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Early View

Correspondence

Authors' reply to correspondence in response to "Will children reveal their secret? The coronavirus dilemma"

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Dear editors,

We thank Dr. Porter for his commentary to our recent published editorial: "Will children reveal their secret? The coronavirus dilemma" [1]. In the editorial, we reviewed some of the strongest evidences that may support our perspective, thus being beyond the purpose of our manuscript a full description of renin-angiotensin-aldosterone system (RAAS) and angiotensin converting enzyme 2 (ACE2) receptor literature. We strongly agree that evidences about ACE2 role in respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are somehow conflicting and our putative perspective was clearly pointed out in the paper. The debate around ACE2 role in Sars-CoV-2 infection is ongoing and we appreciated the chance that Dr. Porter gave us to better elucidate some of its aspects.

A robust evidence against all the body of literature about ACE2 downregulation in chronic conditions was recently provided by Leung et al., which demonstrated an increased ACE2 expression in lung biopsies of current smokers and in patients with chronic obstructive pulmonary disease [2]. Despite not investigating the association between their findings and the risk of SARS-CoV-2 infection, they suggested that ACE2 upregulation could partially explain the increased risk of SARS-CoV-2 infection in these subpopulations.

In his letter, Dr. Porter also stresses the uncertainty about RAS and ACE2 derangement during Sars-CoV-2 infection in children and their variability both under physiological and pathological conditions, providing evidences that we would like to discuss further. To our knowledge, in Liu et al. study, ACE2 serum levels were not investigated. On the contrary, plasma concentrations of angiotensin II were measured, resulting in a markedly higher concentration of its plasma levels in patients with Coronavirus Disease 2019 (Covid-19) than healthy controls [3]. These findings are in accordance with our hypothesis, where ACE2 dysregulation and angiotensin II elevated levels could lead to inflammation and lung injury.

ACE2 age-related expression was also questioned. We agree with Dr. Porter that preclinical studies on rat models about ACE2 age-related expression could not be fully translatable in humans. In Fernandez-Atucha et al. report, 118 healthy individuals, ranging from 41 to 70 years old, were enrolled and serum ACE2 activity measured, showing significantly higher ACE2 activity in older women and no differences in men [4]. However, in this study, childhood was not investigated. In addition, concerns about serum ACE2 activity measurement have been recently pointed out since it may not be a reliable indicator of the membrane-bound form [5, 6]. Regarding ACE2 age-related variability, Schouten et al. reported no significant difference in lung ACE2 activity among patients of all ages with acute respiratory distress syndrome (ARDS) [7]. However, as authors state, considered the relatively small sample size of each age group, the results might have been underpowered. Moreover, dilution differences of bronchoalveolar lavage return fluid could have influenced biomarkers final concentration. Notably, ACE2 levels were only measured on alveolar compartment, which could not reflect the whole host RAAS status under pathological response.

Finally, Vaduganathan et al. recently discussed RAAS inhibitors role in patients with Covid-19 with a clear lookout around their protective rather than detrimental effect in SARS-CoV-2 infection,

highlighting that the hypothesis of ACE2 beneficial role led to recombinant ACE2 protein administration trials in order to prevent organ injury (ClinicalTrials.gov number, NCT04287686) [5]. Recent clinical trials also offered us the opportunity to clarify that chronic use of angiotensin-receptor blockers (ARBs) and angiotensin-converting-enzyme (ACE) inhibitors (and thus, hypothetically, the lung-specific upregulation of ACE2) is not associated with increased risk of Covid-19 or Covid-19 severe outcomes [8-10]. Interestingly, in Mehra et al. study but not in others, use of ACE inhibitors was associated with a better survival among patients with Covid-19. However, these results must be considered with caution due to the unmeasured confounding of this non-randomized trial and due to the lacking of data about ARBs/ACE inhibitors effect on lung-specific expression of ACE2 [10].

In conclusion, we agree with Dr. Porter that the role of ACE2 receptor in SARS-CoV-2 infection and in COVID-19 outcomes is still debated, especially in children. Data about lung-specific ACE2 expression in healthy children and in those with Covid-19 are lacking. Further studies about the interconnection of RAAS system and SARS-CoV-2 infection are needed, especially in paediatric age group, in order to reveal children hidden secret.

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