Biotechnology & Biotechnological Equipment

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/tbeq20

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To cite this article: Evelina Marinova, Dimitar Dabov & Yani Zdravkov (2020) Ophthalmic complaints in face-mask wearing: prevalence, treatment, and prevention with a potential protective effect against SARS-CoV-2, Biotechnology & Biotechnological Equipment, 34:1, 1323-1335, DOI: 10.1080/13102818.2020.1838323

To link to this article: https://doi.org/10.1080/13102818.2020.1838323

Published online: 31 Oct 2020.

BIOTECHNOLOGY & BIOTECHNOLOGICAL EQUIPMENT
2020, VOL. 34, NO. 1, 1323–1335
https://doi.org/10.1080/13102818.2020.1838323

Ophthalmic complaints in face-mask wearing: prevalence, treatment, and prevention with a potential protective effect against SARS-CoV-2

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ABSTRACT:
The global pandemic of severe acute respiratory syndrome, COVID-19 affects the world's economics, social and health systems and has a great impact on every person's life. In an attempt to control the spread of the disease, regular usage of face masks became an ordinary routine. A large proportion of the population is reporting ocular symptoms through the period of mask-wearing that are still underestimated. Thus the eyes are not only widely exposed to a potential viral invasion but are also under the influence of an additional irritant factor, the face mask usage. The results of our pilot study indicate that the presence and severity of the ocular complaints are dependent on the type of mask and the duration of usage. Now, in the COVID-19 outbreak, the protection of the anterior ocular surface is necessary more than ever to contribute to personal eye health. Based on the concept for the protective role of the tear film and specifically, its lipid layer against the SARS-CoV-2 invasion, all substances sustaining tear film balance and lipid layer thickness could be beneficial in ensuring the local defense mechanisms. Some medications approved for the treatment of dry eye symptoms may have a defensive effect against the viral invasion, which should be additionally evaluated. The topical ophthalmic application of Cyclosporine A, Chloroquine, Azithromycin, Povidone Iodine, Hypertonic saline drops might contribute to local protection and ensure high local dose in minimum systemic effects.

ARTICLE HISTORY
Received 1 September 2020
Accepted 14 October 2020

KEYWORDS
SARS-CoV-2; COVID-19; dry eye; face mask; local protection; ocular complaints

Introduction

On 11th March 2020, WHO declared the severe acute respiratory syndrome, COVID-19, caused by the new coronavirus 2019-nCoV (SARS-CoV-2), a global pandemic, the greatest in the past hundred years since the Spanish flu pandemic in 1918–1920 [1]. Until now the 2019-nCoV virus has infected over 41.9 million persons with more than 9.6 million active cases and is responsible for over 1.1 million deaths in 215 countries and territories [2]. The infection is spreading with uncontrollable speed and the end of the pandemic is not coming in the foreseeable future. The predictive model of the Massachusetts Institute of Technology (MIT) projects 271 (254–412) million cases in 86 nations by the spring of 2021, and all over the world the number would be much greater [3]. The COVID −19 pandemic is a global health problem with an unpredictable outcome and no proven treatment. Until the appropriate therapy or vaccine is invented, only non-pharmaceutical interventions could be applied to impact that medical disaster. So far the only measures that have proved to be effective are social distancing, hygiene and the usage of personal protective equipment. Relying on the guidance of the World Health Organisation (WHO), many governments have already recommended wearing protective face coverings (scarfs or masks) in public where social distancing is impossible, in an attempt to slow the spread of the coronavirus. The healthcare personnel is obliged to use personal protective equipment including masks (surgical, FFP2, FFP3), gloves, face shields, disposable gowns and goggles, according to the circumstances and the level of viral exposure to prevent and control the infection spread and to ensure the personnel's and patients' health [4,5]. Despite the controversial effectiveness of face mask wearing, their usage in public is mandatory in many countries [6]. Irrespective of the type of face masks, their usage leads to new complaints, ranging from discomfort to reactive conditions and provoked disease, which have to be mentioned and clarified [7,8]. Skin irritations have already been reported [9] but problems with

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eyes have remained underestimated. Since the beginning of the pandemic there has been a noticeably great increase in the number of patients complaining of redness, discomfort, burning, stinging, tearing and foreign body sensation, irrespective of the major reason for their visit [10]. The magnitude of the problem is even higher in people who use face masks regularly and for a long period and are exposed to disinfectant usage. Disinfectant solutions that evaporate in the air also impact on the anterior ocular surface and could cause an allergic reaction, faster evaporation of tears and even punctate keratitis.

