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ORIGINAL PAPER

Effects of chronic smoking on the meibomian glands

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Abstract

Purpose To evaluate the effects of chronic smoking on tear function tests and meibomian glands.

Methods This prospective study included 40 volunteers with a long-term (> 5 years) cigarette smoking history (study group) and 43 non-smoking healthy individuals (control group). The symptoms of all the participants were scored using the Ocular Surface Disease Index (OSDI) questionnaire, and a detailed ophthalmological examination was performed including the tear breakup time (TBUT) and Schirmer test (with anaesthesia). The upper and lower lid meibomian glands were evaluated with meibography using the Sirius anterior segment analysis system (Sirius, CSO, Florence, Italy).

Results The groups showed homogenous distribution in respect of age and gender ($p > 0.05$). The patients in the study group were determined with 22.59 ± 17.25 packet/year cigarette usage. The mean OSDI score was 36.67 ± 21.47 in the study group and 31.65 ± 15.60 in the control group ($p = 0.64$). The TBUT and Schirmer test values were determined as 9.65 ± 6.14 s and 8.90 ± 4.95 mm, respectively, in the study group and 11.23 ± 5.94 s and 13.08 ± 8.61 mm in the control group ($p > 0.05$). In the upper lid meibography, loss of 24.68 ± 16.54% was determined in the study group and 17.87 ± 7.06% in the control group ($p = 0.01$). No statistically significant difference was determined between the groups in respect of the lower lid meibomian gland loss: study group 14.70 ± 8.49% versus control group 12.48 ± 6.44% ($p = 0.20$).

Conclusions Smoking results in meibomian gland damage which may be a risk factor for dry eye. In cases of ocular surface disorders related to chronic smoking, meibomian gland damage should be taken into consideration.

Keywords Smoking · Tear function tests · Meibography

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Introduction

Cigarette smoking is currently a severe public health problem throughout the world. Diseases associated with tobacco smoke occur not only in active smokers but may also develop in those passively exposed to

smoke [1, 2]. It has been reported that tobacco use results in mortality in more than 5 million people per year, and this has been estimated to increase to 8 million by 2030 [2]. The heavy metals and toxic minerals that are the greatest constituent of cigarettes are known to contain > 4000 chemicals [3]. Smoke particles, nicotine and harmful gases such as carbon monoxide damage tissues by causing vasospasm and platelet aggregation. The toxic components in cigarettes lead to damage primarily in the respiratory and circulatory systems, and in several organs, including the eyes [2, 4].

By increasing coagulum formation in the ocular capillaries, toxins in cigarette smoke reduce blood flow, and thus, sufficient nutrients essential for eye health are prevented from reaching the eye [4, 5]. Free radicals that are produced because of cigarette smoking cause oxidative stress in proteins, lipids and cell DNA [6]. Consequently, the cells can not function normally and ocular diseases develop [7]. Epidemiological studies have shown that cigarette smoking could be a high risk factor for various diseases such as dry eye, cataract and age-related macular degeneration [8–10]. Conjunctival mucosa is highly sensitive to chemicals, smoke and irritative gases in the air originating from cigarette smoking. The free nerve ends on the ocular surface are stimulated by these gases, causing stinging, conjunctival redness and excessive lacrimation [7, 10, 11]. Toxic and irritative gases in smoke cause damage in the cornea and epithelium of ocular surface in cigarette smokers [12].

Cigarette smoking causes irritative eye complaints such as itching, burning and stinging. These symptoms are thought to be due to the effects of cigarette smoke on the precorneal tear layer [13, 14]. The Blue Mountains Eye Study reported that cigarette smoking could be a significant risk factor for dry eye [15]. There has been reported to be a higher rate of dry eye in active smokers and those with a history of smoking [10]. Despite several important epidemiological studies related to the harmful effects of cigarette smoking, which is a widespread public health problem, very few studies have been related to the ocular surface and tear functions. Therefore, there is ongoing research into the effects of cigarette smoking on the ocular surface.

