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How Mandibular Movement Intersects with Ocular Lacrimation: A Literature Synthesis

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Abstract

The COVID-19 epidemic has led to the widespread use of face masks in an effort to reduce disease transmission. Face masks may contribute to the severity of dry eye disease. Possible mechanisms have been proposed, including leakage of air from the superior edge of the mask, passing over the eyes. There may be other factors as well. There is a direct association between the salivary flow rate and the jaw muscle activity during speaking, chewing and mastication. There is also a positive association between dry mouth and dry eye. Agents that stimulate salivary gland secretions may concomitantly alleviate dry eye symptoms. This may provide a therapeutic opportunity that has not been explored in the past. Results of a recent experiment showed that chewing gum or candy alleviated dry eye. We hypothesize that chewing, mastication or speaking may have stimulated ocular lacrimation. We also suggest that impeded mandible jaw movement while wearing face masks may contribute to reduced lacrimation, leading to a worsening of dry eye disease. Face masks can additionally inhibit contagious yawning in community settings through impairment of both face recognition and emotion recognition, and thereby can diminish yawning-mediated tear production. We discuss in this paper the role these mechanisms may play in the worsening of preexisting dry eye disease, as a result of face mask wearing. This may have implications for pharmaceutical and nutraceutical industries aiming to relieve dry eye and mouth and may provide ideas for improvements in face mask design that might reduce their impact jaw motion, and secondarily on dry eye disease.

Keyword: COVID-19; dry eye; face mask; mandibular movement; facial nerve

Introduction:

Ocular problems due to face mask use during COVID-19 pandemic were first reported by Moshirfar et al [1]. Regular face mask wearing is accompanied with an increase in dry eye symptoms among some people [2-6] including contact lens wearers [2 ,7], negatively impacting visual quality. This phenomenon is especially important since it is expected that face mask use will continue for the foreseeable future. Many people including the young, are already at increased risk of dry eye disease because of increased screen time, as a result of the shift to online education [8], and other activities such as online shopping, web surfing and the use of mobile phones [9]. Since the beginning of the pandemic, people spend more time looking at screens which may exacerbate dry eye symptoms [5].

Factors contributing to dry eye are not homogenous. Thus, it is important to elucidate the underlying mechanism(s) in order to determine the best strategy to prevent and/or alleviate dry eye symptoms. We categorized possible mechanisms by which use of face masks may negatively impact dry eye disease, which led to our complementary hypothesis regarding the various factors affecting this problem.

Currently Proposed Explanations and Mechanisms:

Mechanical Explanation:

This explanation mainly focuses on poor fit of the mask or looseness of mask apposition against the face and nose, so that some airflow is directed towards the eyes. The face mask may also interfere with lubricating agents reaching the eyes, because of fears

patients may have about potential contamination from hands and drug containers during mask wear [10]. Other mechanical ventilation factors may possibly intensify and exacerbate airflow effects as well.

Recent experiments by Ding et al [11] (using infrared thermography with measurement of maximum interblink period and ocular surface temperature) support this hypothesis and provide a pathway by which faster tear evaporation leads to a faster onset of ocular discomfort and thereby shortens the amount of time one can refrain from blinking [12]. Enhanced tear evaporation leads to thinner localized areas of the tear film and thereby localized tear hyperosmolarity, which in turn activates the inflammation pathway associated with dry eye disease [13]. Inflammation then results in stimulation of polymodal and mechanonociceptor nerve endings and enhances activity of cold thermoreceptors to evoke sensations of ocular dryness and pain [11].

This study [12] provides a mechanistic explanation of this concept. A similar mechanism was described by Hayirci et al [14] in the setting of continuous positive airway pressure for patients with obstructive sleep apnea syndrome.

In nurses working in ICUs wearing sealed goggles during COVID-19, dehydration has been proposed as a mechanism for Meibomian oil hardening and chalazion formation [15].

Eyelid/Ocular Microbiota Explanation:

Just as the term microbiome or microbiota refers to all types of microorganisms present in or on the human body, the term ocular microbiota refers to all types of microorganisms present in or on the eyes. It has been shown that commensal microbiota play a critical and fundamental role in regulating host physiology, including the induction and development of the immune system and host defense mechanisms against the invasion of pathogens. In this regard, dysbiosis (referred as unbalanced microbiota) could lead to pathogenic microbial overgrowth and cause local or systemic inflammation [16]. The ocular surface is directly exposed to the outside environment, and can be affected by numerous pathogenic microorganisms [17].

