



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Sodium status and kidney involvement during COVID-19 infection

Adrian Post*, Robin P.F. Dullaart, Stephan J.L. Bakker

Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, 9700 RB, The Netherlands

ARTICLE INFO

Keywords:
 COVID-19
 SARS-CoV-2
 Sodium
 Kidney
 ACE2 receptor

ABSTRACT

The angiotensin-converting enzyme 2 receptor (ACE2) is expressed in epithelial cells of many tissues including the kidney, and has been identified to interact with human pathogenic coronaviruses, including SARS-CoV-2. Although diffuse alveolar damage and acute respiratory failure are the main features of COVID-19 infection, two recent studies demonstrate that kidney impairment in hospitalized COVID-19 patients is common, and that kidney involvement is associated with high risk of in-hospital death. Interestingly, studies in rats have demonstrated that high dietary sodium intake results in down-regulation of the ACE2 expression in kidney tissue. We hypothesize that low sodium status makes kidney involvement during the course of COVID-19 infection more likely due to upregulation of membrane bound ACE2 in the kidneys. We propose that sodium intake and status should be monitored carefully during severe COVID-19 infections, and that low sodium intake be corrected early in its course, despite a potential conflict regarding common dietary recommendations to restrict dietary sodium intake in patients with hypertension, diabetes, and kidney disease.

The angiotensin-converting enzyme 2 receptor (ACE2) is expressed in epithelial cells of many tissues including the kidney, and has been identified to interact with human pathogenic coronaviruses, including SARS-CoV-2 (Letko et al., 2020). Although diffuse alveolar damage and acute respiratory failure are the main features of COVID-19 infection, two recent studies demonstrate that kidney impairment in hospitalized COVID-19 patients is common, and that kidney involvement is associated with high risk of in-hospital death (Cheng et al., 2020; Li et al., 2020). If SARS-CoV-2 becomes systemic after the respiratory system has served as porte d'entrée, the kidney is a potential target for the virus, which is supported by results of RNA-sequencing studies, which found up to 100 times higher tissue ACE2 expression in the kidneys compared to the lungs (Fagerberg et al., 2014). Interestingly, studies in rats have demonstrated that high dietary sodium intake results in down-regulation of the ACE2 expression in kidneys (Cao et al., 2017; Berger et al., 2015). Indeed, Cao et al. demonstrated that a high sodium diet for 3 weeks more than halved the expression of ACE2 in rat kidney (Cao et al., 2017). Concordantly, Berger et al. demonstrated a nearly 5-fold higher ACE2 expression in spontaneously hypertensive rats fed a low sodium diet when compared to those on a high sodium diet (Berger et al., 2015). It should be noted that the high sodium group in the study by Cao et al. was exposed to a 20-times higher sodium intake than the low sodium group (Cao et al., 2017), while such an extreme difference in sodium intake is rarely seen between humans. Moreover, these experimental studies did not differentiate between cell membrane-bound

ACE2 and soluble ACE2, which may be important in light of SARS-CoV-2 exposure to cells. Soluble ACE2 is formed through proteolytic cleavage of membrane bound ACE2 but probably represents only a small fraction of membrane bound ACE2 (Larouche-Lebel et al., 2019). It has been proposed that low sodium balance may lead to more severe COVID-19 (Post et al., 2020). Indeed, studies on electrolyte disturbances during COVID-19 have shown significantly lower sodium concentrations in patients with severe COVID-19 infection (Lippi et al., 2020). Here, we hypothesize that low sodium status also makes kidney involvement during the course of COVID-19 infection more likely due to upregulation of membrane-bound ACE2 in the kidneys. The hypothesized interaction between sodium balance, the ACE2 receptor, SARS-CoV-2, and the kidney is shown in Fig. 1. We propose that sodium intake and status should be monitored carefully during severe COVID-19 infections and low sodium intake be treated early in its course, despite a potential conflict regarding common dietary recommendations to restrict dietary sodium intake in patients with hypertension, diabetes, and kidney disease.

Funding

None.

* Corresponding author.

E-mail addresses: a.post01@umcg.nl (A. Post), dull.fam@12move.nl (R.P.F. Dullaart), s.j.l.bakker@umcg.nl (S.J.L. Bakker).

