Intended for healthcare professionals

Rapid response to:

Editorials

Preventing a covid-19 pandemic

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Rapid Response:

Re: Preventing a covid-19 pandemic - Is there a magic bullet to save COVID-19 patients? We can give it a try!

Dear Editor,

I read with interest this article and related rapid responses.

The ongoing spread of novel SARS-CoV-2 virus and the disease COVID-19 that is caused by SARS-CoV-2, is a serious challenge for humankind. Saving lives and slowing the pandemic are of utmost importance.

The SARS-CoV-2 virus enters into human cells via the same receptor, angiotensin-converting enzyme 2 (ACE2), as its relative the SARS-CoV (1). During the course of infection virus particles bind to ACE2 and get internalized into human cells. This way the virus particles bind to numerous ACE2 molecules and sequester them from the cell surface. Moreover SARS-CoV was shown to downregulate ACE2 protein expression in a replication dependent manner (2). This would imply that loss of ACE2 function may develop during SARS-CoV-2 infection. Since ACE2 is a key-player in the renin-angiotensin system (RAS), its loss of function can lead to serious consequences.

ACE2 acts together in balance with angiotensin-converting enzyme (ACE), another major player in RAS, and a well-known target of antihypertensive drugs, during finely tuned processes, such as blood

pressure regulation and inflammation, among others. In disease models, a RAS imbalance with higher ACE and/or lower ACE2 results in atherosclerosis, hypertension, heart failure, chronic kidney disease, serious lung injury. Conditions wherein ACE2 increases seem to be protective (3).

RAS activity is intrinsically higher in the lung, where ACE2 is highly expressed as well, to balance ACE Angiotensin II production, which means, the stakes are raised here in the lung. This situation may be further enhanced in patients on ACE inhibitor hypertensives. In the known escape phenomenon of ACE inhibitors, there is a significant increase in renin that is accompanied by higher ACE2 levels, likely as a balancing factor (4). If RAS activity is balanced so much higher above normal, one has to count with more severe events upon RAS imbalances. This can be the case when SARS-CoV-2 starts downregulating ACE2. There the loss of ACE2 function can be a prime event that leads to increased neutrophil infiltration in the lung and results in exaggerated inflammation and injury, as it was observed in disease models (5). As soon as the ongoing lung infection results in hypoxia, the stakes are further raised by induction of renin release and increase in renin gene expression that can lead to a vicious circle (6). Hypertension is indeed a key risk factor in COVID-19 disease according to Chinese medics who fight the virus at the front-line. They also suggest to start ventilation as soon as the blood oxygenation cannot be maintained by other means (7). I believe early ventilation exactly would try to balance the vicious circle triggered by unbalanced, activated RAS; but unfortunately, it is often too late...

Patients with chronic diseases exhibit lower ACE2 levels. Moreover, as others suggested, it decreases by age, which would explain the vulnerability of this part of the population. In addition, significantly lower ACE2 levels were seen in aged males (8). This could be explained by the fact that ACE2 gene is X chromosome located and so males have less of a reserve capacity of ACE2 production under the extreme challenge of a SARS-CoV-2 infection. Since ACE2 protein is also expressed in the heart, kidney, small intestine enterocytes, and testes, one can indeed expect COVID-19 patients developing pathological changes at these locations, if vireamia is present.

If we can put on ice, a high running, SARS-CoV-2 unbalanced RAS, we could have a chance of saving lives before uncontrolled events would begin in COVID-19 patients.

Replacing prescribed ACE inhibitors in SARS-CoV-2 positive patients maybe worth a try, as others already suggested (9), however decoupling a SARS-CoV-2 unbalanced RAS may bring more advantage for COVID-19 patients.

Mounting evidence indicates that vitamin D is a negative endocrine regulator of RAS, and that normalization of vitamin D levels can lower RAS activity via transcriptional suppression of renin expression (10).

Since at this time of the year, the lack of vitamin D in the population of the northern hemisphere is widely observed, quasi exhibits a pandemic, it is likely that the role of RAS in COVID-19 disease is not negligible. Indeed the world distribution of COVID-19 fatalities appears to well overlap with that ofthe vitamin D lacking population. Not to mention that people lacking vitamin D have a weaker innate immune defense against SARS-CoV-2.

Targeting the unbalanced RAS with vitamin D supplementation in SARS-CoV-2 infection may be an approach with excellent cost and benefit ratio, to fight the widening of COVID-19, in the name of our professional principle, the 'primum nil nocere'.

Clinicians standing in front of SARS-CoV-2 positive patients may easily corroborate the herein assumed correlation between low vitamin D level and worse COVID-19 disease outcome, and so assure us in applying this novel support for COVID-19 patients. If fewer COVID-19 patients need to go on ventilation, the known bottleneck of this pandemic, we are already starting to win this battle, and can avoid the higher mortality rates that we are facing.

The outlined hypothesis that SARS-CoV-2 can unbalance a high running RAS in the lung via ACE2 downregulation, which is followed by inflammation, and hypoxia induced renin release, needs to be further investigated for the precise understanding of the involved molecular mechanisms. Likewise we should investigate the hypothesized mechanism by which the due supplementation of vitamin D could allow balancing of a high running RAS in COVID-19 patients.

These certainly await for pioneering researchers, but it should not prevent us from saving lives, and humankind from COVID-19.

Sincerely yours,

Attila R Garami, M.D., Ph.D.

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Competing interests: No competing interests

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Attila R Garami
MD, PhD, Senior Biomarker Consultant, CEO
BL, Switzerland
drag@quickline.ch