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ORIGINAL PAPER

The effects of facial mask use on ocular surface parameters and tear film cytokine profile in prolonged use

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Abstract

Objective To compare tear fluid levels of matrix metalloproteinase 9 (MMP-9) and IL-1ß cytokines between healthcare workers wearing facial masks and controls with correlations in clinical findings.

Methods In a prospective, controlled clinical trial tear fluid was analyzed for MMP-9 and IL-1ß levels using a commercially available test (Invitrogen; Thermo Fisher Scientific Inc. Waltham, Massachusetts, USA). Symptoms and signs of dry eye disease (DED) were evaluated using the ocular surface disease index (OSDI), noninvasive tear break-up time (NIBUT), tear meniscus height (TMH), Oxford corneal staining, meibomiography, and clinical findings of meibomian gland dysfunction (MGD).

Results In the 38 eyes of healthcare workers and 30 eyes of controls, there was no statistically significant difference between the groups in terms of age and sex ($p > 0.05$). The mean OSDI score, daily mask wear time, meibomiography degree, and rate of positive clinical findings of MGD were higher in group 1 than in group 2, and the mean NIBUT was higher in group 2. ($p > 0.05$). The mean values of IL-1ß and MMP-9 were higher in group 1 ($p = 0.036$ and $p = 0.001$, respectively). The TMH and Oxford score percentages were similar between the two groups ($p > 0.05$).

Conclusions Elevated levels of IL-1ß and MMP-9 in the basal tear fluid reveal increased ocular inflammation in healthcare professionals. Lower NIBUT values with higher OSDI and meibomian gland loss scores support ocular surface disturbance depending on regular mask use.

Keywords Dry eye disease · Facial mask · IL-1ß · MADE · MMP-9 · Tear fluid cytokines

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Introduction

In the current COVID-19 pandemic, mandatory usage of protective face masks over the nose and mouth has been one of the cornerstones of disease prevention because the infection spreads primarily through aerosolization and fomites [1]. From the beginning of the pandemic, more than 500 million people have been infected around the world [2] and healthcare professionals are at a particular risk due to their continuous interaction with patients [3]. Thus, hospital staff must wear facial masks for a longer time than the normal population.

The prolonged use of masks has been associated with complaints such as headache, difficulty in breathing, skin irritation, and sweating [4]. Moreover, breathing air directed toward the ocular surface causes complaints of ocular dryness and discomfort in regular mask-users. This phenomenon is called mask-associated dry eye (MADE) [5]. The most accepted mechanism for MADE is carbon dioxide-rich breathing air escaping upward from the mask into the eyes, which is likely to increase the evaporation of the tear film and lead to ocular irritation [6]. The poor fitting of the upper mask edge, resulting in the leakage of air toward the ocular surface, makes the onset of MADE easier [7]. So, it is important to recognize the effects of facial mask use on the ocular surface to determine a treatment strategy for ocular surface abnormalities related to facial masks.

According to the TFOS DEWS II report, assessment of subjective complaints and risk factors, evaluation of the ocular surface with tests such as noninvasive tear break-up time (NIBUT), tear osmolarity, and corneal-conjunctival staining are essential for both diagnosis and severity of the disease [8]. Same study reported the major role of inflammatory processes in the pathogenesis of dry eye disease (DED) [9]. The proinflammatory cytokine IL-1ß is an important mediator of inflammation and immunity [10]. The Elevated levels of IL-1ß are directly correlated with the intensity of corneal fluorescein staining and inversely correlated with conjunctival goblet cell density in patients with DED [11]. Among a number of different varieties evaluated, matrix metalloproteinase-9 (MMP-9) was found to be the most efficient activator of precursor IL-1ß [12]. Uncontrolled increase in MMP-9 levels have been detected in the tear fluid and ocular surface in patients with DED, which has been proven to be associated with severe signs of DED [13].

Although it is not possible to evaluate in daily practice, increased levels of various inflammatory cytokines in tear fluid have been found to be closely correlated with the severity of DED [14]. Tear film instability and increase in the different proinflammatory biomarkers were evaluated before and after facial mask use [6]. But, alterations in the basal tear film parameters and comparison of MMP-9 and IL-1ß levels in normal individuals have not yet been investigated.

