

# ACE2 and prognosis of COVID-19: Insights from Bartter's and Gitelman's syndromes patients

To the Editor,

The relationship between renin-angiotensin system (RAS) and coronavirus disease 2019 (COVID-19) pandemic and, in particular, RAS as part of the coronavirus 2 (CoV-2) infection process via angiotensin-converting enzyme 2 (ACE2), the entry point of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in conflicting suggestions regarding how RAS and its role(s) should inform treating COVID-19. ACE inhibitors or angiotensin II (Ang)-type 1 receptor blockers (ARBs), in fact, have been suggested to be avoided as they potentially upregulate ACE2<sup>1</sup> and, conversely, there are suggestions that ARBs might be beneficial<sup>2</sup> as SARS-CoV-2 causing ACE2 downregulation slows the Ang II conversion to the vasodilatory, anti-inflammatory, antioxidant and antiatherosclerotic Ang 1-7,<sup>3-5</sup> and the use of ARBs by blocking the excessive Ang II type-1 receptors activation, would be beneficial upregulating ACE2 activity and increasing Ang 1 to 7 levels.


We have read with great interest the very recently published article by Cheng and coworkers,<sup>6</sup> who reviewed the correlation between severe risk factors for COVID-19 and ACE2. Their review highlighted the potential protective role of ACE2 in SARS-CoV-2 infection-induced acute respiratory distress syndrome, the major cause of COVID-19 mortality as well as other risk factors such as hypertension, diabetes, and cardiovascular disease that are linked to COVID-19 morbidity and mortality.

We feel that our studies in Bartter's and Gitelman's syndrome patients (rare genetic tubulopathies) to explore and better define the human RAS system<sup>7</sup> provide further insight on the protective effects of ACE2 in humans including the effects on prognosis of COVID-19. Specifically, these patients have an activated RAS and high Ang II levels, yet blunted Ang II-mediated cardiovascular effects and normotension or hypotension, activation of antiatherosclerotic and anti-inflammatory defenses, reduced oxidative stress<sup>7</sup> and, directly relevant to the discussion regarding ACE2, they have increased and correlated levels of both ACE2 and Ang 1-7,<sup>8</sup> therefore, a prevalence of the counterregulatory ACE2-Ang 1-7-MasR axis over the classical ACE-Ang II-AT1R regulatory axis of RAS.<sup>9</sup> These data suggest that increasing ACE2 via ARBs and ACE inhibitors might be beneficial via effects on Ang 1-7 for patients infected by SARS-CoV-2 as this has been shown for ACE2 in hyperoxic lung injury.<sup>10</sup>

Moreover, our cohort of Gitelman's and Bartter's patients provides evidence, admittedly anecdotal, and circumstantial, allaying the concerns raised that increased ACE2 might provide more targets for the CoV-2 virus. A telephone survey of over 100 of our Gitelman's and

Bartter's patients, all from the Northern Italy Regions Veneto, Lombardia and Emilia Romagna, the hotspots of the COVID-19 pandemic in Italy, found none of them infected with COVID-19, making increased risk to COVID-19 due to increased ACE2 unlikely.<sup>11</sup>

Finally, the increased and correlated levels of both ACE2 and Ang 1-7 noted in Gitelman's and Bartter's patients also add support to Cheng and coworkers,<sup>6</sup> suggestion that drugs enhancing ACE2 activity may become one of the most promising approaches for the treatment of COVID-19 in the future.

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