It has been previously determined that the breakup time of the tear film which provides removal of pathogens and debris and allows nutrients and oxygen to reach the eye, which is shorter in cigarette smokers [12–14, 16]. The outer layer of the tear film that provides lubrication of ocular surface and slows the evaporation of the aqueous components of the tears is formed of lipids, which are expressed from the meibomian glands. [17]. Meibomian gland dysfunction (MGD) is a chronic ocular surface disease characterised by obstruction of the terminal secretion ducts of the gland or qualitative changes in the gland secretion [18]. It has been reported that the frequency of MGD can be seen at rates varying from 3 to 70% in the general population [19]. By leading to impairments in the tear lipid layer, MGD causes evaporative dry eye and has a great effect on daily living activities and is a disorder frequently encountered in clinical practice [19]. Although some studies have investigated the relationship between cigarette smoking and dry eye, there are very few studies that have researched the relationship between smoking and the meibomian glands. The aim of this study was to investigate the effects of chronic cigarette smoking on tear function tests and the meibomian glands.

Methods

This prospective study included 40 volunteers with a long-term (> 5 years) cigarette smoking history (study group) and 43 non-smoking healthy individuals (control group). To exclude passive smokers from the control group, they were asked whether they were exposed to cigarette smoke at home or in the workplace. Those who smoked < 10 cigarettes per day were not included in the study group. Approval for the study was granted by the Local Ethics Committee, and the study was conducted in accordance with the Helsinki declaration. Informed consent was obtained from all the study participants. Subjects were excluded if they had any rheumatological or dermatological diseases that could affect the ocular surface such as Sjögren's syndrome, rheumatoid arthritis, lupus erythematosus, acne rosacea, seborrhoeic dermatitis, acne vulgaris, psoriasis or pemphigoid. Subjects were also excluded if they had a history of use of medications that could lead to MGD such as isotretinoin, antiandrogen, antidepressant and antihistaminic drugs. Exclusions were also made from both groups if the subjects had pterygium, used contact lenses and had giant papillary conjunctivitis or demodex infestation. In the study group, the packet/year value was

calculated by multiplying the mean number of packets smoked per day by the duration of smoking. Ocular Surface Disease Index (OSDI) (Allergan, Irvine, CA, USA), tear breakup time (TBUT), Schirmer test and meibography were performed, respectively, by an experienced ophthalmologist who did not know which patient belongs to which group.

All the participants were first applied with a routine ophthalmological examination, including visual acuity, and biomicroscopic anterior segment and fundus examinations. Then, the symptoms of all the participants were questioned using the Ocular Surface Disease Index (OSDI) (Allergan, Irvine, CA, USA). The OSDI is a questionnaire of 12 items that evaluates ocular discomfort symptoms associated with dry eye, and the relationship of these with visual functions. The questions include ocular symptoms, environmental stimuli and vision-related functions. The severity of the effect is marked on a scale from 0 = never to 4 = always [20]. After calculation of the OSDI score, the TBUT and Schirmer test (with anaesthesia) were applied to evaluate tear functions.

To determine the TBUT, fluorescein-impregnated papers were wet and touched to the lower fornix. The patients were instructed to blink 3–4 times, and the fluorescein was spread across the ocular surface. Using a cobalt blue filter on a biomicroscope, the tear film layer was examined. After the final blink, the time was calculated until the first dry point on the cornea was seen. The Schirmer test was applied by dropping a topical anaesthetic (0.5% proparacaine, HCl, 0.5% Alcaine, Alcon), and then, standard filter paper was placed on the lower fornix at the junction of the mid- and outer-third of the lower eyelid. Care was taken that the paper did not touch the cornea. After placement of the Schirmer paper, the patient was instructed to look at a point opposite and blink normally. After 5 min, how many millimetres from the edge of the eyelid the Schirmer test paper was wet, were calculated and recorded.