We hypothesized that an increased concentration and/or activity of both IL-1ß and MMP-9 could be predictive factors for the immunopathology of MADE. This study was designed to test this hypothesis by comparing the basal tear fluid concentrations of IL-1ß and MMP-9 between healthcare professionals who had to wear masks for extended periods and normal asymptomatic subjects wearing facial masks for a limited time in their daily routine.

Methods

Study design

This was a cross-sectional comparative clinical study. The subjects were enrolled in the study at the Cornea and Ocular Surface Department of Dr. Lutfu Kirdar Training and Research Hospital between March 2022 and May 2022. The study protocol was performed in accordance with the tenets of the Declaration of Helsinki and approved by the Ethical Committee of the Kartal Dr. Lutfu Kirdar Training and Research Hospital. All participants provided written informed consent after receiving oral and written information about the study.

Study subjects

Healthcare professionals aged between 18 and 40 attending the same workplace environment and wearing surgical facial masks for at least 8 h per day from the beginning of the pandemic (March 2020, since the facial mask use had become mandatory) were included in the study as group 1. Healthy subjects aged between 18 and 40 who had no ocular disease history or ocular complaints and wore facial masks

less than 2 h per day or 16 h per week were included in group 2 for comparative analyses. Subjects using glasses or contact lenses, using a different facial mask other than the surgical masks, subjects with active ocular allergy findings (papillary conjunctivitis), corneal vascularization, current or previous history of herpetic keratitis, severe meibomian gland dysfunction, pregnancy, retinal problems or glaucoma, history of ocular surgery, and any systemic or ocular medical treatment, including artificial tear drops, were excluded from the study.

Endpoints

The primary endpoint of this study was to evaluate tear fluid levels of IL-1ß and MMP-9. The subjects of the study were screened for secondary endpoints with NIBUT, tear meniscus height (TMH), meibomiography, Oxford corneal staining score, and ocular surface disease index (OSDI) test for subjective analyses.

Collection of tear fluid

Tear fluid was collected in capillary tubes (Marienfeld-Superior, Paul Marienfeld GmbH & Co. KG, Germany) at 8:00–9:00 am to evaluate basal alterations in tear fluid and avoid the potential effects of mask usage for a daily period. The capillary tubes were made of soda-lime glass, and the internal diameter of the tubes was 1,1 -1,2 mm. Collection was performed without topical anesthesia or nasal stimulation. Wearing gloves, the examiner placed capillary tubes at the lateral eyelid margin to avoid contact with the eyelid or bulbar conjunctiva. The participants wanted to deviate from the globe to the nasal side to prevent corneal injury during the procedure, and samples were collected from the left eye of all participants. To ensure sufficient tear fluid for analyses, Schirmer tests with 5-mm wetting or less were discarded. The tear fluid samples were stored in a deep freezer at − 81 C. Cytokine concentration in the tear fluid was measured using immunoassay technology.

Analyses of tear film cytokines

MMP-9 concentrations in tear fluid were evaluated using an Invitrogen Human MMP-9 enzyme-linked immunosorbent assay (ELISA) kit (Thermo Fisher Scientific Inc. Waltham, Massachusetts, USA) (Catalog No: BMS2016-2) according to the manufacturer's recommendations, with a 1/100 sample dilution for application of tear sample concentration into the measurement range of the kit. IL-1β concentrations were evaluated using an IL-1β Invitrogen Human IL-1β ELISA kit (Thermo Fisher Scientific Inc. Waltham, Massachusetts, USA) (Catalog No: BMS224-2) according to the manufacturer's recommendations, with a 1/20 sample dilution for application of tear sample concentration into the measurement range of the kit. A phosphate buffer was used to dilute the samples. The results were validated by five-parametric logistic curve modeling and used to determine protein levels in tear fluid samples. All values were within acceptable range according to recommendations from the manufacturer; intra-assay coefficient of variation of 8.6% and intra-assay coefficient of variation of 5.1%.

