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Exploring the protective effects of vasoactive intestinal peptides on dry eye disease in SARS-CoV-2 survivors

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Purpose: This study aimed to investigate the association between proton pump inhibitors and dry eye disease (DED) among hospitalized SARS-CoV-2 patients.

Methods: We conducted a retrospective cohort study using electronic medical records from patients hospitalized for SARS-CoV-2 between April 2020 and December 2023. Eligible participants were aged over 18 years and hospitalized for SARS-CoV-2 without preexisting DED. Exclusions included ICU admissions, malignancies, recent ocular interventions, or chronic medications known to induce dry eye disease. Logistic regression adjusted for age, gender, and vaccination status evaluated associations between gastrointestinal (GI) medications and the subsequent development of dry eye disease within 6 months following hospital discharge.

Results: The age and gender distributions within the cohort were representative of the general SARS-CoV-2 infected population. Among 1165 patients, 167 (14.3%) developed dry eye disease post-hospitalization. Laxative use (lactulose and polyethylene glycol) correlated positively with dry eye disease (OR 1.939, $p = 0.016$; OR 2.094, $p = 0.015$, respectively). Metoclopramide treatment showed the strongest association (OR 13.413, $p < 0.001$), with over 50% incidence in affected patients. Conversely, omeprazole showed an inverse correlation with dry eye disease (OR 0.332, $p < 0.001$). Polypharmacy increased the odds of DED (odds ration [OR] 1.629, $p = 0.015$), while age, gender, and vaccination status did not significantly influence the outcomes.

Conclusions: Our findings emphasize significant correlations between GI medications and dry eye disease in SARS-CoV-2 survivors. Proton pump inhibitors may mitigate the risk of dry eye disease, contrasting with adverse effects linked to laxatives and metoclopramide. Vasoactive intestinal peptide (VIP), which links gut and lacrimal gland functions, is a strong candidate for the basis of the underlying pathophysiological mechanisms.

Dry eye disease (DED) is a common chronic morbidity that causes discomfort and visual disturbances and impairs quality of life [1,2]. This multifactorial condition is sometimes caused or aggravated by systemic disease or oral medications [3,4]. Among the systemic diseases contributing to DED, SARS-CoV-2 infection has gained significant attention. Reports have suggested that 10–40% of individuals affected by SARS-CoV-2 experience ocular symptoms, most commonly DED [5-7]. Although the precise pathophysiology remains unclear, it has been speculated that SARS-CoV-2 inoculation and subsequent inflammatory changes in the ocular conjunctiva [8] are underlying mechanisms of DED resulting from infection.

Proton pump inhibitors (PPIs) are known to increase levels of vasoactive intestinal peptide (VIP) [9], which possesses immunomodulatory agent properties [10-14] and is a potent stimulant of lacrimation [15,16]. A study combining systemic anti-reflux medications with topical ocular lubricants showed promising results in alleviating DED symptoms [17]. Despite this, the impact of PPIs on DED has not received much attention from researchers. We aimed to fill this gap by exploring potential associations between PPIs and DED among hospitalized SARS-CoV-2 patients.

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METHODS

This retrospective cohort study was based on the electronic medical records of patients admitted to the Shaare Zedek Medical Center in Jerusalem, Israel, for SARS-CoV-2 infection between April 1, 2020, and December 31, 2023. All medical care, including hospitalization, outpatient follow-up, and ophthalmologic diagnoses, was provided exclusively by Shaare Zedek Medical Center to the patients within our study cohort. The report adhered to the ethical principles outlined in the Declaration of Helsinki, as amended in 2013. The Institutional Review Board waived (document #48755) the need for ethics approval and obtaining consent for the collection, analysis, and publication of retrospectively obtained and anonymized data for this noninterventional study.

Rationale for choosing COVID-19 patients: COVID-19 patients were selected as the study population because they provide a unique and clinically relevant setting to investigate the effects of proton pump inhibitors (PPIs) on dry eye disease (DED). Several key factors supported this choice. First, COVID-19 is widespread, affecting a broad demographic, which allowed for an adequate sample size. Second, COVID-19 patients exhibit a higher prevalence of DED—nearly double that of the general population (~10% versus ~6% in the USA)—making them an appropriate cohort to explore DED-related research questions. Third, COVID-19 is typically an acute, self-limiting disease that rarely imposes long-term impacts on patients' lives post-recovery, unlike conditions such as stroke or hip fractures. This reduces the likelihood of significant lifestyle changes that could introduce confounding factors into the study. Moreover, COVID-19 seldom necessitates starting or modifying medication regimens, as is common in conditions such as myocardial infarction (MI). This helps minimize confounders related to medication changes. Finally, hospitalized COVID-19 patients receive extensive medical attention and regular checkups, ensuring reliable data collection.