Finally, meibography was applied to the right eye of the participants. The Sirius anterior segment analysis system (Sirius, CSO, Florence, Italy) combines a monochromatic Scheimpflug camera that rotates 360° and a 22-ring Placido disc. The device provides non-contact visualisation of the meibomian gland structure using an infrared light in meibography mode. In the current study, the structure of the meibomian glands was evaluated by obtaining images of the lower and upper lid meibomian glands from the Sirius anterior segment analysis system in meibography mode. First, images were acquired of the meibomian glands from the tarsal conjunctival surface by everting the upper and lower lids. To select the clearest image, at least six images were taken from the upper and lower tarsal conjunctival surface. On the images, the meibomian glands are seen as hyper-reflective and damaged areas of meibomian gland as hyporeflective. During the analysis process, the image with the clearest meibomian gland structures was selected from these 6 images and firstly the borders of the lid were marked. Then, the borders of the meibomian glands were marked using the device software. The loss in the meibomian gland was calculated by the device, and the result was given by classifying according to the loss percentage. Finally, an image is produced on the screen showing the areas of loss in red and the healthy areas in green. Figure 1 shows meibomian gland loss rate of a patient from smoking group of our study.

Statistical analysis

Data obtained in the study were analysed using SPSS version 18.0 software (Statistical Package for the Social Sciences, IBM). Descriptive statistics were used for the age and gender of the patients. Only the right eyes of the participants were evaluated in the statistical analyses. In comparison of two independent groups, the Student's t test and the Mann–Whitney U test were applied. Evaluations were made in a 95% confidence interval. A value of $p < 0.05$ was accepted as statistically significant.

Results

The groups showed homogenous distribution in respect of age and gender ($p > 0.05$). The patients in the study group were determined with 22.59 ± 17.25 packet/year cigarette usage. The mean OSDI score was 36.67 ± 21.47 in the study group and 31.65 ± 15.60 in the control group ($p = 0.64$). The TBUT and Schirmer test values were determined as 9.65 ± 6.14 s and 8.90 ± 4.95 mm, respectively, in the study group and 11.23 ± 5.94 s and

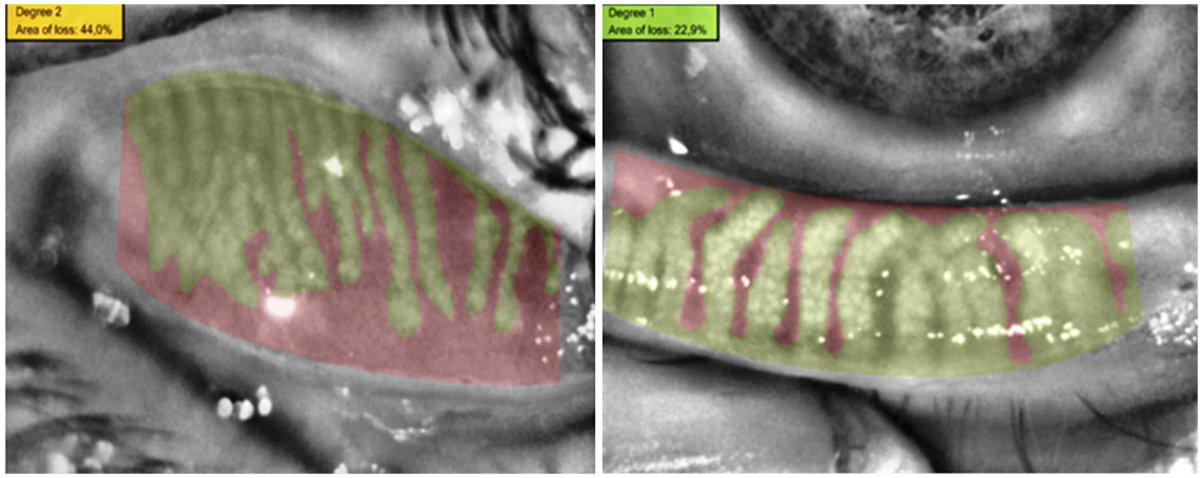

Fig. 1 Meibomian gland loss rate of a patient's upper and lower eyelid from study group

Table 1 Tear function test results and the loss rates on meibography of the participants

	Study group (n = 40)	Control group (n = 43)	p value
OSDI	36.67 ± 21.47	31.65 ± 15.60	0.64
TBUT (s)	9.65 ± 6.14	11.23 ± 5.94	0.25
Schirmer (mm/5 min)	8.90 ± 4.95	13.08 ± 8.61	0.09
Loss on upper eyelid meibography (%)	24.68 ± 16.54	17.87 ± 7.06	0.01
Loss on lower eyelid meibography (%)	14.70 ± 8.49	12.48 ± 6.44	0.20

TBUT tear breakup time and *OSDI* Ocular Surface Disease Index

13.08 ± 8.61 mm in the control group (p = 0.25, p = 0.09, respectively) (Table 1).