Measurement of tear film volume and stability with ocular surface staining

NIBUT was measured using a Sirius corneal topographer, which is a combination of the Scheimpflug camera and the Placido disk topography system (Costruzione Strumenti Ophthalmici, Florence, Italy). NIBUT is the first distribution time of the Placido disk image on the corneal surface between the two blink periods. TMH was measured using anterior segment optical coherence tomography (AS-OCT) (Triton Swept source OCT, Topcon, Japan). Cross-sectional images of the lower TMH were taken vertically across the central cornea of each subject. TMH was defined as the line distance from the fluid surface of the meniscus junction to the lower eyelid–meniscus junction. Lower TMH values were calculated using the cross-sectional AS-OCT images. The normal values of TMH were > 200 µm [17]. After placing fluorescein sodium test strips (Fluoro Touch, Madhu Instruments Pvt Ltd, India) were inserted into the conjunctival sac. Fluorescein vital staining of the conjunctiva and cornea was then assessed using the Oxford grading scheme [15].

Examination of meibomian glands

Meibomian gland dysfunction (MGD) was defined as either present or absent in each of the following findings: opaque or yellowish debris on the gland orifices

at the lid margin, occlusion or absence of gland orifices, irregularity of the lid margin, telangiectasia on the gray zone of the lid margin, and anterior or posterior displacement of the mucocutaneous junction [16].

The quality of meibomian glands (MGs) was assessed using the meibomiography module of the Sirius corneal topographer (CSO, Florence, Italy). MGs were visualized using infrared images with keratography. MG loss in the upper and lower eyelids was evaluated subjectively and staged using a four-point software program. The percentage area of MG loss was defined as the area of MG loss in relation to the total visible tarsal area and scored from 0 to 3. A score of 0 represented an area of MG loss of 0–25%, a score of 1 represented an area of MG loss of 26–50%, a score of 2 represented an area of MG loss of 51–75%, and score of 3 represented an area of MG loss of > 75%.

Subjective grading of ocular surface disease

Each patient completed the Turkish version of the OSDI questionnaire to assess the severity of ocular surface symptoms. Subjects were considered symptomatic if the value was ≥ 13.5 [17].

Statistical analysis

R program version 2.15.3 (R Core Team, 2013) was used for statistical analysis. Minimum, maximum, mean, standard deviation, median, first quartile, third quartile, frequency, and percentages were used to report the study data. The conformity of the quantitative data to the normal distribution was evaluated using the Shapiro–Wilk test and graphical examinations. The independent groups t test was used to evaluate normally distributed variables between the two groups. The Mann–Whitney *U* test was used to evaluate variables that did not show a normal distribution between the two groups. Pearson's chi-square test and Fisher-Freeman-Halton exact tests were used to compare qualitative variables. Statistical significance was set at $p < 0.05$.

Results

There were 38 eyes of healthcare professionals (20 (52.6%) female and 18 (47.4%) male) with a mean age of 26.11 ± 5.04 (range:18–39) years included to group 1. There were 30 eyes of healthy subjects (14 (46.7) female and 16 (53.3) male) with a mean age of 25.37 ± 6.3 (range:19–40) years in group 2. There were no statistically significant differences between the groups in terms of age and sex ($p > 0.05$). The mean daily mask use time was 7, 26 ± 1.05 h in group 1 and was 1, 34 ± 0.6 in group 2. When the study groups were compared, the difference was statistically significant ($p < 0.001$). (Table 1).

There were statistically significant differences between the groups in terms of NIBUT, OSDI, meibomiography degree, and clinical findings of MGD ($P < 0.001$, $P < 0.001$, $P = 0.043$, and $P = 0.047$, respectively). (Table 2, Table 3).

While the mean OSDI score, meibomiography degree, and rate of positive clinical findings of MGD were higher in Group 1 than in Group 2, the mean NIBUT was higher in Group 2 than in Group 1. On the other hand, the percentage of the symptomatic subjects according to the OSDI scores was higher in group 1 (27 (73.7%) when compared to group 2 scores 9 (22.5%), ($p < 0.001$).

However, the TMH and Oxford score percentages were similar between the two groups ($p > 0.05$).