The purpose of this report is to highlight the risk of ophthalmic complaints in the face mask-wearing, to discuss some pathogenic mechanisms for their occurrence, and to offer therapy and ocular protection with a potential beneficial effect on the local resistance to viral invasion. A pilot study was designed to estimate the prevalence of ocular complaints in face mask-wearing and their relation with mask type and the duration of usage.

Subjects and methods

Ethics statement

The study was performed in accordance with the principles in the Declaration of Helsinki. All subjects provided written informed consent.

Subjects

A pilot study including 144 persons, 55.6% women, $N=80$ and 44.4% men, $N=64$, median age of 43 years (22-79 years), was performed in two medical centers in Sofia, the capital of Bulgaria. Three groups with an equal number of attendants were formed, according to the type of face mask and the duration of daily usage. The medical personnel of both centers was also included in the study. All the attendants were asked to fill in a short questionnaire with information about the type of mask and the regimen of usage, ocular and extraocular complaints related to the mask-wearing, medical history, and comorbidities. All patients underwent a thorough ophthalmic examination including best-corrected visual acuity, slit-lamp biomicroscopy, tonometry, fundoscopy, ocular surface fluorescein staining evaluation, Shirmer test and tear break up time measurement.

Data analysis

The results are presented as absolute values and percentages. The groups were compared by using the Pearson *Chi*-square test. Differences were considered statistically significant at $p < 0.05$ level.

Literature review

A literature survey was performed focused on the ocular involvement in COVID-19 disease, the mechanisms of SARS-CoV-2 viral invasion, the proposed therapeutic approaches for prevention, and local treatment. The following keywords were used to perform searches in PubMed, Google Scholar, Scopus, Mendeley, ScienceDirect, MedRixv and Web of Science: COVID-19, SARS-CoV-2 transmission, COVID-19 ocular manifestation, face mask wearing, dysfunctional tears syndrome, dry eye treatment, COVID-19 treatment, COVID-19 protection.

Results and discussion

A total of 144 persons were included in the pilot study. Two major groups were formed, by the duration of daily usage of face masks: regular and occasional mask wearers. The group of regular mask users ($N=96$) included persons wearing face masks 6 h/day or more. It was divided into two subgroups based on the type of face masks: regular protective mask users (RPMU), $N=48$, formed from the medical personnel of both centers, who usually use surgical masks (and occasionally wear FFP2, FFP3), and regular ordinary, non-medical (single- or multi-layer) masks users (ROMU), $N=48$. The group of occasional users was formed by individuals who wear masks incidentally or for a short period ($N=48$).

The results were analyzed to evaluate the relationship between clinical symptoms and the period of mask usage. There was a significant difference in the prevalence of the symptoms among the three groups. Persons who wear ordinary, non- medical single- or multiple-layer masks, usually used by the major part of the population, reported fewer side effects.

Of all the participants, 90.2% ($n=130$) reported some kind of physical and social disturbance, 59.7% ($n=88$) reported skin irritations, 82% ($n=118$) shortness of breath with the mask, 10.4% ($n=15$) complained of a headache at the end of the day. The skin problems included itching, rash, burning, acne, dermatitis, intertrigo, impetigo, miliaria, etc. Additional complaints included pain in the zones of contact with a mask, sweating, irritated and painful skin of the ears,

Table 1. Prevalence of the ophthalmic symptoms in different groups.

Symptoms	Regular users ($N = 48$ in each group)				Occasional users	
	Regular protective mask users (RPMU)		Regular ordinary (non-medical) mask users (ROMU)		$N = 48$	
	N	%	*N*	%	*N*	%
Discomfort in the eyes	40	83.3	28	58.3	20	41.2
Redness	38	79.2	25	52.1	16	33.3
Tearing	33	68.8	22	45.8	13	27.1
Burning	27	56.3	18	37.5	11	22.9
Dry eye feeling	25	52.1	16	33.3	8	16.7
Foreign body sensation	21	43.8	14	29.2	7	14.6
Itching	16	33.3	9	18.8	3	6.25
Blurred vision	9	18.8	5	10.4	1	2.1

Note: Regular users: persons wearing face masks 6 h/day or more; RPMU: regular protective (surgical, FFP2, FFP3) mask users; ROMU: regular ordinary, non- medical mask users; Occasional users: individuals wearing face masks incidentally or for a short period.

blurring of eyeglasses and problems with their position, etc. 70.1% ($n = 101$) reported ocular symptoms, including burning, redness, tearing, foreign body sensation, itching, blurred vision, dry eye feeling and undefined eye discomfort.