Study population: Eligible participants were adults aged over 18 without a previous diagnosis of DED who were hospitalized at Shaare Zedek Medical Center for at least 24 h due to acute SARS-CoV-2 infection. All study participants had undergone an ophthalmologic examination within the 12 months preceding their hospitalization and were confirmed to be negative for DED through a review of their electronic medical records.

Exclusion criteria are summarized in Appendix 1. These criteria encompassed admission to an intensive care unit; diagnoses of Sjögren's syndrome or other autoimmune or rheumatologic disorders; malignancy; neurological conditions such as cerebrovascular accident or Parkinson's disease; history of topical ocular medication, contact lens use, or ocular surgery during the preceding 24 months; any corneal refractive surgery, ocular trauma, or history of chemical exposure. Additionally, individuals receiving chemotherapy or initiating chronic medications known to induce DED during the 12 months preceding acute SARS-CoV-2 infection were excluded. These medications included anticholinergics, anxiolytics, antipsychotics, antidepressants, oral steroids, beta-blockers, analgesics, hormonal treatments, and diuretics [3,7,18]. However, patients who had been on the same chronic medication regimen, including DED-inducing treatments, for more than 12 months prior to their hospitalization—and had been confirmed negative for DED in ophthalmologic examinations within the preceding year—were included in the study.

Exclusion criteria also applied to participants who did not have an additional ophthalmic checkup within 12 months following hospital discharge, as well as to those with an ophthalmic follow-up period of less than 6 months or incomplete follow-up. Patients who had a change in chronic medications throughout the follow-up period—whether in type, dosage, or through the addition of new medications—were also excluded from the study. We categorized the SARS-CoV-2 cohort into two groups: patients who were diagnosed with DED within six months after hospitalization, and those who did not develop DED.

Observation procedures: Diagnosis of DED was determined through a review of ophthalmologists' reports and International Classification of Diseases, Tenth Revision (ICD-10) diagnoses (Appendix 2 and Appendix 3). Reports with DED diagnosis and mention of pertinent ophthalmic findings (e.g., superficial punctate keratopathy, short tear breakup time), ocular dryness in free text, or ocular lubricant recommendation/prescription, were considered positive for DED. Patients with severe DED requiring intervention, such as punctal occlusion or tarsorrhaphy, were referred to an oculoplastic surgeon. In SARS-CoV-2 patients, the incidence of DED was compared between patients treated with a given medication and those who were not.

Definition of GI medications: "GI medications" refers to a broad class of drugs used to treat conditions affecting the digestive system, including the stomach, intestines, esophagus, and other components of the gastrointestinal tract. These medications can serve various purposes, such as reducing stomach acid (e.g., PPIs or H2 blockers), enhancing gastrointestinal motility (e.g., metoclopramide), or addressing symptoms such as constipation (e.g., laxatives) and diarrhea.

Determining the cause of DED post-hospitalization: While it is challenging to definitively attribute the emergence of DED within six months of hospital discharge solely to the use of GI medications, as lifestyle changes may also play a role, our study focused on examining the statistical correlations between GI medications and DED. If a significant correlation was observed, either as a risk factor or as a protective factor, it strongly suggested that the medications themselves might have influenced the development of DED. This correlation would warrant further investigation into the specific GI medication subgroup, offering valuable insights into how these medications could contribute to or prevent DED. Such findings could ultimately help inform preventative strategies for dry eye disease in patients exposed to certain GI treatments.

Statistical analyses: For two-group comparisons, the Student's *t* test was employed for continuous variables, while proportions underwent $\chi 2$ test with Yates' correction. Logistic regression was used for multivariate analysis, incorporating age, gender, and vaccination status as covariates. Data analysis was performed using SPSS ver. 27 (SPSS Inc., Chicago, IL). P values of less than 0.05 were deemed statistically significant.