Tear fluid concentration of IL-1β and MMP-9 showed statistically significant differences between mask wearers and control groups. The mean values of

Table 1 The demographical data of the study groups

	Group 1 *n* (%)	Group 2 *n* (%)	Total *n* (%)	*p*
Gender				[a]0.625
Female	20 (52.6)	14 (46.7)	34 (50)	
Male	18 (47.4)	16 (53.3)	34 (50)	
Age (*Meant* ± *Sd*)	26.11 ± 5.04	25.37 ± 6.3	25.78 ± 5.6	[a]0.593
Mask use time (*h*/*day*)	7,26 ± 1.05	1,34 ± 0.6	4,67 ± 2.1	[a] < 0.001*

[a]Pearson ki-square test

*$p < 0.05$

Table 2 Oxford corneal staining scores and evaluation of the meibomian glands

	Group 1 *n* (%)	Group 2 *n* (%)	Total *n* (%)	*p*
Meibomian gland loss				[a]0.043*
Degree 1	11 (28.9)	21 (70)	32 (47.1)	
Degree 2	16 (42.1)	5 (16.6)	21 (30.9)	
Degree 3	6 (15.8)	2 (6.7)	8 (11.7)	
Degree 4	5 (13.2)	2 (6.7)	7 (10.3)	
Oxford score				[a]0.256
Degree 0	8 (21.1)	14 (46.7)	22 (32.4)	
Degree 1	18 (47.4)	11 (36.6)	28 (41.2)	
Degree 2	7 (18.4)	2 (6.7)	10 (14.7)	
Degree 3	3 (7.9)	2 (6.7)	5 (7.4)	
Degree 4	2 (5.3)	1 (3.3)	3 (4.4)	
MGD				
Positive	9 (23,7)	4 (13.3)	13(19.1)	[b]0.047*
Negative	29 (76.3)	26 (86,7)	55(80.9)	[b]0.643

[a]Fisher-Freeman-Halton exact Test

[b]Independent Samples t Test

*$p < 0.05$

Abbreviations: MGD: Meibomian gland disfunction

Table 3 Comparison of the objective and subjective ocular surface parameters and tear fluid cytokine measurements of the study groups

	Group 1 Meant ± Sd	Group 2 Meant ± Sd	Total Meant ± Sd	*p*
NIBUT (s)	6.82 ± 2.44	12.05 ± 2.62	9.13 ± 3.62	[a] < 0.001*
OSDI	45.34 ± 11.13	22.73 ± 9.55	35.37 ± 15.36	[a] < 0.001*
OSDI asymptomatic *n*(%)	11 (26.3)	31 (77.5)	15 (19.2)	[a] < 0.001*
OSDI symptomatic *n*(%)	27 (73.7)	9 (22.5)	63 (80.8)	[a] < 0.001*
TMH (µm)	208.74 ± 63.97	205.4 ± 81.65	206.97 ± 83.81	[a]0.647
MMP-9 (pg/ml)	149.71 (60.94, 1010.79)	38.46 (28.42, 67.57)	62.29 (32.51, 286.44)	[b]0.001*
IL-1β (pg/ml)	90.69 (25.98, 197.48)	45.37 (11.22, 100.81)	52.83 (16.94, 128.51)	[b]0.036*

[a]Independent Samples t Test

[b]Mann–Whitney U test, results are presented as median (first quartile, third quartile)

*$p < 0.0$

both cytokines were higher in Group 1 ($p = 0.036$ and $p = 0.001$, respectively). (Fig. 1, Fig. 2).

The association between tear fluid cytokine levels and the OSDI score profile was investigated. According to the Spearman rank correlation test, there were significant positive correlations between both IL-1β ($r = 0.210$ and $p = 0.010$) and MMP-9 ($r = 2.36$, $p = 0.014$).

Discussion

In this study, we aimed to compare the tear fluid concentrations of IL-1ß and MMP-9 and ocular surface parameters for DED between healthcare professionals wearing masks for long periods and healthy participants wearing facial masks for a limited time in their daily routine. Our major findings were as: (1) healthcare professionals had higher levels of IL-1ß and MMP-9 than healthy subjects. (2) Healthcare professionals had lower NIBUT, higher OSDI score, and higher rate of MGD findings than healthy participants.

Since MADE was first described in June 2020 by an American ophthalmologist, D.E. White, this condition has become a well-known entity with the results of several studies [18, 19, 20]. The prevalence of dry eye-like symptoms in MADE is highly variable depending on the current status of the ocular surface and the habits of regular mask-users.