Ocular symptoms, summarized in Table 1, were reported by the patients for the time of mask using.

The medical personnel complained significantly more often than the occasional users of masks ($p < 0.01$), whilst the difference between regular protective mask users (RPMU) and regular ordinary mask users (ROMU) was not always significant (Table 2).

According to Pearson's *Chi*-square test, there were no significant differences between regular ordinary mask users (ROMU) and occasional users for most of the symptoms. In the group of regular mask users, including medical personnel and regular users of ordinary masks, all of the symptoms appear significantly more often than among the occasional users. There was a positive correlation between the time of mask usage and the presence and severity of the complaints (Spearman's Correlation coefficient $\rho = 0.437$, $p < 0.001$). The incidence of all complaints was higher among the regular users of protective masks. Healthcare personnel had the highest prevalence of ocular complaints with the most severe clinical picture related to the necessity of prolonged usage of protective equipment. The clinical findings included conjunctival congestion, inflammation, superficial punctate corneal erosions, shortened tear break up time and Shirmer test. The usage of the N95 respirators was related to rarer ocular complaints but skin problems were often found. Subjective and clinical symptoms were more frequent and more severe in persons who wear eyeglasses. Milder complaints were estimated among persons who wear ordinary masks but these masks provide the weakest level of protection. A recent report showed a general increase in the number of persons (patients and personnel) that complain of ocular irritation and dry eye disease since it became an ordinary routine to wear protective masks [10] Among the participants in our study, 8.3% of regular users of ordinary (cloth, fabric) face masks, 20.8% of healthcare workers and 4.17% of occasional users reported that they had started using lubricating eye drops and had felt diminishing of their complaints.

Mechanisms leading to ocular damage in face mask-wearing

Different mechanisms lead to ocular complications in face mask usage. The major factor is the outflow of exhaled air, with a temperature around 36-37 °C, passing over the upper border of the face mask to the ocular surface. This direct hot airflow leads to instability, increased evaporation, hyperosmolarity, and a decline in tear film turnover and clearance and results in ocular damage and dry eye symptoms. The severity of the symptoms correlates with the tear lipid layer thickness [11]. In cases with the additional use of a face shield, the temperature is even higher and the stream of fresh air diminished, which aggravates the complaints. The effect resembles the desiccating environmental conditions with increased airflow, which is proved to increase the incidence of dry eye disease and worsen its symptoms [12,13]. Besides, the exhaled air has a decreased level of oxygen and an increased carbon dioxide concentration, which decreases the tear pH levels and consequently impairs the ocular surface [14,15]. The increased carbon dioxide concentration reduces the stromal pH [16], which excites the corneal nociceptors and thus evokes corneal pain sensations [17]. Ocular hypoxia results in excessive production of reactive oxygen species that promote inflammation and neovascularization by the activation and apoptosis of leucocytes, expression of pro-inflammatory factors, including vascular endothelial growth factor and interleukins by endothelial and epithelial cells [18–20]. Ocular surface irritation has been reported in continuous positive airway pressure masks

Table 2. Results of the comparison between the different groups by Pearson *Chi*-square test. *P*-values smaller than 0.05 are considered significant.

