

ASSOCIATION BETWEEN DIABETES MELLITUS AND OCULAR ANTERIOR SEGMENT MANIFESTATIONS IN COVID-19 PATIENTS

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ABSTRACT

Background: COVID-19 is an acute respiratory disease caused by the infection of SARS-CoV-2, which was also found to have ocular manifestations. In the previous study, SARS-CoV-2 was found in patients' conjunctival swabs and tear specimens. The SARS-CoV-2 binding sites were found on the conjunctiva and cornea of the eye. Diabetes mellitus is one of the most common comorbidities found in COVID-19 patients, at the same time, hyperglycemia in diabetes mellitus increases the risk of eye infections. This study aims to determine the association between diabetes mellitus and anterior segment ocular manifestations in COVID-19 patients.

Methods: This research is an observational analytic cross-sectional study. Anterior segment ocular manifestations data were collected by patient-reported questionnaire due to high infection risk.

Results: In the total of 169 COVID-19 patients in this study, 35 patients (20,7%) experienced anterior segment ocular manifestations, 50 patients (29,6%) had diabetes mellitus, and 12 patients (7,1%) experienced both. The most common ocular manifestations experienced were watery eyes (34,3%), red eyes (20,0%), and blurred vision (20,0%), as well as other complaints in the form of discharge from the eyes, itching, burning, foreign body sensation, pain, and glare at the light. While 12 of 50 diabetes mellitus patients (24%) had anterior segment ocular manifestations, 23 of 119 patients without diabetes mellitus (19.32%) experienced similar conditions. The results of data analysis with Chi-Square ($p \geq 0.05$) showed no significant association.

Conclusions: There is no association between diabetes mellitus and anterior segment ocular manifestations in COVID-19 patients.

Keywords: COVID-19, diabetes mellitus, anterior segment ocular manifestations

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by SARS-CoV-2 infection. SARS-CoV-2 spreads from human to human through droplets or aerosols by inhalation. ⁽¹⁾ At the end of August 2020, COVID-19 cases in Indonesia reached 174.796 cases and continued to increase until it reached a total of 1.450.132 cases in March 2021. ⁽²⁾

The most common comorbidities found in COVID-19 patients are diabetes mellitus, hypertension, and cardiovascular disease. ^(3,4) Diabetes mellitus increases the susceptibility to infection with SARS-CoV-2 due to increased viral affinity with host cells, decreased viral clearance, T-lymphocyte dysfunction, and tissue hypoperfusion, including the eye. ^(5,6) Ansari et al. reported a significant association was found between diabetes mellitus and the occurrence of eye infections (OR 1.08; $p < 0.0001$) without any association with glycemic control. ⁽⁷⁾

Besides nasopharyngeal swabs, SARS-CoV-2 was also found in conjunctival swabs and tear specimens from COVID-19 patients. ⁽⁸⁾ In the anterior segment of the eye, the expression of ACE2, TMPRSS2, and Basigin (CD147) receptors was found on the cornea and conjunctiva as the binding sites of SARS-CoV-2. ⁽⁹⁾ There were some COVID-19 cases with ocular manifestations, including conjunctivitis, keratitis, kerato-conjunctivitis, episcleritis, and uveitis. ⁽⁸⁾ It has been found positive results conjunctival swabs from two out of 12 COVID-19 patients with ocular manifestations in a study by Wu et al. ⁽¹⁰⁾ Viral eye infections are suspected to occur through droplet exposure or hand-eye contact. ⁽⁵⁾ The prevalence of ocular manifestations of COVID-19 patients varies from 0,8% to 50%. ⁽¹¹⁾ Anterior segment ocular symptoms reported in COVID-19 patients are red eyes, watery eyes, discharge, itching, burning, foreign body sensation, pain, photophobia, and blurred vision. ⁽¹²⁾

The incidence of ocular manifestations in COVID-19 is not as much as in the respiratory system. Thus the manifestations of COVID-19 in the anterior segment of the eyes draw less attention. Eye complaint is listed as one of the less common COVID-19 symptoms and requires health workers' attention in identifying SARS-CoV-2 infection. ⁽¹³⁾ There are few studies on the characteristics and prevalence of COVID-19 patients with anterior segment ocular manifestations. This study aims to find the association between diabetes mellitus and the occurrence of anterior segment ocular manifestations in COVID-19 patients.

