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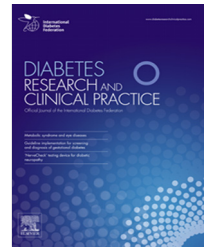
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Letter to the Editor

## Retinal outcomes of COVID-19: Possible role of CD147 and cytokine storm in infected patients with diabetes mellitus



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To the editor,

In December 2019, coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged in China and quickly spread worldwide. Despite COVID-19 is primarily associated with viral pneumonia, ophthalmological symptoms have also been reported in patients infected with SARS-CoV-2 [1,2]. In this context, a recent study reported retinal findings in 12 patients (six men and six women, between 25 and 69 years old) with COVID-19 [3]. Although changes in visual acuity and pupillary

reflex were not found, microhemorrhages and subtle cotton wool spots were observed along the retinal arcade of four patients. In addition, by optical coherence tomography (OCT), hyper-reflective lesions in the ganglion cell (GC) and inner plexiform (IP) layers were observed in both eyes of all patients [3]. Notwithstanding this, it was not discussed whether the patients already presenting changes in the retina before infection with COVID-19, or even if there was any systemic disease (e.g. type 2 diabetes mellitus) that could also be associated with retinal lesions. Considering these data, this

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letter draws attention to the possible trinity of diabetes mellitus (DM), COVID-19 and retinal lesions.

Accordingly, diabetic retinopathy (DR) is the most common microvascular complication of type 2 DM and one of the main causes of visual loss in working-age populations worldwide [4,5]. Diabetic retinopathy has long been recognized as a microvascular disease, being characterized by microaneurysms, hemorrhages and neovascularization in the retina [6]. People with DM and mice models of DM may have reduced thickness of the GC and IP layers before microvascular changes, with retinal neurodegeneration being an early event in DR [7]. Furthermore, inflammation plays an essential role in DR pathogenesis, with endothelial cell adhesion molecules, chemokines, and proinflammatory cytokines [e.g. tumor necrosis factor alpha (TNF- $\alpha$ ), and interleukin 6 (IL-6)] levels being upregulated in patients with DM and correlated with DR severity [6].

A cytokine storm, characterized by increased levels of proinflammatory cytokines (e.g. TNF- $\alpha$  and IL-6), has also been associated with COVID-19 severity [8]. In addition, a meta-analysis study reported DM as a risk factor for a worse prognosis for COVID-19, which may be related to impaired innate immune response and greater susceptibility of patients with DM to a cytokine storm [9,10]. Since inflammation is associated with retinal lesions in people with DM, it seems reasonable to imagine that COVID-19 can aggravate or precipitate these lesions, and vice versa, with the cytokine storm playing an important role in this relationship.

It is important to point out the possible role of receptors mediating SARS-CoV-2 entry into host cells in the hypothetical relationship proposed here between DM, COVID-19 and retinal lesions, seeing that SARS-CoV-2 was recently identified in human retina [11]. In this respect, the classical mechanism of cellular infection by SARS-CoV-2 is mediated by the binding of coronavirus spike protein to the cellular angiotensin-converting enzyme 2 (ACE2) and by serine protease TMPRSS2, which promotes spike protein priming [12]. Although ACE2 is expressed in rat retina, predominantly in the inner nuclear layer, a pre-print recently reported a low expression of ACE2 and TMPRSS2 in human retinal cells [13,14]. However, on the one hand, hyperglycemia can affect the immune response and make the organism more susceptible to COVID-19; on the other hand, treatment of DM and its complications with some drugs (e.g. ACE1 inhibitors and angiotensin II receptor blockers) may supposedly lead to over-expression of ACE2 in different organs, also making people with DM more susceptible to SARS-CoV-2 infection [15]. Therefore, it would be interesting that future studies also evaluate the impact of different pharmacological treatments on patients with DM infected by SARS-CoV-2, assessing whether some drugs may also be related to an increased risk of retinal injuries.

Transmembrane glycoprotein CD147 (also known as basigin) has recently been reported as a novel invasive route for SARS-CoV-2 [16]. In contrast to ACE2, CD147 is expressed at moderate-to-high levels in all cell types of human retina, especially in retinal GCs [14]. Curiously, CD147 also mediates breakdown of neurovascular barrier induced by proinflammatory cytokines *in vitro* and impairs the blood-retinal barrier function in streptozotocin-induced diabetic mice [17]. Thus,

it is possible that CD147, by mediating the breakdown of the blood-retinal barrier in a hyperglycemic context, may facilitate the invasion of retinal cells by SARS-CoV-2 in people with DM, which deserves to be investigated by future studies with animal models and humans.

In summary, DM has been associated with COVID-19 severity and, in view of the evidence presented here, it is also possible that DM can increase the risk of retinal lesions previously reported in patients with COVID-19 (e.g. lesions in GC and IP layers, and microhemorrhages), with CD147 and/or proinflammatory cytokines possibly mediating this association. The reverse is also possible, with COVID-19 being able to precipitate or worsen retinal lesions present in patients with DM in the short- or long-term, either by direct effects of retinal SARS-CoV-2 infection, or by the indirect effects of the cytokine storm associated with COVID-19. However, it is noteworthy that these are hypotheses, which need to be explored in clinical and experimental contexts. Finally, it is critical that studies investigating COVID-19 retinal outcomes assess factors that may confuse the results, such as the presence of retinal lesions prior to infection, associated with other diseases previously diagnosed or not (e.g. DM). At this time, ophthalmological examination in patients with DM infected by SARS-CoV-2 should be given more value, aiming at the early diagnosis and adequate treatment of retinal lesions possibly associated with both conditions.

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