Symptoms	RPMU vs. ROMU	RPMU vs. Occasional users	ROMU vs. Occasional users	Regular users (RPMU + ROMU) vs. Occasional users
	p-values			
Discomfort in the eyes	0.007	<0.001	0.102	0.001
Redness	0.005	<0.001	0.006	<0.001
Tearing	0.023	<0.001	0.054	<0.001
Burning	0.066	<0.001	0.120	0.005
Dry eye feeling	0.063	<0.001	0.059	0.002
Foreign body sensation	0.138	0.002	0.084	0.006
Itching	0.104	<0.001	0.064	0.005
Blurred vision	0.247	0.008	0.092	0.021

Note: Regular users: persons wearing face masks 6 h/day or more; RPMU: regular protective (surgical, FFP2, FFP3) mask users; ROMU: regular ordinary, non- medical mask users; Occasional users: individuals wearing face masks incidentally or for a short period..

as a result of the leakage of air and regurgitation through the nasolacrimal ducts [21,22]. The usage of N95 respirators excludes most of the mechanisms for mask-induced dysfunctional tear syndrome (DTS) because of the very tight contact between the mask and the face. This tight contact prevents the airflow over the top of the mask. However, in that case, the normal position of the palpebrae could be harmed leading to incomplete blinking and exposure keratopathy. The usage of protective goggles is related to a higher air temperature, increased carbon dioxide concentration, and changes in the palpebral position and movements resulting in dry eye symptoms [23]. Higher exposure to disinfectant solutions most of which evaporate in the air, has an additional influence on the anterior ocular surface and could provoke either chemical or allergic reactions and is an additional mechanism for ocular irritations among medical staff. It has already been discussed that symptoms of dry eye are more severe and often found among persons who wear eyeglasses as a result of the exhaled airflow entrapped between the anterior ocular surface and posterior surface of the eyeglasses. It has to be emphasized that tear film deficiency and instability not only lead to ocular surface symptoms, inflammation and visual complaints [24,25] but also violate the defense mechanisms of the anterior ocular surface and thus make the cornea and conjunctiva more susceptible to infections.

Ocular manifestations of COVID-19

Ocular manifestations have been registered as an initial symptom or in the course of COVID-19 and could be found in mild or severe cases [26–29]. Among them, conjunctivitis is most often found with prevalence ranging from 0.9 [30] to 31.2% [31,32]. The possibility of some ocular symptoms in hospitalized patients to emerge as a result of prolonged mask usage has to be mentioned. In patients with only mild respiratory symptoms, Cheema et al. [33] reported keratoconjunctivitis as an initial presentation of the disease and Dinkin et al. [34], two cases of ophthalmoparesis consistent with abducens nerve palsies, neurological deficits, and abnormal perineural or cranial nerve findings on magnetic resonance imaging. Ocular manifestations were also reported in the middle phase of COVID-19 or after the occurrence of systemic complaints. Chen et al. [28] represented a case of a young COVID-19-positive male with acute bilateral follicular conjunctivitis that developed 13 days after the onset of the disease. Navel et al. [35] described pseudomembranous and hemorrhagic conjunctivitis 19 days after the beginning of symptoms. In patients with COVID-19, retinal lesions and papillophlebitis were also described [36,37]. Results of murine models of other coronaviruses suggest the possibility of uveitis, secondary optic neuritis, viral-induced retinitis, and signs of neuroretinal degeneration to be found in the long term [38–40]. Patients with more severe systemic manifestations of COVID-19 are reported to have a higher incidence of ocular symptoms [31]. It is important not to neglect the possibility of ocular inflammatory events to be manifestations of the systemic disease or the risk for ocular symptoms to remain underestimated due to the major, life-threatening conditions that need intensive treatment [39]. Several cases of conjunctivitis that occurred prior to pneumonia in the course of COVID-19, including a Chinese respiratory specialist who visited patients in Wuhan, fully gowned with a protective suit and N95 respirator, focused attention on the eye as a potential pathway for viral invasion [27, 28]. Besides, SARS-CoV-2 was detected in conjunctival scrape samples and tears in a small number of COVID-19 positive patients without [41] or with symptoms of conjunctivitis [42–45] and even after the virus was undetectable in nasal swabs [46]. Colavita et al. [46] reported a case of a hospitalized patient with SARS-CoV-2 positive conjunctival swabs up to 21 days from the onset of the symptom when nasal swabs were negative. Five days later the virus was undetectable in the conjunctival test and on day 27 the conjunctival test was positive again. These findings suggest viral replication in the conjunctiva [46].

Despite the controversy of the findings of SARS-CoV-2 viral transmission, invasion and COVID-19 clinical characteristics, more detailed information is urgently needed to prevent the spread of the outbreak. The possibility of an ocular surface to be a target for viral replication and transmission should not be excluded and needs to be further explored [47].

