Diabetology

Extended Abstract

COVID-19, diabetes mellitus and ACE2: The conundrum, Rimesh Pal - Post Graduate Institute of Medical Education and Research- India

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Abstract

A novel coronavirus disease (COVID-19), caused by severeacute respiratory syndrome coronavirus 2 (SARS-CoV-2) hasscourged the world since its outbreak in December 2019 atWuhan, China resulting in the World Health Organizationdeclaring it as a pandemic. As of March 22, 2020, COVID-19has affected over292,000peoplein at least 185countriesworld-wide with most of the cases being reported from China, Europeand the United States of America. The absolute number ofdeaths has already surpassed 12,750 globally and is expectedto increase further as the disease spreads rapidly. The diseasehas also infiltrated the Indian masses and is spreading fast.India being a developing nation with more than 1.3 billion peo-ple, failure to contain the virus can lead to disastrous conse-quences 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 sev-ere disease and subsequent mortality[1,2]. Most of the avail-able studies have shown that diabetes mellitus (DM) as adistinctive comorbidity is associated with more severe dis-ease, acute respiratory distress syndrome and increased mor-tality[1,3,4]. Amongst the 32 non-survivors from a group of 52intensive care unit (ICU) patients, DM (22%) was a predomi-nant underlying comorbidity[3]. Of the 1099 confirmedCOVID-19 patients reported by Guan et al. from China, 173had severe disease; patients with severe disease had a higherprevalence of DM (16.2%) as compared to those with non-sev-ere disease (5.7%)[1]. Further, in the largest series reported bythe Chinese Center for Disease Control and Prevention com-prising of 72,314 cases of COVID-19, patients with DM hadhigher mortality (7.3% in DM vs. 2.3% overall)[2].It can be assumed that patients with DM are more likely tobe older than those without DM and advancing age has consis-tently been shown to be associated with poor prognosis inCOVID-19, however, most of the aforementioned studies didnot adjust for age. Nevertheless, diabetes has been uniformlyreported to be associated with poor prognosis in other viralinfections, notably seasonal influenza, pandemic influenza AH1N1 (2009), Severe Acute Respiratory Syndrome (SARS) andMiddle East Respiratory Syndrome (MERS)[5–8]. Multipleexplanations can be put forward for this apparent associationbetween pre-existing DM and COVID-19 severity. Innateimmunity, the first line of defense against SARS-CoV-2, isinevitably compromised in patients with uncontrolled DMthereby allowing unhindered proliferation of the pathogenwithin the host[9]. Even short-term hyperglycemia has beenshown to transiently stun the innate immune system[10].Moreover, DM is characterized by exaggerated pro-inflamma-tory cytokine response, notably interleukin (IL)-1, IL-6 andhtumor-necrosis factor (TNF)-a, in the absence of appropriateimmunostimulation; this may be further exaggerated inresponse to a stimulus as seen in patients with COVID-19 com-plicated by acute respiratory distress syndrome (ARDS)[9].The role of angiotensin-converting enzyme 2 (ACE2) in theassociation between DM and COVID-19 is plausible. ACE2 is atype 1 integral membrane glycoprotein that is constitutivelyexpressed by the epithelial cells of the lungs, kidney, intestineand blood vessels. In normal physiology, ACE2 breaks downangiotensin-II and to a lesser extent, angiotensin-I to smallerpeptides, angiotensin (1–7) and angiotensin (1–9), respectively[11]. ACE2/Ang (1–7) system plays an important anti-inflam-matory and anti-oxidant role protecting the lung againstARDS; indeed ACE2 has been shown to be protective againstlethal avian influenza A H5N1 infection[12]. ACE2 expressionis reduced in patients with DM possibly due to glycosylation;this might explain the increased predisposition to severe lunginjury and ARDS with COVID-19[4,11].Strange it might sound, even overexpression of ACE2would be counterproductive in COVID-19. SARS-CoV-2 utilizesACE2 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 sowidely used in DM. The expression of ACE2

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is markedlyincreased in patients with DM (and hypertension) on ACEior ARBs as an adaptive response to counteract the elevatedlevels of Ang-II and Ang-I. Thus, use of ACE2-stimulatingdrugs would facilitate the entry of SARS-CoV-2 into pneumo-cytes and consequently might result in more severe and fataldisease[14]. Amongst others, pioglitazone and liraglutidehave also been shown to be associated with ACE2 upregula-tion in animal studies[14,15]. Unfortunately, none of thestudies have taken into account the baseline treatment.Furthermore, a recently concluded study showed that severeand critically ill patients with COVID-19 had a higherprevalence of hypokalemia that resulted from renal potas-sium wasting. This can be explained by downregulation ofACE2 following viral intrusion resulting in decreased degrada-tion of angiotensin-II, increased aldosterone secretion andsubsequent increased urinary potassium loss. Infact earlynormalization of serum potassium has been proposed to bea predictor of good prognosis in COVID-19[16]. Thus, ACE2overexpression, while facilitating entry of SARS-CoV-2, isunable to protect against lung injury as the enzyme getsdegraded by the virus (see Fig. 1).Whatever may be the underlying etiology, people with DMare definitely at an increased risk of severe and fatal COVID-19 disease. The prevalence of DM in India is 7.3%[17], therebypredisposing a large section of the community to COVID-19and its complications. Hence it is advisable that commu-nity-dwelling residents having underlying DM take extra pre-cautions not to contract the virus. Social distancing, stricthand and respiratory hygiene are the need of the hour. Peoplewith DM should ensure good glucose control as improvementin glycemia does boost host immune response[9]. Althoughnot recommended due to lack of robust data, use of ACEi/ARBs/thiazolidinediones/liraglutide merits reconsiderationin patients with DM during this outbreak.

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