack of radicals, causing lipid peroxidation. The tear film lipid layer plays a fundamental role in minimizing the evaporation of the aqueous component of the tear film in physiologic states and in adverse environments (Doane, 1994). Thus, a damage of the lipid layer can lead to tear film instability and subsequent dry eye symptoms.

Lipid layer abnormalities can be investigated by interferometry (Altinors et al., 2006). This technique, based on the specular light reflected by the tear film, evidences the lipids spread. A normal tear film generates a uniform grey pattern, whereas altered conditions result in multicolor non-uniform images. In the study by Altinors and coworkers, control subjects had a smooth distribution (Altinors et al., 2006), corresponding to grade 1 or 2 of the grading established by Yokoi and coworkers (Yokoi et al., 1996). For both levels of the grading scale, the pattern is grey, but with different levels of uniformity. The smoking group (smokers who smoked >20 cigarettes/day for >5 years), had higher grades of interferometry, scoring 3 or 4. This means that their patterns were not uniform and presented a variable number of different colors. Moreover, the images displayed many areas lacking lipid spread over the cornea. These effects are often associated with dry eye changes and the subjects reported also clinical signs of this pathology, such as burning, grittiness, foreign-body sensation, scratchiness.

A following study employed interferometry to measure the lipid spread time, determined as the time necessary to obtain a stable layer fringe pattern after a complete blink (Matsumoto et al., 2008). The mean lipid spread time was significantly higher in heavy smokers (2.5 ± 0.5 s) than in non-smoker controls (1.2 ± 0.2 s). Moreover, two types of lipid layer spread abnormality were observed in smokers, but not in non-smoker controls: a complete lipid spread after a full blink followed by instant appearance of multiple break-up points or an incomplete and irregular lipid spread.

The same approach was employed to study the effect of passive smoking, measuring the lipid spread time 5 minutes and 24 hours after smoking exposure (Rummenie et al., 2008). Passive smoking caused an irregular and incomplete lipid spread over the ocular surface. Furthermore, the lipid spread time changed significantly, increasing from 1.07 ± 0.56 s before smoking exposure to 1.56 ± 0.72 s and 1.54 ± 0.35 s 5 minutes and 24 hours after smoking exposure, respectively.

In order to investigate the connection between the lipid layer instability and the oxidative stress caused by cigarette smoking, Matsumoto and coworkers measured the amount of hexanoyl-lysine (HEL), which is a biomarker for initial stage of lipid oxidation (Kato et al., 2005). The mean tear HEL level was significantly elevated in smokers (380 ± 18 nmol/L) compared to non-smoker controls (336 ± 20 nmol/L) (Matsumoto et al., 2008). Passive smoking caused similar effects, increasing the mean tear HEL levels (297 ± 66 nmol/L) of non-smoker controls to 330 ± 51 and 409 ± 188 nmol/L, 5 minutes and 24 hours after smoking exposure, respectively. Despite this evidence, the increase in tear HEL levels could be ascribed either to toxic changes resulting from lipid peroxidation or to a physiological response to an increase in reactive oxygen species.

As far as lipids are concerned, it is worth mentioning that a possible explanation for tear film alteration induced by smoking can be ascribed to changes in the meibomian glands (MG), which secrete lipids. Among several negative effects on the anterior eye, smoking has been related to a statistically significant decrease in MG density (Ağın et al., 2020) and to MG loss of the upper eyelid (Muhafiz et al., 2019). Smoking may cause a hyperkeratinization of orifices and excretory ducts, causing a block of meibum

expression that could lead to acinar atrophy. A similar obstructive process was proposed to be at the basis of meibomian gland dysfunction (MGD) (Knop et al., 2011). Smoking is considered a risk factor for MGD, and MGD-affected patients that smoke are associated with increased scores of lid margin abnormality and a decrease in meibum secretion (Wang et al., 2016). Additionally, the lid margin abnormality score was found to be significantly and positively correlated with the smoking index.

9. Tear proteins

Smoking affects not only the lipid layer, but also the proteins present in the aqueous layer underneath. Heavy smokers have been reported to have an alteration of their tear protein profile (Grus et al., 2002; Yoon et al., 2005; Uchino et al., 2016). A rapid approach to investigate protein abnormalities is by SDS-PAGE (Sodium Dodecyl Sulphate - PolyAcrylamide Gel Electrophoresis), which separates proteins by gel electrophoresis according to their molecular weight. Grus and coworkers compared non-smokers, smokers, and severe smokers (>20 cigarettes/day), and reported no significant variation in the concentration of the most abundant tear proteins, represented by lactoferrin, IgA, albumin, lipocalin, and lysozyme (Grus et al., 2002). However, in this study there was a significant increase in the number of proteins in tears of severe smokers. In particular, the region between 25-40 kDa was the most important in discriminating between smokers and non-smokers. This can be ascribed to the oxidative damage of proteins, leading to degradation and thus to an increase in smaller fragments, and to an altered body vessel permeability to proteins (Grus et al., 2002).

