Inquiring into Benefits of Independent Activation of Non-Classical Renin-Angiotensin System in the Clinical Prognosis and Reduction of COVID-19 mortality

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DEAR EDITOR

We have read with great interest the elegant manuscript by Hanff et al [1] proposing a very interesting association between the classical renin-angiotensin system (RAS) and angiotensin-converting enzyme 2 (ACE2) dysregulation present in cardiovascular disease (CVD) and the high mortality index in patients with CVD and coronavirus disease 2019 (COVID-19). The authors state that pharmacological inhibition of classical RAS could have two simultaneous and incompatible outcomes. On the one hand, it will decrease the proinflammatory effect of Angiotensin II with its subsequent benefit on decreasing the risk of acute respiratory distress syndrome (ARDS) observed in these patients, and on the other hand, it will increase ACE2 expression and therefore the virulence of SARS-Cov2.

It has been shown that coronaviruses, in order to access the inside of their host cells, first must bind to a host receptor to be able to fuse both viral and host membranes [2]. In humans, the host receptor is ACE2 and, like SARS coronavirus (SARS-CoV), SARS-CoV-2 also needs ACE2 to attack human alveolar epithelial cells [3]. Therefore, this also makes ACE2 crucial in the infectivity and pathogenesis of SARS-CoV-2.

In addition to the heart and kidneys, the classical RAS and ACE2 are also present in the lungs [4]. It is pertinent to evoke that ACE2 is also a fundamental component in the ACE2-Angiotensin(1-7)-MasR axis, also known as non-classical RAS, indicating, therefore, the existence of non-classical RAS also in the lungs. Non-classical RAS is a counter-regulatory system of the classical RAS in that its end product, Angiotensin(1-7), which after binding to the Mas receptor, presents important anti-inflammatory, anti-proliferative, anti-fibrotic, natriuretic and vasodilator effects [5], actions completely opposed to those promoted by the end product of the classical RAS Angiotensin II.

While pharmacological exclusion or initiation of classical RAS inhibition as an adjuvant treatment for SARS-Cov2 in patients with CVD is elucidated, and considering that COVID-19 patients present downregulation of ACE2 [1], and hence low Angiotensin(1-7), the direct pharmacological activation of the non-classical RAS would be an attractive and plausible approach to tackle the reduction of Angiotensin(1-7) to lessen the unwanted effects of Angiotensin II.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a group of oral medications used to treat type 2 diabetes, however, large epidemiological studies have demonstrated that SLGT2 inhibitors present strong nephro- and cardiovascular-protective effects. In addition, in vitro studies in human renal cells treated with SLGT2 inhibitors have shown an increment in Angiotensin(1-7) due to the independent activation of the non-classical RES, leading to important anti-inflammatory and anti-

fibrotic effects [6,7]. By analogy, it is reasonable to assume that SLGT2 inhibitors could also activate the non-classical RES in the lungs.

A vast majority of diabetic patients also present CVD and many of them are treated with SLGT2 inhibitors to both lower blood glucose and protect the kidney and heart. Hence, would diabetic patients with CVD and treated with SLGT2 inhibitors present a milder ARDS as compared to those with a different treatment? Would they have a better clinical prognosis? And, would the use of SLGT2 inhibitors in non-diabetic patients improve clinical prognosis as well? These are interesting questions since the answers might open a new door to counteract the devastating consequences of the proinflammatory cytokine storm present in COVID-19 patients.

We declare no conflict of interest.

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