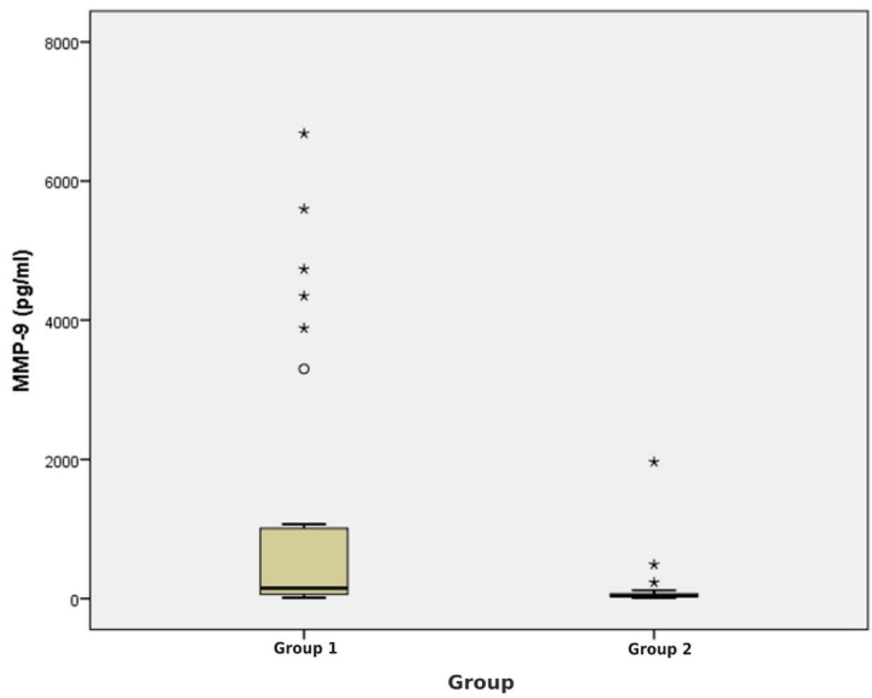

Fig. 1 The measurement of the tear film IL-1β levels in study groups

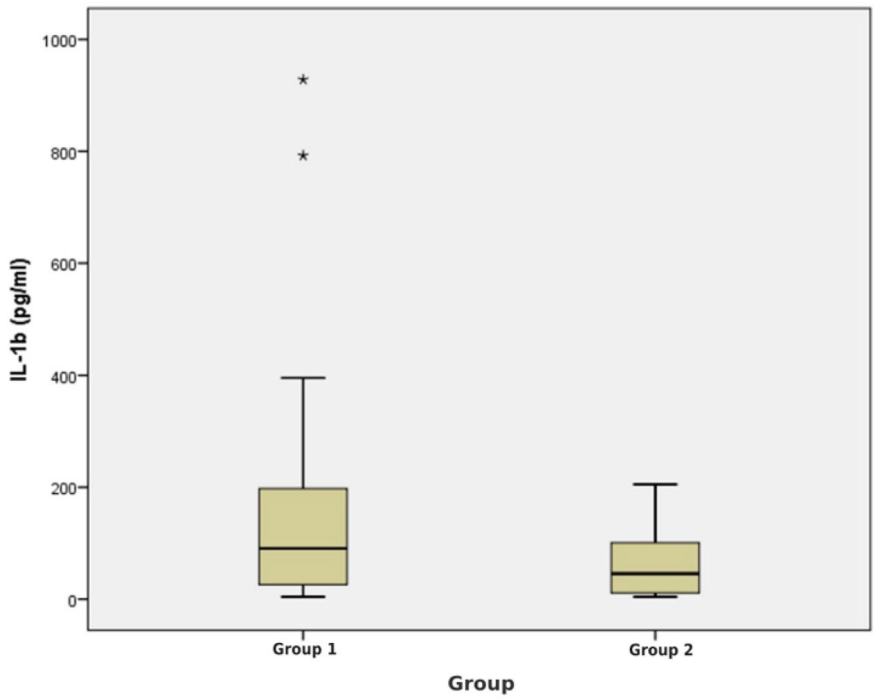

Fig. 2 The measurement of the tear film MMP-9 levels in study groups

People who had DED symptoms previously or had a long screen time would experience worsening of their symptoms when wearing a face mask [21].