Meibomian glands located in the eyelids are in charge of secretion of oily components for the tear film to protect the ocular surface from overt dryness, discomfort, or damage. Dysfunction of Meibomian glands often leads to evaporative dry eye syndrome. Despite some inconsistencies in the literature, mostly due to technical issues, it has been shown that altered ocular microbial species can sometimes be associated with dry eye syndrome and dysfunction of Meibomian glands [18-20]. *Corynebacterium*, as ocular surface "resident microbiota", is possibly associated with dry eye syndrome. However, it might be argued that alteration in the ocular surface microbiota may not be a cause, but rather it might be a corollary to ocular surface disorders.

Chalazion development, though primarily caused by a non-infectious obstruction of eyelid Meibomian glands, may also be associated with multiple specific bacterial isolates related to changes to the gut microbiome [21;22]. It is worth remembering that oral flora (including bacterial pathogens and normal flora) can easily be incorporated into expired droplets capable of reaching the ocular surface, while talking, sneezing, or coughing [23].

Therefore, as Silkiss et al [24] have nicely explained, mask wear can provide a funnel for enhanced bacterial exposure to the eyelids and cheeks, which in turn may promote inflammation. This is because an unbalanced ocular microbiota may lead to pathogenic microbial overgrowth, which may then cause local or systemic inflammation [17].

Frequent hand washing or use of hygienic/alcoholic disinfectants drastically changes the microbiome of hands [25-27]. This might lead to facial, eyelid or ocular surface microbiota alterations during the COVID-19 pandemic. There is currently no direct empirical evidence to support this hypothesis. However, an altered skin surface or gut microbiota community might theoretically be transmitted to the face, cheeks and eyelids, because mask wearers frequently manipulate their masks. This, in turn, may increase the chances of transferring bacteria from the hands to the face.

This is especially important in people who are already at increased risk of dry eye. In diseases such as Sjögren's syndrome (SS), there is a combination of Meibomian gland dysfunction and dry eye syndrome, with changes in ocular surface microbiota [28-30]. An altered gut-eye-lacrimal gland-microbiome axis has been previously implicated in dry eye in SS [31]. It might be conjectured that in addition to altered ocular/facial microbiota, unbalanced gut microbiota due to obsessive hand washing and sanitizing/cleaning practices in the home, and more specifically in the kitchen, may be partially responsible for dry eye. This may exacerbate pre-existing dryness, caused by wearing a face mask.

Causal Explanation:

A recent systemic review by Nasiri et al [32] concluded that the mechanism of dry eye or foreign body sensation is unclear in COVID-19 patients and may not be directly associated with the SARS-CoV-2 virus. After an extensive search in PUBMED, SCOPUS and Scholar using the terms 'dry eye', 'COVID-19', 'SARS', and 'SARS-CoV-2', there was no record of a causal association between COVID-19 infection and dry eye. Below, we will summarize some very recent evidence to show that the possibility exists that damage to lacrimal and Meibomian glands may occur due to COVID-19.

Recently, Grajewski et al [33] demonstrated the presence of angiotensin converting enzyme 2 (ACE2) expression in the conjunctiva by immunohistochemistry. This was previously shown to be present by Sungnak et al [34] on an RNA level. This was also observed in other pioneering studies, which demonstrated high expression of ACE2 mRNA in the conjunctiva and cornea of the human eye. [35;36]. A review of SARS-CoV-2-related English language articles from December 2019 through mid-April 2020 found in online databases, has concluded that ACE2 receptors and their expression on the ocular mucosal surface may explain the development of conjunctivitis in COVID-19 patients, although it may go unnoticed due to its mild nature [37]. ACE2 expression has been reported in the lacrimal glands of animal models such as mice [38] and rhesus monkeys [39]. However so far, we are unaware of any human study that has reported the presence or absence of ACE2 expression or ACE2 receptors in lacrimal glands and/or

Mebomian glands. Hong et al [40] studied 56 subjects before and after the development of COVID-19. It was found that 6 patients (11%) had ocular redness before the onset of respiratory symptoms. Scores on the OSDI (Ocular Surface Disease Index) and SEEQ (Salisbury Eye Evaluation Questionnaire) tests, both of which assess dry eye symptoms, were significantly worse after contracting COVID-19, even in patients without visible conjunctivitis. Similar studies confirm a worsening in ocular symptomatology following onset of COVID-19 in nearly all patients [41]. The worsening of dry eye symptoms in these patients suggests that the possibility of a direct causal association between COVID-19 infection and dry eye, via direct damage to the lacrimal and Meibomian glands. Conversely, healthy individuals without COVID-19 generally remain asymptomatic.