RESULTS

Baseline variables: The cohort comprised 1165 patients, with 167 (14.3%) diagnosed with DED following hospitalization and 998 (85.7%) without a DED diagnosis. The mean follow-up period was 26.4 months (range 6.0–37.1 months). Patients with and without DED exhibited similar characteristics to the reference population of individuals hospitalized with SARS-CoV-2 in terms of age, gender distribution, and length of hospitalization. These characteristics, as well as SARS-CoV-2 vaccination status, were similar between those who were subsequently diagnosed with DED and those who did not develop DED (Table 1).

Comparison with the reference population: While our study group was selected based on detailed and specific criteria that differed from the broader population of hospitalized SARS-CoV-2 patients, these criteria were designed to exclude individuals with other known risk factors for developing DED. Despite these differences, our selected study group remained comparable to the reference population in terms of key characteristics that are known to influence DED incidence, such as age, gender distribution, and length of hospitalization. This similarity in relevant demographic and clinical factors strengthens the validity of the comparisons between the study and reference populations.

Laxatives, antiemetics, and secondary bile acids were associated with more dry eye disease: We assessed the prevalence of DED in different GI medication treatment regimens. In our cohort, patients treated with lactulose or polyethylene glycol exhibited a significantly higher prevalence of DED compared to those who did not receive this treatment (24.2% versus 13.5%, $p = 0.005$, and 24.3 versus 13.7%, $p = 0.014$, respectively). Furthermore, those who received metoclopramide treatment exhibited a significantly higher prevalence of DED compared to those who did not (58.8% versus 13.0%, $p < 0.001$). We also observed a significantly higher prevalence of DED in patients treated with ursodeoxycholic acid compared to those who were not (50% versus 14.2%, $p = 0.041$). No significant differences in the prevalence of DED were found between individuals who received bisacodyl or domperidone and those who did not (Table 2).

PPIs were associated with less DED: In our assessment of DED prevalence in patients treated with PPIs, a different association emerged. We found that patients treated with omeprazole or lansoprazole exhibited a significantly lower prevalence of DED compared to those who did not receive this treatment (9.8% versus 17.5%, $p < 0.001$, and 0% versus 14.7%, $p = 0.032$, respectively). However, we found no significant differences in the prevalence of DED between those who received esomeprazole and those who did not (Table 2).

More systemic medications were associated with more DED: The proportion of patients treated with at least one GI medication was 38.3% among patients with DED and 48.9% among patients with no DED ($p = 0.011$); this was explained by the higher prevalence of PPI users in the latter group. In addition, there were no statistically significant differences between patients with and without DED regarding the quantity of all medications (Table 3).

Table 1. Baseline characteristics of SARS-CoV-2 hospitalized patients.

Baseline characteristics	Study cohort (n=1165)	Reference population	p-value
Age (y)	59.1±18.1	59.8±21.9 (n=22,636) [37]	0.284
Females (%)	537 (46.1%)	46.8% (n=156,204) [38]	0.631
Hospitalization length (d)	3.49±8.61	3.56±6.12 (n=156,204) [38]	0.698
Study cohort	**DED - (n=998)**	**DED + (n=167)**	
Age (y)	59.1±18.4	59.0±16.5	0.947
Females (%)	460 (46.1%)	77 (46.1%)	0.998
Hospitalization length (d)	3.48±8.74	3.61±7.75	0.857
Vaccinated (%)	547 (54.8%)	91 (54.5%)	0.936

Data are given as mean±SD or absolute number and proportions. For two-group comparisons, qualitative data were analyzed with the two-factor χ^2 with Yates' correction and continuous variables with the Student *t* test. DED; dry eye disease. Vaccinated; received at least one vaccine dose.

Table 2. Distribution of 167 dry eye disease cases regarding gastrointestinal medications among 1165 SARS-CoV-2 hospitalized patients.

Drug (n=-/+)	Number (incidence) of patients with DED		p-value
Antiemetics (dopamine antagonists)			
Metoclopramide (1131/34)	147 (13.0%)	20 (58.8%)	**<0.001**
Domperidone (1160/5)	165 (14.2%)	2 (40%)	0.103
Laxatives			
Lactulose (1074/91)	145 (13.5%)	22 (24.2%)	**0.005**
Bisacodyl (1101/64)	159 (14.4%)	8 (12.5%)	0.674
Polyethylene glycol (1095/70)	150 (13.7%)	17 (24.3%)	**0.014**
Proton pump inhibitors (PPIs)			
Omeprazole (684/481)	120 (17.5%)	47 (9.8%)	**<0.001**
Lansoprazole (1138/27)	167 (14.7%)	0 (0%)	**0.032**
Esomeprazole (957/208)	141 (14.7%)	26 (12.5%)	0.412
Secondary bile acid			
Ursodeoxycholic acid (1161/4)	165 (14.2%)	2 (50%)	**0.041**

Data are given as absolute numbers and proportions of patients with dry eye disease. For two-group comparisons, qualitative data were analyzed with the two-factor χ^2 with Yates' correction. DED; dry eye disease. Bold for p value less than 0.05.