<https://doi.org/10.1016/j.virusres.2020.198034>

Received 11 May 2020; Received in revised form 17 May 2020; Accepted 18 May 2020

Available online 21 May 2020

0168-1702/ © 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

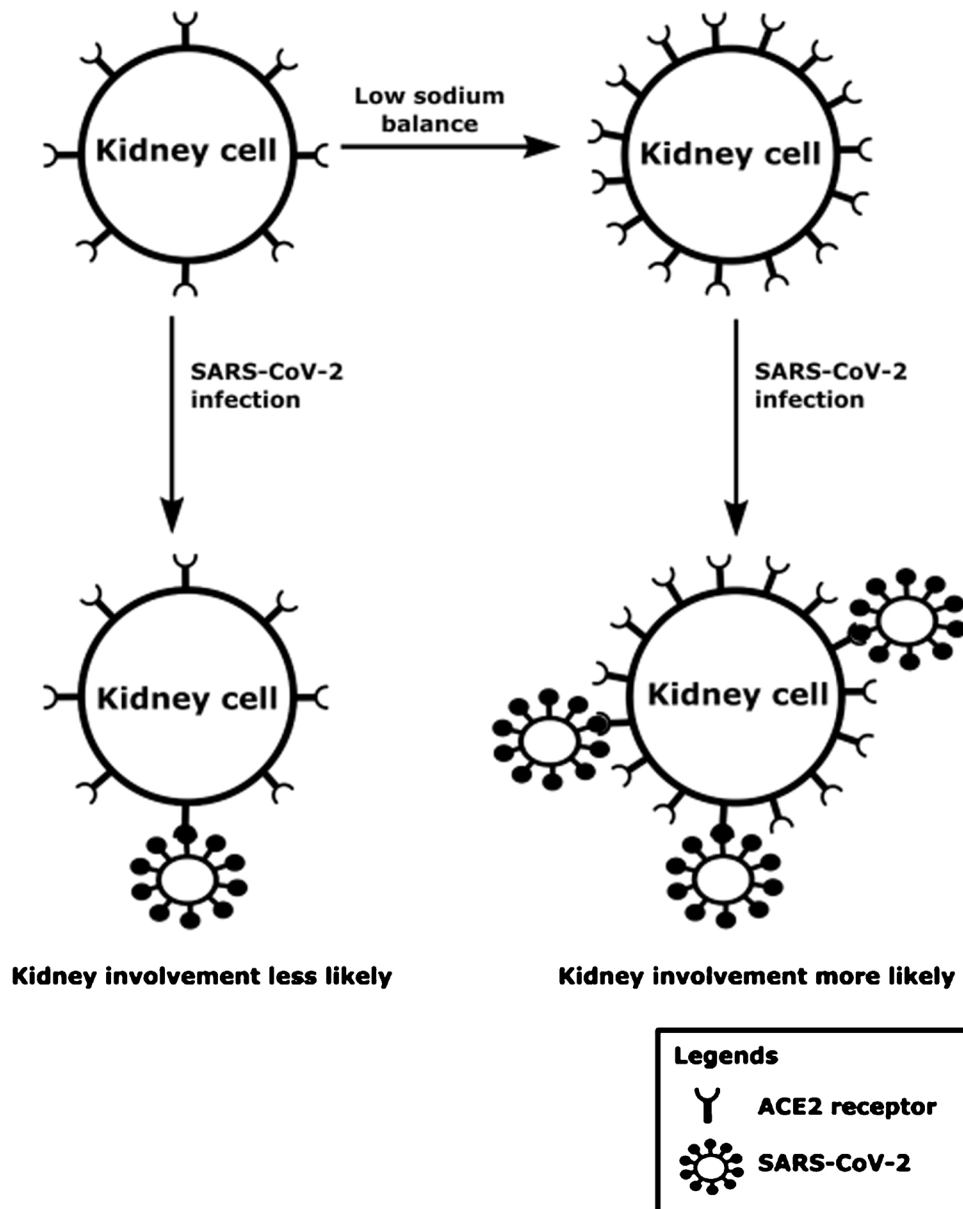


Fig. 1. A schematic overview of the hypothesized interaction between sodium balance, the ACE2 receptor expression, SARS-CoV-2 and the kidney.

CRedit authorship contribution statement

Adrian Post: Conceptualization, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Robin P.F. Dullaart:** Conceptualization, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Stephan J.L. Bakker:** Conceptualization, Investigation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.virusres.2020.198034>.

References

Berger, R.C., Vassallo, P.F., Crajoins Rde, O., et al., 2015. Renal effects and underlying molecular mechanisms of long-term salt content diets in spontaneously hypertensive rats. *PLoS One* 10 (10), e0141288.

Cao, G., Della Penna, S.L., Kouyoumdzian, N.M., et al., 2017. Immunohistochemical expression of intrarenal renin angiotensin system components in response to tempol in rats fed a high salt diet. *World J. Nephrol.* 6 (1), 29–40.

Cheng, Y., Luo, R., Wang, K., et al., 2020. Kidney impairment is associated with in-hospital death of COVID-19 patients. *Kidney Int.* 97 (5), 829–838.

Fagerberg, L., Hallstrom, B.M., Oksvold, P., et al., 2014. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol. Cell Proteomics* 13 (2), 397–406.

Larouche-Label, E., Loughran, K.A., Oyama, M.A., et al., 2019. Plasma and tissue angiotensin-converting enzyme 2 activity and plasma equilibrium concentrations of angiotensin peptides in dogs with heart disease. *J. Vet. Intern. Med.* 33 (4), 1571–1584.

Letko, M., Marzi, A., Munster, V., 2020. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat. Microbiol.* 5, 562–569.

Li, Z., Wu, M., Guo, J., et al., 2020. Caution on kidney dysfunctions of 2019-nCoV patients. medRxiv. (available <http://medrxiv.org/content/early/2020/02/12/2020.02.08.20021212.abstract>; (date of access: 16th May 2020)).

Lippi, G., South, A.M., Henry, B.M., 2020. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). *Ann. Clin. Biochem.* 57 (3), 262–265.

Post, A., Dullaart, R.P.F., Bakker, S.J.L., 2020. Is low sodium intake a risk factor for severe and fatal COVID-19 infection? *Eur. J. Intern. Med.* 75, 109.