In contrast with these results, a following study reported a significant decrease ($p<0.05$) in tear lysozyme concentration (1217 ± 478 μg/mL in smokers, 1472 ± 419 μg/mL in non-smokers) (Satici et al., 2003). There are different explanations for low concentration of lysozyme in smoking subjects: this difference may be explained either by the destruction of this enzyme in the conjunctival sac or by its binding to toxins in the smoke or by dilution caused by excessive tearing in smokers or by chemical conjunctivitis caused by smoking (Sen and Sarin, 1986). Smoking has been reported to cause a reduction not only in lysozyme but also in mucin (MUC5AC) quantity (Uchino et al., 2016), a glycoprotein that is thought to be responsible for the attainment of tear stability (Gipson et al., 2004). Indeed, in the study of Uchino and coworkers, the smoking group had a significant lower MUC5AC concentration (4.1 ± 3.9 ng/mg) than the control group (7.6 ± 9.3 ng/mg, $p = 0.024$) (Uchino et al., 2016). A statistically significant reduction was reported also for passive smoking. In a recent study, it has been highlighted that the number of MUC5AC mRNA copies decreased drastically from 2036.00 ± 1977.20 to 755.94 ± 586.79 copies/ng at 24 hours after smoking exposure (Rummenie et al., 2008). This reduction might be caused by the decrease in conjunctival goblet cells, which solely secrete this major mucin. Nevertheless, a difference in cell density between smokers and non-smokers is still controversial: a significant difference was reported in some recent studies (Matsumoto et al., 2008; Uchino et al., 2016; Acar et al., 2017), but not in previous ones

(Satici et al., 2003; Yoon et al., 2005; Altinors et al., 2006). A drastic decrease in goblet cell density was reported also 24 hours after smoking exposure (Rummenie et al., 2008).

Goblet cell density is strongly influenced by inflammatory states (Kinoshita, 1983; Tseng et al., 1984). For this reason, a recent study focused on cytokines, which play a fundamental role in modulating the immune response: all cytokines increased after smoking exposure, with a significant increase in interleukin 6 levels 24 hours after exposure (Rummenie et al., 2008).

10. Discussion and conclusions

Most studies support the hypothesis that smoking is harmful to ocular health and detrimental to the tear film. In fact, active, but also passive and ECs smoking, have been proven to reduce tear film stability and quality. The mechanism is highly complex and still not fully understood because smoke interacts with every component of the tear fluid, but it seems that the most critical aspect concerns the natural functions of the lipid layer.

This review highlighted a strong consistency among studies regarding a significant decrease in TBUT values in subjects exposed either to active or passive smoking. A possible mechanism underlying this decrease in tear film stability could be ascribed to a damage of the lipid layer, caused by lipid peroxidation by radicals (Pryor, 1987; Duthie et al., 1993; Kirkham et al., 2004). The alteration of the lipid layer in smokers was directly demonstrated by employing interferometry (Altinors et al., 2006; Matsumoto et al., 2008; Rummenie et al., 2008). Damage to the lipidic component causes an impairment of its function of delaying the evaporation of the aqueous component of the tear film. Also with regard to evaporation, TER was directly tested and found to be increased in smokers, as well as osmolarity (Aktaş et al., 2017). Specifically, the increase of TER has been associated with an irregular distribution of the lipid layer for both active (Altinors et al., 2006; Matsumoto et al., 2008) and passive smoking (Rummenie et al., 2008).

Another important effect of cigarette smoke exposition is the increasing ocular surface symptoms such as dryness, burning, and itching sensation (Wieslander et al., 2000; Isa et al., 2019; Ağın et al., 2020).

Li and coworkers have recently tried to elucidate the mechanism responsible for the dry eye symptoms induced by cigarette smoke exposition on *in-vitro* cultured human corneal epithelial cells and *in-vivo* ocular surfaces of mice (Li et al., 2020). They found that longer-term cigarette smoke exposure leads to damage of ocular surfaces (defects and ultrastructural changes in corneal epithelial cells, decrease in conjunctival goblet cell density, thickening of the corneal and conjunctival epithelium) and induces dry eye symptoms in mice. This cell and tissue damage (i.e., apoptosis of the corneal and conjunctival epithelia) leads to inflammation and pathological changes, which are mediated via the secretion of proinflammatory cytokines IL-1β and IL-6, chiefly dependent on the activation of NF-κB. Damage of the corneal epithelial cells has also been recently reported *in vivo* in humans as an effect of chronic cigarettes smoking (Ağın et al., 2020).

In order to mitigate or avoid the negative effects of smoke exposure on the tear film the best approach would be a cessation, or at least a reduction, in smoking. If this is not possible, several options to manage dry eye could be used (Jones et al., 2017). Prescribing artificial tear substitutes to increase the volume (aqueous supplementation products) or to stabilize the tear film (viscosity-enhancing agents), which ultimately reduce the hyperosmolarity shift (also osmoprotectants could be considered), might be beneficial for smokers to avoid the ocular surface damage and the ignited inflammatory response, especially in long-term perspective. Finally, antioxidant eye drops to prevent oxidative stress of smoking could be considered, as well as lipid containing eye drops or sprays to directly impact the damage of the lipid layer caused by oxidative attack of free radicals and oxidizing molecules carried by smoking.

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HIGHLIGHTS

- Active, passive and e-cigarette smoking affects tear film
- Passive and e-cigarette smoking effects on tear film are similar to active smoking
- Smoking causes lipid oxidation, damaging the lipid layer
- Smoking alters tear volume, stability, ferning, osmolarity and composition
- A single test is not sufficient to describe the effect of smoking on tear film