SARS-CoV-2 ocular surface interactions

Viruses can enter the eye directly by exhaled air from respiration, by droplets or aerosols spread by an infected person while talking, coughing and sneezing, and by contact with a contaminated surface. The possibility of viral transmission through contact with asymptomatic patients has also been suggested [48]. The infection could be also secondarily transmitted by migration through the nasolacrimal duct from the upper respiratory tract, or *via* hematogenous spread in infection of the lacrimal glands [40,49].

SARS-CoV-2 invades the host cell through binding its spike (S) protein to the entry receptor, membrane-bound angiotensin-converting enzyme 2 (ACE2) and in the presence of the transmembrane protease serine 2 (TMPRSS2) [26,50], with the number of expressed receptors in the membranes being limiting for the viral adhesion and invasion. There is high expression of the ACE2 receptors in multiple tissues in the human body, including the nasal mucosa, upper respiratory tract, lungs, kidneys, conjunctiva and the cornea [51]. The presence of ACE2 and TMPRSS2 was found in the conjunctiva, limbus, cornea, non-pigmented epithelial cells of the ciliary body, trabecular meshwork, ganglion cells, in the inner nuclear layer, photoreceptors, and endothelial cells of the retinal and choroidal vessels. Controversially, the results of Lange et al. [50] show no expression of the SARS-CoV-2 receptor ACE2 in conjunctival samples. The expression of ACE2 and TMPRSS2 in the ocular structures suggests the eye to be an additional portal for viral invasion, a potential reservoir for the transmission of the infection, and to be susceptible to SARS-CoV-2 infection with multiple clinical expressions [52–54]. The ocular tropism of the virus was also postulated [28].

Ocular surface defense mechanisms

Despite the direct exposure of the eye to potentially infectious material, with the ocular surface area estimated at 1600-1896 sq. mm/eye with a total of around 10,000 sq.mm including palpebral and brow skin and the highly expressed conjunctival ACE2 receptors, the incidences of ocular involvement in COVID-19 positive patients are low [55]. The tear film is supposed to have a major role in the defense. The tear film covers the ocular surface, providing an appropriate pH (7.14-7.82), osmolarity and electrolyte concentration. The secretion of tears of 2 μL/min with a regular turnover of its volume at a rate of 5.4-20.6% per minute ensures the dilution of the viral titer and wash-out through the nasolacrimal duct. Additionally, the tear film resilience prevents access to the apical corneal and conjunctival epithelium by viral adherence to the tear film. The tear film lipid layer is of great importance for the balance of the anterior ocular surface by protecting against evaporation and spillage of tears [11,56]. The adhesion and cell entry of coronavirus require the presence of cell membrane cholesterol and lipid rafts but the role of the tear lipid layer in this process is still unclear. Tear film lipids could be supposed to prevent the adhesion of the viruses to their entry receptors providing the same barrier function ensured by the skin surface lipids [21]. On the other hand, it could be speculated that free cholesterol in the tear lipid layer, albeit under 0.5%, could facilitate viral adhesion ensuring the required “lipid rafts” [44,57]. Synergistically working lactoferrin, lysozyme, lipocalin, mucins, IgA and complement in the tear film have antiviral properties and would inactivate viruses [55,58,59]. Hence, even if the concept that tear film could prevent viral adhesion and invasion in conjunctival and corneal cells is valid, the possibility for viral invasion trough the ocular structures should not be eliminated. The anatomical linkage between the eye and the upper respiratory tract through the nasolacrimal duct, the ocular–respiratory immune interdependence by the nasolacrimal lymphoid tissue are additional factors that could lead to respiratory tract infection [44, 47, 55, 60]. Despite the concept of potential tropism of the SARS-CoV-2 virus to the ocular tissues and the theories that the eye is not only a pathway for viral invasion but also a reservoir of infection, the low positive test rate in tears and conjunctival secretions from infected patients could be a result of their relatively low sensitivity [29] and the inappropriate time of sample collection [50]. Other factors that could also contribute to a low positive test rate are the dilution of tears by their continuous production, drainage through the nasolacrimal duct [61,62] as well as the presence of lactoferrin in the tear film, which can inhibit the binding of SARS-CoV to ACE2 receptors [63], and the IgA antiviral activity [44].