Multivariate analysis: After adjusting for potential confounders, including the patient's age, gender, and vaccination status, an inverse association between GI drugs and DED persisted. Polypharmacy (i.e., five or more chronic medications) was associated with increased odds of developing DED (OR 1.629; 95% CI 1.099–2.416, p = 0.015, Table 4). Logistic regression analysis revealed no significant association between the patient's age, gender, or vaccination status and DED in hospitalized SARS-CoV-2 individuals (Table 4). After correcting for potential confounders, a positive association persisted between the laxatives lactulose and polyethylene glycol and the development of DED (OR 1.939; 95% CI 1.133–3.316, p = 0.016 and 2.094; 1.150–3.801, p = 0.015, respectively). Metoclopramide treatment also demonstrated a persistent association with the development of DED (13.413; 6.288–28.609, p < 0.001). In contrast, an inverse association persisted between omeprazole and the development of DED (0.332; 0.199–0.553, p < 0.001).

DISCUSSION

The etiology of DED is intricate and multifaceted. Disruption of any one of the numerous hormonal and neural pathways related to lacrimation can cause debilitating symptoms. This is particularly important among SARS-CoV-2 hospitalized patients, who exhibit various pathological changes in the ocular surface, such as reduced lipid layer thickness and shorter tear film breakup time, placing them at higher risk for DED [6].

While some medication groups, such as anticholinergics and diuretics, have been linked to DED [3,18], they account for only a fraction of cases. In our pursuit of identifying new risk factors for this condition, we deliberately excluded patients who had recently started on these potential confounders. Within our cohort, we observed several correlations between chronic GI medications and acute DED among SARS-CoV-2 hospitalized patients. First, we found a significant inverse correlation between omeprazole and DED. Second, we found

Table 3. Number of chronic medications among 1165 SARS-CoV-2 hospitalized patients.

N° of drugs	DED + (n=167)	DED - (n=998)	p-value
N° of all drugs	3.90±5.80	3.88±2.65	0.941
N° of GI drugs	0.78±1.21	0.73±0.87	0.519
At least one GI drug	64 (38.3%)	488 (48.9%)	**0.011**
Seven or more drugs	41 (24.6%)	176 (17.6%)	**0.028**

Data are given as mean±SD or absolute numbers and percentages. For two-group comparisons, qualitative data were analyzed with the two-factor χ^2 with Yates' correction and continuous variables with the Student *t* test. Bold for p value less than 0.05.

Table 4. Logistic regression analysis adjusted for age, gender, and vaccination status among 1165 SARS-CoV-2 hospitalized patients.

Multivariate analysis of risk factors		Odds ratio	95% CI	p-value
Demographics	Age	1.000	(0.990, 1.010)	0.958
	Female gender	0.967	(0.686, 1.363)	0.847
Vaccination	Vaccinated	1.023	(0.725, 1.443)	0.896
Antiemetics	Metoclopramide	13.413	(6.288, 28.609)	**<0.001**
	Domperidone	5.929	(0.797, 44.082)	0.082
	Any antiemetic	2.342	(5.070, 21.353)	**<0.001**
Laxatives	Lactulose	1.939	(1.133, 3.316)	**0.016**
	PEG	2.094	(1.150, 3.801)	**0.015**
	Bisacodyl	0.573	(0.254, 1.289)	0.178
	Any laxative	1.257	(0.775, 2.039)	0.354
PPIs	Omeprazole	0.332	(0.199, 0.553)	**<0.001**
	Lansoprazole	0.185	(0.025, 1.384)	0.100
	Esomeprazole	1.354	(0.706, 2.595)	0.362
	Any PPI	0.318	(0.209, 0.483)	**<0.001**
Secondary bile acids	UDCA	4.666	(0.612, 35.568)	0.137
Total drugs	Seven or more	1.733	(1.106, 2.717)	**0.017**

CI; confidence interval, PEG; Polyethylene glycol, PPIs; Proton pump inhibitors. UDCA; Ursodeoxycholic acid. Total drugs; Total number of chronic oral medications, regardless of type. Bold for p value less than 0.05.

a positive correlation between DED and chronic treatment with the laxatives lactulose and polyethylene glycol. Polypharmacy also emerged as a significant risk factor, consistent with prior studies [7,19].