In the upper lid meibography, loss of 24.68 ± 16.54% was determined in the study group and 17.87 ± 7.06% in the control group (p = 0.01). No statistically significant difference was determined between the groups in respect of the lower lid meibomian gland loss: study group 14.70 ± 8.49% versus control group 12.48 ± 6.44% (p = 0.20) (Table 1). It is observed that meibomian glands are regular, long, thick, flat, hyper-reflective and similar to each other in control group. While in study group, it is detected that meibomian glands are irregular, less hyper-reflective, thinner and boundaries are more uncertain, the distances between glands are wider, asinies are died back and glands are shortened.

Discussion

It has been previously determined that in chronic cigarette smokers, there is a significant decrease in goblet cell density on the ocular surface and an increase in squamous metaplasia [12, 14]. Passive smoking has been determined to lead to damage in the lacrimal gland by oxidisation forming in the DNA with free oxygen radicals [21]. Although there are studies in the literature that have investigated the effects of smoking on the lacrimal gland and conjunctiva, to the best of our knowledge, there have been no previous studies that have investigated the effects on the meibomian glands. Therefore, in this study, the effects of smoking on the meibomian glands were evaluated by determining meibomian gland damage with meibography. The results of the study demonstrated a significant loss in the meibomian glands of the upper eyelid in the smoking group. In a previous

review that evaluated the effects of cigarettes on inflammation and oxidative stress in human, animal and in vitro models, it was reported that cigarette exposure caused tissue destruction by increasing the production of lipid peroxidation products and degraded extracellular proteins [22]. The loss seen in the meibomian glands in the current study can be considered to have occurred with similar inflammatory and oxidative mechanisms. In a study by Altinors et al. [13], the stability of the tear lipid layer was examined with DR-1 lipid layer interferometry, and there was seen to be no lipid distribution on the ocular surface in the cigarette smoking group. This impairment of the lipid layer in smokers could be a marker of meibomian gland destruction. In the current study, although there was loss in the meibomian glands, that the tear stability was not impaired suggests that meibography allows earlier, objective evaluation than tear function tests.

The ocular surface is one of the mucosal surfaces of the body most exposed to environmentally polluting agents such as cigarette smoke. To protect the ocular surface against these agents, the tear film must be sufficiently stable. In reaction to these agents, the lipid layer on the surface tries to increase tear film stability by preventing evaporation of the aqueous component of tears [16, 23]. Nicotine triggers inflammation by stimulating macrophages, and ocular surface inflammation causes apoptosis. It has been previously determined that in smokers, inflammation is triggered on the ocular surface and the lipid layer tears that expressed from the meibomian glands disrupt [13, 14, 24]. A history of cigarette smoking has been reported to be a risk factor for MGD [25].

In the current study, the effects of cigarette smoking were investigated on tear functions and the meibomian glands. Although there was a significant loss on the upper eyelid meibography of the smoking group compared to the control group, no statistically significant difference was determined between the two groups on the lower eyelid meibography. That there was no significant difference in respect of the lower eyelid could be attributed to the fact that eversion of the lower eyelid is more difficult, and therefore, lower eyelid meibography has low reliability. As smoke particles in the air move counter to gravity, the meibomian glands in the upper eyelid can be expected to be more affected. According to our study results, it can be thought that the lower lid glands were more resistant to cigarette damage because the lower lid glands were less affected in chronic smokers. Maybe in the next years with the increase in smoking duration in the study group patients a significant damage will occur in the lower lid meibomian glands. However, our study needs to be supported by studies evaluating the relationship between severity and duration of smoking and meibomian gland damage. Also a few morphological changes are detected in meibomian glands of chronic smokers. These morphological changes are our observational results. The disadvantage of this observation is that we do not know whether these morphological changes are smoking specific changes or typical changes of meibomian gland atrophy. In order to determine the reasons and characteristics of morphological changes, studies are needed to evaluate and classify the morphology of meibomian glands in a variety of diseases leading to loss of meibomian glands.