METHODS

This study is an observational analytic cross-sectional study involving 169 COVID-19 patients in August 2020-March 2021 at Primasatya Husada Citra Hospital Surabaya, which were taken using a purposive sampling technique according to inclusion and exclusion criteria.

The inclusion criteria were: 1. COVID-19 patients who had filled out a questionnaire about anterior segment ocular symptoms in August 2020-March 2021. 2. COVID-19 patients who were hospitalized at PHC Surabaya Hospital. 3. COVID-19 patients are showing positive PCR swab results for SARS-CoV-2.

The exclusion criteria were: 1. The onset of eye symptoms >24 days before systemic and respiratory symptoms occurred. 2. Absent of blood test data in the medical record. 3. Patients with corticosteroid medication before being diagnosed with COVID-19. 4. Patients with malignancy undergoing chemotherapy. 5. Patients with other immunodeficiency conditions.

The independent variable in this study was COVID-19 patients with diabetes mellitus, diagnosed by an internal medicine doctor with or without laboratory data (HbA1c, blood glucose level).

The dependent variable of this study was the anterior segment ocular manifestations. The data was collected from the patient-

reported questionnaire, not from physical ocular examination due to the hospital's strict patient isolation policy. The questionnaire contained the onset of eye symptoms, previous history, and eye symptoms. The eye symptoms asked were red eyes, watery eyes, discharge, itching, burning, foreign body sensation, pain in the eyes, glare at the light, and blurred vision. These were anterior segment ocular general manifestation symptoms.

The data collected were analyzed using Chi-Square ($p < 0,05$). If the significance value is $p < 0,05$, a significant association is obtained, and if $p \geq 0,05$, it is said that there is no association.

This research has been approved by the health research ethics committee of the Widya Mandala Catholic University Faculty of Medicine Surabaya (Ref. 156/WM12/KEPK/MHSW/T/2021) and Primasatya Husada Citra Hospital Surabaya (No: 016/KEPK/RSPS-2021).

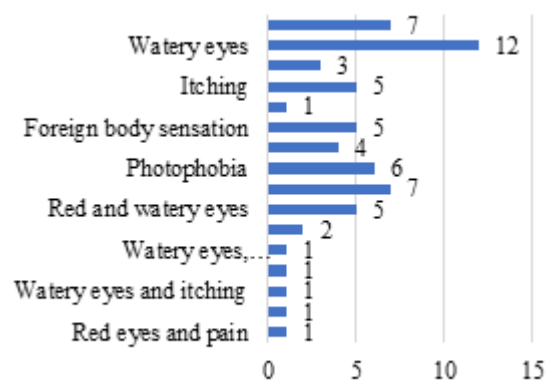
RESULTS

The aged majority of 169 patients in this study were in the range of 26-45 years (41,4%), with more male patients (55,0%) (Table 1). Most of the patients who experienced anterior segment ocular manifestations were aged 46-65 years (37,1%), followed by 26-45 years (31,4%), and females (54,3%) were slightly more than males (45,7%) (Table 1). Similarly, most of the COVID-19 patients with diabetes mellitus were in the age range 46-65 years (68,0%), and males (52,0%) were slightly more (Table 1). One-third of the patients had diabetes mellitus as their comorbidity (29,6%), followed by hypertension (14,2%) and coronary heart disease (9,5%).