Face masks reduce the number of droplets but in most cases, some of the exhaled air escapes through the top of the mask into a person’s eyes and thus causes increased airflow that results in drying of the natural tears, irritation and increases oxidative stress.

The balanced tear film is a major part of the natural defense mechanism of the eye and its damage increases the risk of viral invasion. It has been already mentioned that face mask-wearing leads to eye irritations and dysfunctional tear syndrome (DTS) [64], and treatment of ocular complaints is needed to ensure personal comfort and quality of life. On the other hand, the discomfort, as a result of mask-wearing, generates an impulse for touching the eyes and increases the risk for viral contamination in all groups. [8] Sustaining the balance, the volume and stability of the tear film are of great importance to diminish the risk for a viral invasion through the eyes in the COVID-19 pandemic. Ophthalmic preparations including artificial tears, gels, sprays and ointments have been used for years to treat DTS, and many of them could enhance the ocular surface protection [65]. In patients with low tear volume, osmolarity balanced artificial tears are majorly used, whereas in patients with insufficient tear lipid layer the liposomal sprays are preferred [66].

Treatment and prevention of DTS

Artificial tears

Osmolarity balanced artificial tears are used to increase tear volume in patients with DTS. Products containing sodium hyaluronate, and carboxymethylcellulose alone or combined with glycerin are effective in treating dry eye symptoms and for their prevention, but sodium hyaluronate has faster efficacy [67–71]. Seawater sprays are reported to decrease the level of pro-inflammatory IL-1-beta IL-6 and could be safely and effectively used for the treatment of dry eye symptoms [72].

The usage of artificial tears could be recommended to patients with DTS and to the general population to increase tear volume and drainage and thus decrease potential viral load. Preservative-free formulations show safety and efficacy and could be applied as frequently as needed [70,73].

Lipid emulsions

Replenishment and stabilization of the lipid layer of the tear film are the key points for treating DTS and protecting the ocular surface [74,75]. Application of lipid emulsion eye products could be the most appropriate therapy because they increase the lipid layer thickness, treat and prevent the symptoms of an evaporative dry eye, and could be used as monotherapy or combined with other products [76]. They are also reported to show better effectiveness compared to sodium hyaluronate, hydroxypropyl methylcellulose and hypromellose in reducing tear evaporation and treatment of dry eye disease [71,77,78]. Many anionic emulsions are available including castor oil eye drops, and carbomer-based lipid artificial tears and they have been well-tolerated and effective in treating signs and symptoms of dry eye, additionally showing improvement in meibomian gland functionality [78–80] Cationic emulsion artificial tears eye drops resemble normal tear film, restore and ensure ocular surface homeostasis and are an excellent option for treatment and prevention of the symptoms of dry eye. They increase the tear lipid film thickness and stabilize the aqueous phase of the tears. Additionally, cationic emulsion artificial tears are reported to have high anti-inflammatory properties and to improve ocular surface healing [81–83]. The usage of ointments is also effective in the treatment and prevention of DTS, but with no proven influence on the state of the tear lipid layer. The application of ointments to the lower lid ensures slow and continuous drug release to the anterior ocular surface [79]. Liposomal sprays are applied onto the close eyelids and the polar phospholipids migrate to the anterior ocular surface and improve the tear lipid layer stability and thickness resulting in diminished tear evaporation and less ocular complaints [84]. Liposome based gel formulations may be beneficial for the treatment and protection of DTS by providing prolonged contact time with the anterior ocular surface [85]. Based on the concept of the protective role of the tear film and specifically, its lipid layer against the SARS-CoV-2 invasion in the ocular tissues, all ocular substances that ensure tear film balance and lipid layer thickness could sustain the local defense mechanisms.

Trehalose is a natural plant-based glucose disaccharide that is known to decrease cell apoptosis and protect cells from desiccation and oxidative injury, and thus suppresses inflammation, cicatrization and neovascularization [86,87]. It is an additional substance in some eye lubricants and is also reported to modulate autophagy and to have anti-viral properties [88,89]. Eye formulations containing trehalose could be safely used to protect the ocular surface from the harmful effects of face mask-wearing, and additionally could benefit the local defense barrier against viral invasion of SARS-CoV-2 without side effects.