In the tear function tests of the current study, no significant difference was determined between the study and control groups. A previous study investigated the relationship between cigarette smoking and MGD with evaluation of OSDI, TBUT, corneal fluorescein staining score and meibum score. Just as in the current study, no relationship was determined between cigarette smoking and tear functions. Only eyelid edge abnormalities and the meibum score were determined to be statistically significantly high in the smokers [26]. Those findings were consistent with the findings of the current study. TBUT and Schirmer values were lower in the study group than the control group, but this was not statistically significant. We concluded that there was no significant deterioration in these tear function tests because the lower lid meibomian glands were not significantly affected in the study group. Because we do not know yet how much of the lipid layer of tear is secreted from the upper lid and how much of, it is secreted from the lower lid. We also do not know how much meibomian gland damage causes decompensation in tear function tests. We believe these questions will be clarified with detailed studies evaluating the meibography, tear functions and their correlations. We think that these tear function tests secondary to the damage to the lower meibomian glands of these patients will be significantly impaired in later years.

Several mechanisms have been suggested to explain the negative effects of cigarettes on the ocular

surface. Cigarette smoking has been shown to increase the production of pro-inflammatory cytokines such as tumour necrosis factor alpha and interleukin (IL)-1, IL-6 and IL-8 and suppress the production of anti-inflammatory cytokines such as IL-10 [27]. It has been suggested that by triggering inflammatory reactions in the meibomian glands and ocular surface, cigarette smoking can lead to MGD. It is thought that the main mechanism of the development of MGD is increased viscosity of the meibum and obstruction in the meibomian gland ducts associated with hyperkeratinisation [18].

A limitation of the current study is that inflammatory cytokines in the tears and on the ocular surface were not examined. These inflammatory or autoimmune reactions could have an effect on the meibomian gland damage in smokers. For all the effects of cigarette smoking on the ocular surface and meibomian gland to be understood, there is a need for further studies which examine meibography, inflammatory cytokines on the ocular surface and immune system components together.

In a study performed on a rat model, cytochrome P450 expression produced by free oxygen radicals in the lacrimal gland ducts was observed to be increased in the animals exposed to cigarettes [21]. In the current study, the meibomian glands were examined non-invasively with meibography, and the damage to the glands was observed to be greater in the smoking group. Similar invasive studies are necessary to be able to determine the mechanism of meibomian gland damage in cigarette smokers.

Conclusion

Chronic cigarette smoking constitutes a major threat to the ocular surface by causing damage to the meibomian glands. In cases of ocular surface disorders related to chronic smoking, meibomian gland damage should be taken into consideration.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Approval for the study was granted by the Local Ethics Committee, and all procedures were applied in conformity with the principles of the Helsinki declaration.

Informed consent Informed consent was obtained from all the participants.