Table 1 Clinical characteristics of COVID-19 patients

	COVID-19 patients (N=169) n (%)	With anterior segment ocular manifestations (N=35) n (%)	With diabetes mellitus (N=50) n (%)
Age group (years)			
<26	13 (7,7)	3 (8,6)	2 (4,0)
26-45	70 (41,4)	11 (31,4)	10 (20,0)
46-65	66 (39,1)	13 (37,1)	34 (68,0)
>65	20 (11,8)	8 (22,9)	4 (8,0)
Gender			
Male	93 (55,0)	16 (45,7)	26 (52,0)
Female	76 (45,0)	19 (54,3)	24 (48,0)

Figure 1 Ocular anterior segment manifestations



Watery eyes (34,3%) were the most common symptoms found, followed by red eyes (20,0%) and blurred vision (20,0%). Some patients experienced more than one symptom simultaneously. Red and watery eyes were felt the most in 5 patients (14,3%) (Figure 1).

Table 2 Blood glucose test results from COVID-19 patients with diabetes mellitus

Blood glucose test	Mean ± SD	Results Within normal value*	Results higher than normal value	No data
HbA1c (%)	8,53 ± 2,53	5	20	25
RBG (mg/dL)	252,20 ± 101,79	8	22	25
Postprandial glucose (mg/dL)	242,44 ± 86,54	6	26	18

*Normal value HbA1c <6,5%
 random blood glucose <200 mg/dL
 postprandial glucose <180 mg/dl

Blood glucose tests which included HbA1c, random blood glucose, and postprandial glucose in fifty COVID-19 patients with diabetes mellitus, showed HbA1c in the average of 8,53% ± 2,53%, random blood glucose test in the average of 252,20 ± 101,79 mg/dL, and postprandial glucose test in the average of 242,44 ± 86,54 mg/dL (Table 2). HbA1c test results were obtained from 25 patients, and only five were within the normal value (<6,5%). From 25 random blood glucose test patients, 22 of them were above the normal value (>200 mg/dL). Postprandial glucose was tested in 32 patients. 26 patients were above normal value (>180 mg/dL).

Table 3 Patients with diabetes mellitus and anterior segment ocular manifestations

	Anterior segment ocular manifestations		Total	P-value
	+	-		
DM	12 (7,1%)	38 (22,5%)	50 (29,6%)	0,634
	23 (13,6%)	96 (56,8%)	119 (70,4%)	
Total	35 (20,7%)	134 (79,3%)	169 (100%)	

Twelve patients (7,1% of the total 169 COVID-19 patients and 24% within the 50 diabetes mellitus patients) suffered from diabetes mellitus and experienced anterior segment ocular manifestations (Table 3). Anterior segment ocular manifestations were also felt by 23 of 119 patients without diabetes mellitus (24,6%) (Chi-Square p=0,63).

DISCUSSION

Our study revealed that among 169 patients with RT-PCR nasopharyngeal swab-positive results, 35 patients (20,7%) experienced anterior segment manifestations. This finding was obtained using a patient-reported questionnaire. We didn't collect the patient's conjunctival swab due to its low sensitivity based on the reported study that the conjunctival swab sensitivity rate in COVID-19 cases was 4,9%.⁽¹⁴⁾ This is probably due to the low viral load in the conjunctiva, errors in sampling and sampling techniques, and the present short time of the virus in the conjunctiva. It requires an appropriate collection time.^(8,14)

In this report, the anterior segment manifestation incidence was less than the incidence found in Wu's study involving patients with moderate to critical severity.⁽¹⁰⁾ This probably happened due to the patient's disease severity difference. It is said that ocular manifestations are significantly associated with the severity of systemic illness (p=0,0006)⁽¹⁵⁾. Our study involved patients with mild to severe conditions since this research was conducted at the beginning of the pandemic. All patients, including those with mild symptoms, were also hospitalized.