MADE can affect approximately 18% of the general population [20]. However, Chalmers et al. [22] observed that clinicians often underestimated the severity of participants' self-assessment of dry eye. Previous studies have reported tear film and ocular surface abnormalities in regular mask wearers [5, 18, 19, 20, 21]. To our best knowledge this is the first study evaluating the severity of the ocular surface disease accompanying by basal tear film cytokines profiles of MMP-9 and IL-1ß by comparing normal subjects. The results of the present study showed marked increases in tear film instability and inflammation biomarkers among healthcare professionals who had to wear prolonged facemasks.

Some theories have been proposed regarding how facial masks affect the ocular surface. Devices that mechanically blow air around the face have been found to affect the eye. Powell et al. reported an increase in DED symptoms with a similar mechanism using powered air-purifying respirators in patients in intensive care units [23]. However, hypercapnic stress is another possible mechanism of ocular surface damage based on the outward movement of exhaled air through the mask [6]. In fact, there can be up to a tenfold increase in carbon dioxide levels within the reservoir formed between the face and mask [24].

There is increasing evidence of the role of subclinical ocular surface inflammation in DED [25]. Inflammation can lead to ocular surface epithelial disease and altered corneal epithelial barrier function in DED patients [25]. Increased expression of immune activation markers, such as HLA-DR, intercellular adhesion molecule (ICAM)-1, and CD-40, by the conjunctival epithelium and infiltration of the conjunctiva by inflammatory cells has been reported in previous studies [26, 27]. The anti-inflammatory therapies such as glucocorticoids and cyclosporin improve significantly signs and symptoms of DED [28]. However, in the past, the TFOS Dry Eye Workshop in 2007 concluded that levels of inflammatory factors in tears were increased only in Sjögren's syndrome and rosacea dry eye, but not necessarily in evaporative and undifferentiated dry eye [29]. In contrast, in 2017, the TFOS Dry Eye Workshop demonstrated elevated levels of cytokines such as IL-1ß and MMP-9 in the tears of both the aqueous tear deficient form of dry eye and the evaporative form of dry eye [9].

The accurate detection of elevated MMP-9 levels in the tear film with a point-of-care immunoassay (InflammaDry), which is a noninvasive, relatively inexpensive test, was found to be effective in early diagnosis and improved treatment of ocular surface disease by Sambursky et al.[30]. The results of a quantitative immunobead assay showed that the concentration of MMP-9 in tears had a direct relationship with tear osmolarity, and results of measuring tear production by Schirmer's test showed an inverse correlation between tear amount and MMP-9 concentration [31]. Therefore, the design of novel MMP-9 inhibitors for the ocular surface, leading to improvement in tear production and recovery of corneal epithelial barriers, will yield great benefits for the treatment of DED [32]. In our study, the clinical findings of dry eye and subjective discomfort scores were increased in healthcare professionals wearing facial masks compared to normal subjects. Similarly, MMP-9 levels were significantly higher in the mask-user group, as expected. Regular mask use has been proven to negatively affect the ocular surface, leading to an increase in evaporation rate. Thus, facial masks could be a promoter factor for increasing dryness and inflammation biomarkers in tear fluid for regular mask-users.

The expression of IL-1ß, another frequently studied proinflammatory cytokine in tear fluid, was found to be increased in Sjögren's syndrome and non-Sjögren's syndrome DED [9]. In our study, IL-1ß was found to be significantly increased in the prolonged mask-user group, accompanied by clinical findings of DED. In a study by Landsend et al., correlations were demonstrated between cytokines, including IL-1ß, and clinical parameters for DED and MGD [33]. Similarly, Enriquez-de-Salamanca et al. were reported that the IL-1ß levels were increased in 30% of patients with moderate forms of evaporative DED due to MGD and correlated with pain and with clinical parameters measuring tear stability, tear production, or ocular surface integrity [34]. However, in another study in which IL-1β, IL-6, and pro-MMP-9 tear levels were measured in patients with different types of ocular diseases, including moderate dry eye patients, only pro-MMP-9 was found to be significantly increased in DED patients [35].