References

1. Avunduk AM, Avunduk MC, Evirgen O, Yardımcı S, Güven H, Çetinkaya K (1997) Histopathologic and ultrastructural examination of the rat conjunctiva after exposure to tobacco smoke. Ophthalmologica 211(5):296–300
2. WHO (2010) Why tobacco is a public health priority. http://www.who.int/tobacco/health_priority/en/. Accessed 20 Aug 2010
3. Chiba M, Masironi R (1992) Toxic and trace elements in tobacco and tobacco smoke. Bull World Health Organ 70(2):270–276
4. Hara K (1991) Effects of cigarette smoking on ocular circulation chronic effect on choroidal circulation. Nippon Ganka Gakkai Zasshi 95(10):939–943
5. Williamson TH, Lowe GDO, Baxter GM (1995) Influence of age, systemic blood pressure, smoking, and blood velocity on orbital blood velocities. Br J Ophthalmol 19(1):17–22
6. Kiyosawa H, Suko M, Okudaira H, Murata K, Miyamoto T, Chung MH, Kasai H, Nishimura S (1990) Cigarette smoking induces formation of 8-hydroxydeoxyguanosine, one of the oxidative DNA damages in human peripheral leukocytes. Free Radic Res Commun 11(1–3):23–27
7. Solberg Y, Rosner M, Belkin M (1998) The association between cigarette smoking and ocular diseases. Surv Ophthalmol 42(6):535–547
8. DeBlack SS (2003) Cigarette smoking as a risk factor for cataract and age-related macular degeneration: a review of the literature. Optometry 74(2):99–110
9. Lu ZQ, Sun WH, Yan J, Jiang TX, Zhai SN, Li Y (2012) Cigarette smoking, body mass index associated with the risks of age-related cataract in male patients in northeast China. Int J Ophthalmol 5(3):317–322
10. Moss SE, Klein R, Klein BE (2000) Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol 118(9):1264–1268
11. Cometto-Muniz JE, Cain WS (1992) Sensory irritation. Relation to indoor air pollution. Ann N Y Acad Sci 641:137–151
12. Satıcı A, Bitiren M, Özardalı I, Vural H, Kılıç A, Guzey M (2003) The effects of chronic smoking on the ocular surface and tear characteristics: a clinical, histological and biochemical study. Acta Ophthalmol Scand 81(6):583–587
13. Altinors DD, Akca S, Akova YA, Bilezicki B, Goto E, Dogru M, Tsubota K (2006) Smoking associated with damage to the lipid layer of the ocular surface. Am J Ophthalmol 141(6):1016–1021
14. Matsumoto Y, Dogru M, Goto E, Sasaki Y, Inoue H, Saito I, Shimazaki J, Tsubota K (2008) Alterations in tear film and ocular surface health in chronic smokers. Eye 22(7):961–968
15. Chia EM, Mitchell P, Rochtchina E, Lee AJ, Maroun R, Wang JJ (2003) Prevalence and associations of dry eye syndrome in an older population: the Blue Mountains Eye Study. Clin Exp Ophthalmol 31(3):229–232

16. Tiffany JM (2008) The normal tear film. Dev Ophthalmol 41:1–20
17. Green-Church KB, Butovich I, Willcox M, Borchman D, Paulsen F, Barabino S, Glasgow BJ (2011) The international workshop on meibomian gland dysfunction: report of the subcommittee on tear film lipids and lipid-protein interactions in health and disease. Invest Ophthalmol Vis Sci 52(4):1979–1993
18. Knop E, Knop N, Millar T, Obata H, Sullivan DA (2011) The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci 52(4):1938–1978
19. Schaumberg DA, Nichols JJ, Papas EB, Tong L, Uchino M, Nichols KK (2011) The international workshop on meibomian gland dysfunction: report of the subcommittee on the epidemiology of, and associated risk factors for MGD. Invest Ophthalmol Vis Sci 52(4):1994–2005
20. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL (2000) Reliability and validity of the ocular surface disease index. Arch Ophthalmol 118(5):615–621
21. Higuchi A, Ito K, Dogru M, Kitamura M, Mitani F, Kawakita T, Ogawa Y, Tsubota K (2011) Corneal damage and lacrimal gland dysfunction in a smoking rat model. Free Radic Biol Med 51(12):2210–2216
22. van der Vaart H, Postma DS, Timens W, ten Hacken NH (2004) Acute effects of cigarette smoke on inflammation and oxidative stress: a review. Thorax 59(8):713–721
23. Stern ME (2004) The normal tear film and ocular surface. In: Pflugfelder SC, Beuerman RW, Stern ME (eds) Dry eye and ocular surface disorders. Dry eye: the problem. Marcel Dekker, New York, pp 41–55
24. Kirkham PA, Spooner G, Rahman I, Rossi AG (2004) Macrophage phagocytosis of apoptotic neutrophils is compromised by matrix proteins modified by cigarette smoke and lipid peroxidation products. Biochem Biophys Res Commun 318(1):32–37
25. Viso E, Rodriguez-Ares MT, Abelenda D, Oubina B, Gude F (2012) Prevalence of asymptomatic and symptomatic meibomian gland dysfunction in the general population of Spain. Invest Ophthalmol Vis Sci 53(6):2601–2606
26. Wang S, Zhao H, Huang C, Li Z, Li W, Zhang X, Liu Z (2016) Impact of chronic smoking on meibomian gland dysfunction. PLoS ONE 11(12):e0168763
27. Arnson Y, Shoenfeld Y, Amital H (2010) Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun 34(3):258–265