To the best of our knowledge, the protective role of tears against SARS-CoV-2 outside the eye is not established yet but it could be speculated that if it has a protective function on the ocular structures, a similar effect could be expected on the nasolacrimal duct, nasopharynx and upper respiratory tract. Hence, the addition of ophthalmic preparations that increase the tear lipid layer thickness, which supposedly could have a protective role against SARS-CoV-2 infection, could benefit the local protection of the nasal mucosa and oropharynx. The usage of liposomal lid sprays ensures spreading not only on the anterior ocular surface but also on the palpebral skin, thus increasing its defense and the spreading of the emollient on the anterior ocular surface for a longer period [21,79,90,91].

Only 1% or less of the applied dose of the active ingredients in topical ophthalmic medications penetrate the eye tissues and exert their effect and the rest is systemically absorbed through the ocular structures, lacrimal drainage system, nasal mucosa, nasopharynx, gastrointestinal tract and skin, allowing systemic effect. Based on these findings, local application on the ocular surface could be beneficial to ensure contact of the active substance with those structures. Thus drugs with serious systemic side effects could be successfully used on the ocular surface, reaching high local dose in the nasal mucosa, nasopharynx and upper respiratory and gastrointestinal tract [54,92]. Besides, one of the important mechanisms of intracellular drug delivery is the absorption of liposomes to the cell membrane. Liposomal preparations are broadly used in ophthalmology, and such formulations and experience could be successfully applied as beneficial in the SARS-CoV-2 defense [54,93]. Many medications that are used for treatment of dry eye disease are suggested to have activity against SARS-CoV-2, and their usage in cases with DTS could ensure additional antiviral protection. Some of them could be safely used in cases of COVID-19 with ocular involvement and after exposure to SARS-CoV-2.

Cyclosporin A is used for years as a second-line option for therapy of dry eye showing improvement in the tear secretion, stability, and patients complaints without serious systemic or local side effects [94–97]. Its delivery, penetration, and bioavailability in ocular structures significantly increased when the is encapsulated in liposomes [98,99] Additionally Cyclosporin is found to inhibit the replication of coronaviruses and one drop of 0.05% cyclosporin is calculated to contain 5 folds the lethal dose to SARS-CoV-1 [100]. Based on this, cyclosporin eye drops may be safely recommended for prophylaxis and treatment of COVID-19 related eye complaints.

Chloroquine-containing eye products stabilize the tear film and decrease local inflammation. They are successfully used for the treatment of dry eye disease and are reported to be well tolerated and more effective than artificial tears [101–103]. Besides, chloroquine, and *hydroxychloroquine* have been reported to be effective against various viruses, including coronaviruses [104]. *In vitro* studies reported that both drugs inhibit SARS-CoV-2, by changing the glycosylation of the ACE2 receptor and S protein, blocking the fusion between the virus and the cell, and by inhibition of the lysosomal activity by increasing the pH [105]. Hydroxychloroquine shows similar antiviral activity but with fewer side effects [106,107]. Hydroxychloroquine has also been shown to have immunomodulatory activity and was recommended for prophylaxis after SARS-CoV-2 exposure [104,108]. Both drugs have been recommended and used for treatment of COVID-19 alone or in combination with azithromycin [105,109,110]. Recent studies, however, do not prove the efficacy and safety of treatment with hydroxychloroquine/chloroquine alone or in combination with azithromycin neither the prophylaxis of COVID-19 with those drugs [111,112]. Additional studies are required to estimate the effectiveness of both drugs against SARS-CoV-2. Nevertheless, chloroquine phosphate could be safely applied on the ocular surface in cases of COVID-19 conjunctivitis and after exposure to the SARS-CoV-2 virus. It is suggested that topical application of hydroxychloroquine could achieve a dosage one to two orders of magnitude higher than the plasma levels reached with systemic treatment in minimum side effects. [113]

Topical *azithromycin* is also effective in the treatment of dry eye related to meibomian gland dysfunction but with fewer side effects than its systemic application [114,115]. It is claimed to have anti-inflammatory and immunomodulatory effects and to reduce interleukin IL-6 and IL-1 production and viral replication [116]. Azithromycin is used to treat patients with COVID-19 [117,118]. Its local application in the eye could be considered in cases with COVID-19 with ocular involvement and as prophylaxis after exposure to SARS-CoV-2 [55].