The most common symptoms experienced by patients in this study were watery eyes (34,3%), red eyes (20,0%), and blurred vision (20,0%). Anterior segment ocular symptoms commonly found in COVID-19 patients may vary from one study to another. In a study by Nasiri et al., the most common symptoms found were foreign body sensation (16,0%), red eyes

(13,3%), and watery eyes (12,8%), also other symptoms such as itching, pain, discharge, and blurred vision, burning sensation, and photophobia. Sarkar et al. found burning sensation, red eyes, and foreign body sensation as the most common ocular symptoms experienced by COVID-19 patients. ⁽¹⁵⁾ Blurred vision was not the most common symptom in previous studies mentioned before. Disruption of refraction media in iritis, keratitis, keratoconjunctivitis, and uveitis can cause blurred vision, which still needs further investigations to determine the cause and evaluate the patient's symptoms. ⁽¹²⁾ Iriqat et al. found three COVID-19 patients diagnosed with anterior uveitis, intermediate-posterior uveitis, and iridocyclitis who experienced blurred vision. ⁽¹⁶⁾ Another study by Costa et al. found 20 out of 64 patients who experienced blurred vision emerged or worsened during COVID-19. ⁽¹⁷⁾ Damage to uvea tissue in viral infection was allegedly caused by immune-mediated cell response, but the pathological process of uveitis in SARS-CoV-2 infection was still unknown. ^(17,18)

Conjunctivitis was found to be the most common ocular manifestation in SARS-CoV-2 infections ^(8,10,19,20). In previous studies by Wu et al., 6 of 12 COVID-19 patients with conjunctivitis experienced red with watery eyes. ⁽¹⁰⁾ In this study, most patients experienced red and watery eyes simultaneously (14,3%). Watery eyes or epiphora could happen due to foreign body sensation, burning sensation, itching, and transudation from dilated blood vessels. ⁽²¹⁾ watery eyes might have been experienced simultaneously with other symptoms. But there was a difference in how each patient perceived their symptoms, or there were certain prominent symptoms at the time the data was collected.

Diabetes mellitus was associated significantly with the incidence of eye infections, especially conjunctivitis ⁽⁷⁾, without any significant association with glycemic control. ^(7,22) Yet no significant

result was found between diabetes mellitus and the anterior segment ocular manifestations in COVID-19 patients in this study. This finding could be due to differences in the duration of diabetes mellitus experienced by patients. In a study by Carey et al., there was an increase in the incidence rate ratio in patients with a longer duration of diabetes mellitus. ⁽²²⁾ There are abnormal changes and dysfunction of the endothelium that can increase the susceptibility to infection with a longer duration of diabetes mellitus. Mistra et al., in their study, stated that patients had conjunctival microvascular abnormalities with a longer duration of diabetes mellitus. ⁽²³⁾

It is possible that diabetes mellitus found in COVID-19 patients in this study was a new-onset disease. Farag et al. found that 65 out of 77 COVID-19 patients were newly diagnosed with diabetes mellitus when infected with SARS-CoV-2. HbA1c examination can distinguish the onset of diabetes mellitus ⁽²⁴⁾. Still, in this study, not all patients had HbA1c data, so it was difficult to assess the glycemic condition of patients in the last three months.

There was also a possibility that the hyperglycemic condition of COVID-19 patients is a manifestation of SARS-CoV-2 that occurred before the patient was hospitalized. Tedjamartono et al. reported the possibility that SARS-CoV-2 binds to the ACE2 receptor on pancreatic beta cells, causing impaired insulin secretion. As a result, there was an increase in blood glucose in patients with previously controlled diabetes mellitus or causes hyperglycemia in patients without diabetes mellitus. ⁽²⁵⁾ The condition of hyperglycemia due to SARS-CoV-2 infection can last until after recovering from COVID-19. Farag et al., through their research, found that 37 out of 65 patients who were given anti-diabetic drugs and followed up in the form of fasting blood sugar tests still experienced hyperglycemia after three months of recovering from COVID-19. ⁽²⁴⁾

During the research, we couldn't do an ocular examination on the patients due to the strict policy from the hospital that COVID-19 patients had to be treated in an isolation ward. Also, there was a higher risk of SARS-CoV-2 infection during the ocular examination due to close contact between doctors and patients.

CONCLUSIONS

In this study, there was no association between diabetes mellitus and the occurrence of anterior segment ocular manifestations in COVID-19 patients. Anterior segment ocular manifestations can occur in SARS-CoV-2 infection in patients with and without diabetes mellitus. Health workers need to increase their attention to the ocular symptoms of COVID-19 patients through history taking and ocular examination.

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