Alternatively, it is possible that worsening of dry eye symptoms is mediated via salivary gland dysfunction caused by COVID-19. Recent evidence revealed ACE2 expression in human salivary glands, in patients reporting oral symptoms such as dry mouth and amblygeustia, due to damage to the salivary gland caused by the COVID19 [42]. There is evidence showing a direct anatomical association between salivary glands and lacrimal glands and that treatment of salivary hypofunction, improves dry eye symptoms [43-45]. Targeted AQP1 gene therapy of the submandibular glands in a murine model of SS not only improved salivary flow, but also lacrimal gland function [43], suggesting existence of a direct uni- or bilateral interaction between these two secretory glands. In fact, salivation improves lacrimal gland function in dry eyes. Upon stimulation, the seventh cranial nerve aids in the secretion of tears from the lacrimal glands and creates a sense of relief from mild dryness of the eyes [45]. The facial nerve contains fibers for both the lacrimal gland and the submandibular salivary gland. After the facial nerve passes through the geniculate ganglion, the parasympathetic secretomotor nerve fibers for the submandibular salivary gland travel with the main nerve trunk. The secretory nerve fibers for the lacrimal gland separate from the facial nerve to join the greater petrosal nerve. These secretory nerve fibers then pass through the sphenopalatine ganglion before innervating the lacrimal gland [44]. For a full anatomical description, see these references: [44;45]. Briefly, it there are evidences showing a direct damage to the lacrimal glands by the COVID-19 virus [46;47].

Novel Mechanism:

There is a direct association between the salivary flow rate and jaw muscle activity during mastication [48-51], i.e., the higher the chewing rate, the higher the saliva secretion. There is also a positive association between dry mouth and dry eye in humans (in normal adults [52], in subjects with and without symptoms of dry mouth and/or eyes, in patients with primary SS [53], in the elderly [54], and in patients with dry eye symptoms [55]).

It is not surprising that agents that stimulate salivary gland secretions, such as pilocarpine [56] and cevimeline [57], stimulate lacrimal gland (and/or Meibomian gland) secretion and alleviate dry eye symptoms. However, it was surprising to find that simply chewing gum or candy also alleviated dry eye symptoms, without involvement of receptors, antagonist(s) or agonists(s). Higher salivary secretion brought about by chewing gum or candy led to significantly lower dry eye scores [58], with no drug-receptor interactions involved.

In the only published trial with a double-blinded crossover design, Asakawa et al [58] evaluated eye dryness with the RT-7000 Auto Ref-Topographer and Tear Stability Analysis System (TSAS) (Tomey, Nagoya, Japan). Briefly, healthy participants experiencing eyestrain (n=46, 23 male and 23 female, 20-59 yrs old) were instructed to keep their eyes open for 10 seconds. Severity of eye dryness was then evaluated by measuring ring break-up time (RBUT). The RBUT was measured by analyzing break-up of the tear layer within a 6-mm radius of the center of the cornea and its deformation over time, and measuring the number of seconds required to reach the cut-off value of –0.5 D, in accordance with the algorithm provided by Tomey. Each 10-year age group cohort included 12 subjects, with the exception of the 30s group, which included 10 subjects. A visual task was performed on reading material displayed on a computer screen at a fixed distance for 60 min. Participants were asked to chew gum or candy (two pieces for two 15-min periods) starting 15 and 45 min after starting to read. Subjects chewed gum on Day1 and candy on Day2, and *vice versa*. With regard to the visual analogue scale, there were no significant difference between scores of subjective eye fatigue between chewing gum and chewing candy ($P = 0.397 - P = 0.909$). Those scores of eye heaviness and eye tiredness were significantly longer in duration before and after the visual task with candy ($P = 0.013$ and $P = 0.025$, respectively), but not with chewing gum. The changes of subjective accommodation were significantly lower after the visual task, after chewing candy or chewing gum ($P = 0.043$).