Few studies have assessed the relationship between mask use and tear film cytokine profile. In a recent study that evaluated a large number of tear film cytokines, the authors found that the level of IL-1ß in pre-mask usage significantly increased after mask use in a daily period. In addition, the study indicated that IL-1ß showed a positive correlation with OSDI scores in the study group of practicing ophthalmologists [6]. Similarly, we found positive correlations between OSDI scores and both cytokines, IL-1ß and MMP-9, in our study. The same study found that hypo-osmolar lubrication and mucin secretagogues would be necessary to avoid MADE in view of pre-existing hypo-osmolar tear secretion and increased mucin secretion [6].

In a recent study, the use of face masks throughout the day was found to lead to a significant reduction in NIBUT regardless of age, sex, and OSDI score [36]. In contrast, high activity of MMP-9 in tears was associated with decreased fluorescein tear break-up time and a substantial direct relationship with conjunctival corneal fluorescein staining, sign severity values, topographic surface regularity index, and visual acuity scores [37]. In the current cohort, the percentage of subjects with symptomatic OSDI scores in healthcare professionals' group was 73.7% and was 22.5% in control group. Similarly, Bilici S. et al. reported that 82.4% of the participants who were healthcare professionals showed symptomatic OSDI scores [36].

In addition to the traditional Schirmer strip test, the examination of the quantity of tear secretion with TMH score is an important indicator for the diagnosis of aqueous deficiency-type dry eye [38]. To the best of our knowledge, this is the first study to assess the effect of facial mask use on the basal TMH scores. In a recent study, diurnal changes in the TMH scores were evaluated before and after mask use. The results showed that TMH scores decreased after wearing the facial mask [39]. However, depending on the evaporative nature of MADE, the TMH scores were similar in both study groups, as expected. In contrast, in a recent study, the Schirmer strip test scores and TBUT measurements were reported to increase after facial mask wearing by healthcare professionals [6].

Ocular surface staining is an important endpoint for the treatment of dry eye disease that reflects ocular surface integrity [40]. In the current study the mean Oxford corneal staining score was slightly higher in the mask-user group, but the difference was not statistically significant. However, Aksoy et al. noted a significantly higher score after eight hours of wearing facial masks [41].

MGD and lipid layer deficiency are the main causes of evaporative dry eye, which leads to uncontrolled evaporation and excess water loss from the ocular surface [42]. In a study by Enriquez-de-Salamanca et al., increased levels of inflammatory cytokines were found in patients with moderate forms of evaporative DED due to MGD [34]. In a recent study, the mean score of MG loss was reported as 22.8% in healthcare workers wearing surgical masks [43]. Likely, in the current study, the rate of the clinical findings of MGD and meibomiography scores of the prolonged mask-user group were found to be higher than those of normal individuals. The presence of MGD seems to support the increase in tear film evaporation, in addition to factors related to mask use.

Our study has some limitations. First, the small sample size may have hampered the detection of statistical significance for some parameters. Second, it would be better if the number of evaluated tear film cytokines were higher. Third, we did not evaluate the effect of taping of the upper mask edge, which is highly blocking the breathing air reaching the ocular surface. Finally, left eye of each subject was chosen without being randomized for the analysis.

Conclusion

The results of the current study demonstrated that elevated levels of IL-1ß and MMP-9 in basal tear fluid support the increased ocular inflammation in patients with MADE. In addition, lower NIBUT mean values and higher OSDI and meibomian gland loss scores resulted in ocular surface disturbance based on regular mask use. With previous studies evaluating the role of inflammation in MADE, attention should be directed toward possible treatment options targeting inflammatory pathways.

Author contributions A.P, H.S.K, and M.O wrote the manuscript.M.Z.B and B.E collected the tear fluid.M.T and R.D.G analyzed the data statistically.A.O evaluated the tear fluid samples with ELİSA methods.Ş.Ş did the critical ravisionAll authors reviewed the manuscript.

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Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare no conflict of interest regarding this original research.

Informed consent Written informed consent was obtained for identifiable health information included in this study. The manuscript has been read and approved by all authors. In addition, each author believes that the manuscript represents honest work.

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