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## Commentary

**COVID-19, diabetes mellitus and ACE2: The conundrum**

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A novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has scourged the world since its outbreak in December 2019 at Wuhan, China resulting in the World Health Organization declaring it as a pandemic. As of March 22, 2020, COVID-19 has affected over 292,000 people in at least 185 countries worldwide with most of the cases being reported from China, Europe and the United States of America. The absolute number of deaths has already surpassed 12,750 globally and is expected to increase further as the disease spreads rapidly. The disease has also infiltrated the Indian masses and is spreading fast. India being a developing nation with more than 1.3 billion people, failure to contain the virus can lead to disastrous consequences with death toll perhaps surpassing all other nations.

Although the overall mortality rate of COVID-19 is low (1.4–2.3%), patients with comorbidities are more likely to have severe disease and subsequent mortality [1,2]. Most of the available studies have shown that diabetes mellitus (DM) as a distinctive comorbidity is associated with more severe disease, acute respiratory distress syndrome and increased mortality [1,3,4]. Amongst the 32 non-survivors from a group of 52 intensive care unit (ICU) patients, DM (22%) was a predominant underlying comorbidity [3]. Of the 1099 confirmed COVID-19 patients reported by Guan et al. from China, 173

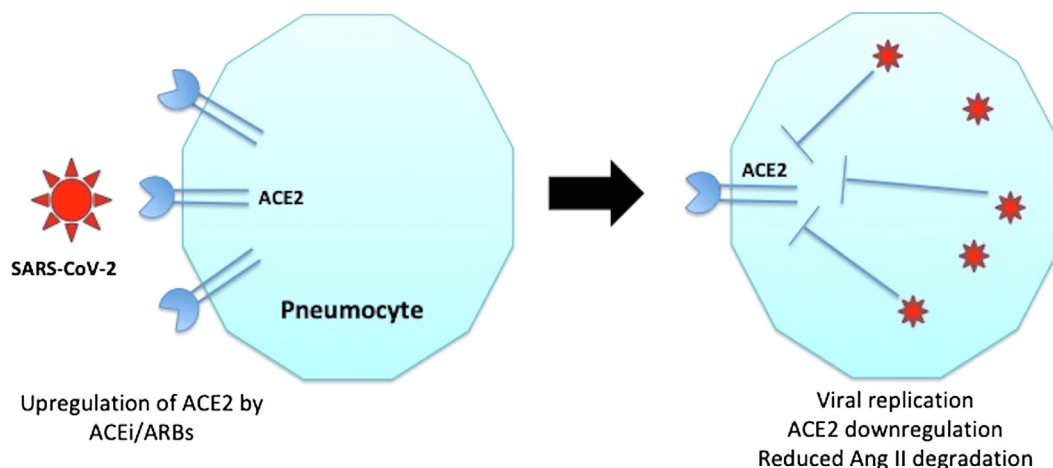
had severe disease; patients with severe disease had a higher prevalence of DM (16.2%) as compared to those with non-severe disease (5.7%) [1]. Further, in the largest series reported by the Chinese Center for Disease Control and Prevention comprising of 72,314 cases of COVID-19, patients with DM had higher mortality (7.3% in DM vs. 2.3% overall) [2].

It can be assumed that patients with DM are more likely to be older than those without DM and advancing age has consistently been shown to be associated with poor prognosis in COVID-19, however, most of the aforementioned studies did not adjust for age. Nevertheless, diabetes has been uniformly reported to be associated with poor prognosis in other viral infections, notably seasonal influenza, pandemic influenza A H1N1 (2009), Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [5–8]. Multiple explanations can be put forward for this apparent association between pre-existing DM and COVID-19 severity. Innate immunity, the first line of defense against SARS-CoV-2, is inevitably compromised in patients with uncontrolled DM thereby allowing unhindered proliferation of the pathogen within the host [9]. Even short-term hyperglycemia has been shown to transiently stun the innate immune system [10]. Moreover, DM is characterized by exaggerated pro-inflammatory cytokine response, notably interleukin (IL)-1, IL-6 and

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**Fig. 1 – Schematic diagram depicting interplay between SARS-CoV-2 and pneumocyte. SARS-CoV-2 gains entry into the pneumocyte using angiotensin-converting enzyme 2 (ACE2) as a receptor. ACE2 is upregulated with the prior use of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin-receptor blockers (ARBs). Following entry into the pneumocyte, the virus replicates and ACE2 gets downregulated. As a result, there is reduced degradation of angiotensin-II which in turn leads to increased secretion of aldosterone and subsequent renal potassium wasting.**

tumor-necrosis factor (TNF)- $\alpha$ , in the absence of appropriate immunostimulation; this may be further exaggerated in response to a stimulus as seen in patients with COVID-19 complicated by acute respiratory distress syndrome (ARDS) [9].

The role of angiotensin-converting enzyme 2 (ACE2) in the association between DM and COVID-19 is plausible. ACE2 is a type 1 integral membrane glycoprotein that is constitutively expressed by the epithelial cells of the lungs, kidney, intestine and blood vessels. In normal physiology, ACE2 breaks down angiotensin-II and to a lesser extent, angiotensin-I to smaller peptides, angiotensin (1–7) and angiotensin (1–9), respectively [11]. ACE2/Ang (1–7) system plays an important anti-inflammatory and anti-oxidant role protecting the lung against ARDS; indeed ACE2 has been shown to be protective against lethal avian influenza A H5N1 infection [12]. ACE2 expression is reduced in patients with DM possibly due to glycosylation; this might explain the increased predisposition to severe lung injury and ARDS with COVID-19 [4,11].

Strange it might sound, even overexpression of ACE2 would be counterproductive in COVID-19. SARS-CoV-2 utilizes ACE2 as a receptor for entry into the host pneumocytes [13]. Herein comes the confounding role of ACE inhibitors (ACEi) and angiotensin-receptor blockers (ARBs), drugs that are so widely used in DM. The expression of ACE2 is markedly increased in patients with DM (and hypertension) on ACEi or ARBs as an adaptive response to counteract the elevated levels of Ang-II and Ang-I. Thus, use of ACE2-stimulating drugs would facilitate the entry of SARS-CoV-2 into pneumocytes and consequently might result in more severe and fatal disease [14]. Amongst others, pioglitazone and liraglutide have also been shown to be associated with ACE2 upregulation in animal studies [14,15]. Unfortunately, none of the studies have taken into account the baseline treatment. Furthermore, a recently concluded study showed that severe and critically ill patients with COVID-19 had a higher prevalence of hypokalemia that resulted from renal potas-

sium wasting. This can be explained by downregulation of ACE2 following viral intrusion resulting in decreased degradation of angiotensin-II, increased aldosterone secretion and subsequent increased urinary potassium loss. Infact early normalization of serum potassium has been proposed to be a predictor of good prognosis in COVID-19 [16]. Thus, ACE2 overexpression, while facilitating entry of SARS-CoV-2, is unable to protect against lung injury as the enzyme gets degraded by the virus (see Fig. 1).

Whatever may be the underlying etiology, people with DM are definitely at an increased risk of severe and fatal COVID-19 disease. The prevalence of DM in India is 7.3% [17], thereby predisposing a large section of the community to COVID-19 and its complications. Hence it is advisable that community-dwelling residents having underlying DM take extra precautions not to contract the virus. Social distancing, strict hand and respiratory hygiene are the need of the hour. People with DM should ensure good glucose control as improvement in glycemia does boost host immune response [9]. Although not recommended due to lack of robust data, use of ACEi/ARBs/thiazolidinediones/liraglutide merits reconsideration in patients with DM during this outbreak.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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