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LETTER TO THE EDITOR | *The Pathophysiology of COVID-19 and SARS-CoV-2 Infection*

COVID-19: is the ACE2 just a foe?

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TO THE EDITOR: I read with great interest and pleasure the recent Letter "Covid-19 infection and mortality: a physiologist's perspective enlightening clinical features and plausible interventional strategies" by Abassi and colleagues (1). In the article, the authors suggested blockage of angiotensin-converting enzyme 2 (ACE2) as a potential strategy for mitigating the clinical picture and reducing mortality in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected subjects. Because the SARS-CoV-2 virus uses ACE2 as a receptor, this approach could be promising to prevent virus entry into the pneumocytes. But, ACE2 inhibition in COVID-19 patients with already developed symptoms could even be detrimental due to the consequent decrease in the production of angiotensin 1–7, which, as has been stated by the authors, shows anti-inflammatory and antifibrotic activity via the Mas receptor. Regarding that, the authors also mentioned that the depletion of ACE2 by SARS-CoV-2 binding may be responsible for the more severe clinical presentation of COVID-19 in the group of high-risk patients (1). Indeed, previous studies showed the protective effect of ACE2 in the animal models of acute respiratory distress syndrome (ARDS) (4, 7, 14), while angiotensin II was found to be a harmful molecule, causing pulmonary edema and fibrosis (8). So, inhibition of ACE2 could lead to reduced clearance of the harmful molecule, while the protective one would be insufficiently produced. Moreover, suggestions considering ACE2 induction as a possible therapeutic strategy for COVID-19 have recently emerged (11). Besides, an increased level of soluble ACE2 isoform, as a consequence of preexisting disease (such as inflammatory bowel diseases), has been assumed as a possible protective factor, acting by intercepting viral particles (9, 12). Interestingly, ACE2 is expressed in the respiratory tract only moderately compared with intestinal epithelia (2, 3), but respiratory symptomatology is incomparably more severe than intestinal, although among COVID-19 patients up to 50% of stool specimens were SARS-CoV-2 positive (10), and some patients remained stool-positive after respiratory samples were negative (13). These observations give rise to the possibility that a higher proportion of "intact" ACE2 molecules provide sufficient protection during infection, and suggest that the role of ACE2 during COVID-19 pathogenesis should be considered relative to viral load.

By all accounts, in the context of SARS-CoV-2 infection, ACE2 could justifiably be referred to as a double-edged sword. Regarding that, it is worth distinguishing "passive" ACE2 expression, which is undoubtedly the main doorway for viral entry, and total ACE2 activity, which seems to be protective. The situation could be further complicated if the SARS-CoV-2 is capable to shed catalytically active ACE2 ectodomains, as is the case with SARS-CoV (5, 6), which would lead to the releasing of active ectodomains in the systemic circulation. If so, in addition to its potential diagnostic relevance, an increase in plasma ACE2 activity may diminish systemic effects of angiotensin II, impairing thus hemodynamics and renal function in critically ill COVID-19 patients.

Withal, it should be emphasized that angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are differently related to ACE2: in contrast to ARBs, ACE-Is deplete its substrate and consequently reduce the production of the final anti-inflammatory product. Moreover, by blocking the receptors, ARBs could divert a larger proportion of generated angiotensin II towards ACE2. These assumptions encourage more detailed stratification of clinical presentation and outcome among COVID-19 patients receiving renin-angiotensin system (RAS) modulating drugs.

Finally, it is reasonable to assume that different *ACE2* gene polymorphisms could underlie a huge variety of COVID-19 clinical presentation and outcome, as well as a propensity for infection.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

H.J. drafted manuscript; edited and revised manuscript; and approved final version of manuscript.

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