Most importantly, before and after the visual task, the RBUT values showed a significant trend (i.e., 10.0 sec and 9.6 sec, respectively, $P = 0.053$) only with chewing gum but not with chewing candy ($P = 0.132$) 58. It is very important to note that participants were asked to chew gum or candy only for two 15-min periods, while in real-world setting; wearing a face mask lasts very long.

Their experiment provides the first experimental evidence supporting our novel hypothesis that salivary secretion can (either directly or indirectly) enhance ocular secretions, possibly *via* a mechanism involving mandibular jaw movement.

Wearing a face mask meanwhile can substantially impair the jaw movement during daily activities such as speaking, chewing, and swallowing [59;60]. For instance, normal yawning which is a physiological behavior could be deregulated due to the restriction of mandibular jaw movement by face mask wearing [59]. It worth to remind that tears can be described as of two types: reflex tears, which are induced by a range of stimuli (eg. yawning, as a very important stimulus), and basal tears, which are the non-stimulated lacrimation of the tear glands [61]. Yawning –i.e., powerful stretching of the mandible jaw– is contagious and can be both conscious and unconscious. Face masks can additionally inhibit contagious yawning in community settings through impairment of both face and emotion recognition [60;62;63] and thereby can diminish yawning-mediated tear production. It is also interesting that even self-induced yawning stimulates aqueous tear [64], and saliva production [65]. Most interestingly, during yawning, muscle sympathetic nerve activity is inhibited [66] and a marked increase of cerebral blood flow [67], and significant increase in blood flow through the ophthalmic veins occurs [68], all of which contribute

to normal tear production.

We use these facts to support the mechanism we propose: Decreased salivary flow rate and to a lesser extent, insufficient lower jaw movement due to the restriction of mandibular jaw movement by face mask wear, may represent a new mechanism by which dry eye is exacerbated in face mask wearers.

Hypothetical Pathway:

Chewing/mastication [69] and speaking [70;71] both of which are activities that entail mandible movement, increase cerebral blood flow (rCBF). Chewing also increases actions of the autonomic nervous system (sympathetic and parasympathetic nerves) [72-74]. Chewing gum also increases blood flow to the eyes and to the parasympathetic nerves which predominantly act to contract the iris sphincter muscle [58]. On the other hand, certain physical activities or psychological situations can alter patterns of rCBF. For example, walking [74], experiencing social phobia during stressful speaking tasks [75], and social phobia treated with citalopram or cognitive-behavioral therapy [76] differentially change the pattern of rCBF. An rCBF pattern of relatively enhanced cortical, as opposed to subcortical perfusion is seen in the nonphobic subjects, showing that cortical evaluative processes are taxed by public performance. Conversely, the social phobia symptom profile is associated with an altered cerebral blood flow, i.e., increased subcortical activity [75] which amazingly is similar to altered cerebral blood flow in patients with SS [77-80] in which dry eyes and dry mouth are clinical hallmarks [81;82]. Altered rCBF patterns are reported in patients with COVID-19 [83-87]. This may be due to a possible neuroinvasive action of SARS-CoV-2, or it may be a partial manifestation of an altered pattern of mandible movement, resulting from the wearing of a face mask .

As for direct association between impaired jaw movement and dry eye, current evidence comes mainly from case series reports of patients with impaired jaw movement 88-90, which all share in the facial nerve impairment and hypofunction of lacrimal component of the nervus intermedius function [91].

There is currently no report to directly link facemask-induced dry eye with lacrimal gland aquaporins (AQPs) expression in humans, however, there is huge amount of evidence to establish this notion in submandibuar glands [92-95]. For instance, pigs fed with different dietary treatments –based on different grinding intensities and compactions of the same diet– showed significantly different AQP5 expression in mandibular gland, with highest AQP5 expression in those fed with coarsely ground pelleted diets compared to other softer diets [92], clearly suggesting that higher jaw movement is positively associated to AQP5 expression in a rate dependent manner. In another recent experiment, Saito et al examined the impact of the decline and recovery of masticatory function on expression and localization of AQP5 in the Wistar rat submandibular salivary gland by inserting and removing an incisor bite plate. Attachment of incisor bite plate resulted in a decrease in the expression of AQP5. Alterations in the localization of AQP5 were confirmed between two weeks and four weeks in the same rats. Conversely, alteration in the expression and localization of AQP5 were not seen in the recovery group. These findings suggest that a loss of molar occlusion and jaw movement decreases AQP5 expression and alters its localization in the rat submandibular salivary gland. Interestingly, removal of the bite plate permitted the recovery of both AQP5 expression and its normal localization in the submandibular salivary glands [94].