The strongest association, however, was between metoclopramide treatment and DED. Within this small subgroup, comprising less than 2% of our cohort, the incidence of DED exceeded 50%. It is noteworthy that patients with malignancy were excluded from the study, and thus the etiology of DED was not attributed to chemotherapy.

Interpretation of GI medication usage in the two groups: While the overall number of gastrointestinal medications used was similar between the two groups, there were notable differences in specific types of medications. Patients who did not develop DED within six months of hospital discharge had significantly higher use of PPIs, which emerged as protective factors, potentially reducing the likelihood of DED development. On the other hand, patients who did develop DED were significantly less likely to use PPIs and more likely to use medications such as metoclopramide or laxatives. These medications were identified as risk factors for the development of DED within six months of discharge. This pattern suggests that the type of GI medication may influence the risk of developing DED.

The literature regarding the impact of PPIs on DED is limited; a single population-based study found no correlation between PPI use and DED severity [20]. However, it is important to note that PPI users in the study were significantly older than nonusers, and aging itself is a known risk factor for DED [21]. This demographic difference may have obscured the potential protective effect of PPIs.

The underlying mechanism of our findings involves VIP, a potent stimulator of lacrimation [22,23], and secretion from conjunctival goblet cells [24]. The immunomodulatory properties of this neuropeptide [10-13] are particularly pertinent in DED [14]. VIP levels are elevated following treatment with PPIs [9], whereas laxatives have been observed to decrease VIP levels [25]. Metoclopramide induces the secretion of somatostatin [26], a hormone that suppresses VIP secretion [27]. This mechanism is supported by clinical studies demonstrating VIP's efficacy in reducing DED symptom severity in post-refractive surgery patients [28], and its role in enhancing secretory function while minimizing immune injury to the lacrimal glands in Sjogren syndrome [29].

We considered several alternative explanations for our findings. Dehydration, a likely risk factor for DED [30], is one possibility. Patients using laxatives may face an increased risk of dehydration due to fluid loss through the bowel. Severe nausea requiring metoclopramide treatment

could also lead to dehydration due to decreased oral intake. Moreover, omeprazole treatment might relieve dyspepsia, encourage better oral intake, and potentially lower the risk of dehydration. However, even if these assumptions hold true, the impact of oral fluid intake on DED remains controversial and, at best, modest [31,32]. Therefore, this explanation lacks strong support.

Laxative-induced hypomagnesemia [33] a known risk factor for DED [34], could serve as another alternative explanation, as well as dopamine dysregulation and decreased blink reflex observed in patients prone to parkinsonism treated with metoclopramide [35,36]. While these models might account for some instances of DED, they do not provide a comprehensive pathophysiological mechanism to explain the entirety of our findings. Therefore, the VIP model remains the most robust explanation for our findings.

Several limitations should be acknowledged in our study. Although our selection criteria focused on SARS-CoV-2 inpatients while excluding ICU hospitalizations, we did not directly assess the severity of SARS-CoV-2 within our study cohort. Furthermore, the retrospective design of our study inherently limits the scope of our findings. It is challenging to determine whether DED is a primary side effect of a GI medication or a secondary manifestation of the disease it is intended to address. Nevertheless, the inverse associations found between PPIs and DED could point to novel therapeutic options for SARS-CoV-2 inpatients experiencing DED.

Further research should include direct measurements of serum and tear fluid VIP levels. In addition, investigating the clinical effects of topical treatment with VIP or PPIs on DED-affected eyes is crucial.

In conclusion, our pilot study revealed significant correlations between DED and various GI medications in SARS-CoV-2 survivors. VIP levels offer a robust framework for understanding the underlying pathophysiological mechanisms. We anticipate that these insights will enhance the current understanding of DED, potentially leading to innovative treatment approaches to improve ocular health and overall quality of life in this expanding population.

APPENDIX 1. EXCLUSION CRITERIA SUMMARY.

To access the data, click or select the words “Appendix 1.”

APPENDIX 2. ICD-10 DIAGNOSES.

To access the data, click or select the words “Appendix 2.”

APPENDIX 3. STUDY FLOWCHART.

To access the data, click or select the words “Appendix 3.”

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