A few studies reported that *benzalkonium chloride (BAK)* at a concentration of 0.02% or higher inhibits various bacteria and viruses, including coronaviruses [113,119,120]. Relying on that finding, regular application of eye lubricant drops containing BAK could be offered to persons without underlying ocular surface diseases and especially to the medical personnel as protection against coronavirus infection. Artificial tears containing BAK could also be useful in cases suspected to have COVID-19 conjunctivitis [113].

Some studies show [121–124] that *povidone-iodine* in different concentrations (10%, 7.5%, 1% and 0.45%) has a virucidal activity against SARS-CoV-2 and effectively reduces viral loads. Besides, povidone-iodine eye drops have been successfully used in the treatment of viral conjunctivitis. Based on these findings, povidone-iodine could be applied on the anterior ocular surface in cases of COVID-19 conjunctivitis and for prophylaxisagainst viral invasion, especially after close contact with an infected person, and it could be very useful for medical personnel [113].

A study shows that increased concentration of *sodium chloride* enhances the antiviral activity of epithelial cells and fibroblasts and inhibits SARS-CoV-2 replication of viruses [125]. An *in vitro* study reveals that 1.5% NaCl ensures 100% inhibition of SARS-CoV-2 in Vero cells [126]. The usage of BAK containing hypertonic saline eye and nasal drops could have an enhanced effect against viral entry. Thus, these products could be broadly recommended to the society and could be a good protective measure for the ocular and nasal tissues with minimum side effects that have to be proven.

Medications with supposed effects against SARS-CoV-2

Oral doxycycline has antimicrobial and anti-inflammatory activity and is successfully used for the treatment of meibomian gland dysfunction related to blepharitis [127]. Studies also reported that it reduces IL-6 levels and has antiviral activity [116]. Based on these observations, it is suggested to be effective in the treatment of COVID-19 [128].

The increase in the intracellular Zn^{2+} concentration is reported to inhibit the viral entry and impair the replication of SARS-CoV and other RNA viruses [129]. It is used in ophthalmic drugs as excipient, zinc sulfate (0.25%), and in astringent eye drops, but their effect against SARS-CoV-2 has to be evaluated [130].

The intake of *food supplements* containing a combination of probiotics, omega 3 fatty acids, lactoferrin, vitamin D and anthocyanins effectively improves dry eye [131]. The same substances as well as vitamin A, C, B6, B12, Zn^{2+} have been shown to play an important role in immune response to infections and could be suggested in COVID-19 prevention [88,132,133].

The flavonoid *quercetin* is reported to be effective for the treatment of corneal inflammation and dry eye disease *in vitro* and *in vivo* [85]. *In vivo* studies show that it has an inhibitory effect on SARS-CoV [134,135] and binds to the S-protein of SARS-CoV-2 [136].

Conclusions

Although a lot is already known about the SARS-CoV-2 virus, the mechanisms of viral transmission and invasion are still not well established and the role of the eye has to be additionally clarified. The results of our pilot study confirmed the hypothesis that face-mask wearing leads to ocular complaints even in healthy individuals and these complaints are dependent on the type of mask and the duration of usage. The subjective ocular symptoms should be treated and protective measures against ocular damage in face mask-wearing should be recommended to the whole community and especially to patients who already have dry eye disease or another anterior ocular surface disease. The regular application of artificial tears increases the volume of tears and thus ensures protection against desiccating conditions in mask-wearing and additionally increases drainage through the nasolacrimal duct and diminishes the viral load on the anterior ocular surface. Based on the concept for the protective role of the tear film and specifically, its lipid layer against the SARS-CoV-2 invasion in the ocular tissues, all formulations sustaining tear film balance and lipid layer thickness could be beneficial in ensuring the local defense mechanisms. Evidence indicates that eye preparations containing trehalose would not only protect the ocular surface from the harmful effects of face mask-wearing but additionally could support local barriers against viral invasion. The topical ophthalmic application of medications that are suggested to prevent SARS-CoV-2 invasion or to treat COVID-19 like cyclosporine A, chloroquine, azithromycin, etc. could contribute to a person's health and protection and ensure high local dose in minimum systemic side effects.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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