Thus, higher jaw movement is associated with higher AQP5 expression in submandibular salivary glands [92-95]. It however remains to be explored whether face mask-induced dry eye is mediated via altered AQPs expressions in lacrimal glands.

AQPs are a group of water channel proteins which mediate the passage of water molecules through membranes [96]. The Meibomian and lacrimal glands are rich in AQPs [97-99]. Altered cerebral blood flow homeostasis results in dysfunction of AQPs both in the brain and secretory glands [13;100-104] which, like the lacrimal and Meibomian glands, are rich in AQPs. [105-107].

There is empirical evidence supporting the hypothesis that these effects are eventually mediated by modulation of parasympathetic nerve and muscarinic receptors 108;109. See reviews [110;111]. In support of this conclusion, in a counterfactual reasoning model, the function of sympathetic and parasympathetic nerves during gum chewing is in harmony with autonomic nerves [112]. The submandibular gland AQP5 is degraded by parasympathetic denervation and is recovered by cevimeline, which is an M3 muscarinic receptor agonist [113].

These observations could have deep implications regarding the effect of social distress and the limitation of physical activity brought about by the COVID-19 pandemic. Social phobia negatively impacts verbal communications, resulting in a further decrease in mandibular jaw movement, possibly adding to the problem of dry eye disease.

Conclusions:

We hypothesize that prolonged wearing of face masks might reduce movement of the mandible. Less frequent face-to-face verbal communication (pre-COVID-19 pandemic vs. post-COVID-19), and possibly impeded yawning, might have further contributed to altered patterns of blood flow to the eyes and rCBF, due in part to social distress and physical confinement. This, in turn, may theoretically have affected modulation of parasympathetic nerve and muscarinic receptors through AQPs in the lacrimal and Meibomian glands. Face masks, meanwhile, can impair contagious yawning in community settings through impairing the performance of both face and emotion recognition and thereby can diminish yawning-mediated tear production. At present this remains a hypothesis that needs to be tested.

Perspective and Suggestions for Future Studies:

In order to come to a better understanding of how COVID-19 might affect dry eye disease, the possible interaction or modification effect between confounding variables should be considered in future studies. This might facilitate the discovery of better preventive measures and therapeutic agents for the management of dry eye symptoms experienced by patients suffering from this pandemic. As an example, a future study might look at whether higher rates of verbal communication by women as compared to men has an impact on the potential effect of face mask wearing on the development of dry eye disease, including the

issues of proper versus improper mask fitment, and continuous versus intermittent mask wear. Another study might seek to compare different types of face masks such as surgical masks versus N95 masks, to see if the relative degree of leakage from the edge of the mask affects eye dryness. Retrospective data collection methods are subject to respondent memory bias, self-bias and self-rating bias. To diminish the memory bias in relation to dry eye, proper web-based registries or online surveys can be utilized. In this regard, there are validated questionnaires such as Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire, which can be used to evaluate the symptomatology of patients. The SPEED questionnaire could be compared to the more diffuse Ocular Surface Disease Index (OSDI) questionnaire [41]. The SPEED questionnaire can discriminate between asymptomatic and symptomatic individuals in relation to dry eye disease [114]. Occupational and prior health history, such as a history of prior refractive surgery, computer professionals with high levels of screen time, and history of systemic conditions such as SS, rheumatoid arthritis or symptoms of dry mouth should be explored. Milder cases can be handled over teleconsultation [115].

It would be interesting to look at dry eye prevalence in a number of categories, such as obsessive people who strictly quarantined at home (which may result in less or no use of a face mask, and reduced exposure to COVID-19), those with high levels of screen exposure, those with little or no viral exposure, and those who strictly observed face mask wearing protocols, versus those who did not.

If it can be shown that COVID-19 adversely impacts ocular lacrimation, this might provide us with an explanation for the magnitude of dry eye disease seen during this pandemic, even among those with mild cases of COVID-19.

Suggestions for Affected Patients:

Individuals wearing a face mask should be instructed to blink more often and to avoid mask displacement or incorrect fitting, which might contribute to air leaking above the mask, increasing dry eye symptoms [116]. Mask designs that permit transparent and freer mandibular movement may also help in this regard.

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Declaration of Competing Interest:

There is no conflict of interest.

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