



Possible Trinity of COVID-19, Diabetes Mellitus, and Retinopathy

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Dear Editor,

On March 11, 2020, the World Health Organization declared that the coronavirus 2019 (COVID-19) disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, had become a pandemic (1). Primarily, it presents with pneumonia; however, a few studies have also reported ophthalmological symptoms (2). Conjunctivitis has been the primary ophthalmic complaint and a recent study reported retinal findings in 12 COVID-19 cases (3). The authors did not mention any systemic illnesses affecting the retina or other existing retinal pathology. In 4 patients, subtle changes in the retina were detected, such as microhemorrhages and cotton wool spots. Additionally, in both eyes of all of the study patients, hyper-reflective lesions in the ganglion cells and inner plexiform were observed on optical coherence tomography examination. Visual acuity was normal and the pupillary reflexes were intact (3).

Diabetic retinopathy (DR) is a common complication of diabetes mellitus (DM), and vision deterioration is often seen in the working-age population (4). Microvascular hemorrhage and a reduction in ganglion cells and inner plexiform layer thickness have been observed in DM animal models (5). Molecular changes, like the levels of endothelial cell adhesion molecules, chemokines, and pro-inflammatory cytokines, detected in DM patients are correlated with DR severity (5).

In severe COVID-19 cases, high levels of pro-inflammatory cytokines (e.g., tumor necrosis factor alpha and interleu-

kin 6) have been observed. DM has been reported as risk factor for a poor COVID-19 prognosis, due to an impaired immune system. Since inflammation plays a key role in aggravating retinal lesions in DM patients, these proinflammatory cytokines can precipitate these lesions or vice versa (6).

It has been observed that viral RNA of SARS-CoV-2 was detectable in the retina of COVID-19 patients and hypothesized that the virus allows entry into host cells (8). Based on published data of COVID-19 cases, we hypothesize that there may be a relationship between DM, COVID-19, and retinal lesions. Angiotensin converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2) allow SARS-CoV-2 to infect cells (9). Human retinal cells have a low expression of ACE2 and TMPRSS2 in the inner nuclear layers (10,11). Diabetics have a lack of innate immunity against SARS-CoV-2, which allows for rapid proliferation. Short-term hyperglycemia can depress the innate immunity system (12). Drugs required for DM treatment and complications may lead to over-expression of ACE2 in various organs, which makes DM patients more prone to SARS-CoV-2 infection (13,14). We hope that future studies will evaluate the impact of pharmacological treatments on SARS-CoV-2-positive DM patients to assess whether these drugs increase risk of retinal injuries.

In addition to ACE2, the transmembrane glycoprotein basigin (CD147) has also been reported to be an invasive route for SARS-CoV-2 (15). CD147 is expressed in human

How to cite this article: Shah SNA. Possible Trinity of COVID-19, Diabetes Mellitus, and Retinopathy. *Beyoglu Eye J* 2021; 6(2): 158-159.

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Submitted Date: February 16, 2021 **Accepted Date:** March 07, 2021 **Available Online Date:** June 08, 2021

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retinal ganglion cells. Pro-inflammatory cytokines allow it to impair the blood-retina barrier in hyperglycemics (16). This may permit the invasion of retinal cells by SARS-CoV-2 in DM patients, which may also be an interesting topic for future pharmacological studies.

In summary, diabetes is associated with COVID-19 severity and the risk of retinal lesions in patients with COVID-19 may be greater due to the role of pro-inflammatory cytokines and CD147 in the short- or long-term. These hypotheses need to be explored in clinical and animal models to precisely determine the potential impact of COVID-19 or other systemic diseases. Greater understanding of ocular sequelae in DM patients infected with SARS-CoV-2 should be given priority. In the words of Winston Churchill, "I never 'worry' about action, but only about inaction."

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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