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*Published in:*  
Virus research

*DOI:*  
[10.1016/j.virusres.2020.198034](https://doi.org/10.1016/j.virusres.2020.198034)

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*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Post, A., Dullaart, R. P. F., & Bakker, S. J. L. (2020). Sodium status and kidney involvement during COVID-19 infection. *Virus research*, 286, [198034]. <https://doi.org/10.1016/j.virusres.2020.198034>

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## Sodium status and kidney involvement during COVID-19 infection

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### 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.

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<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

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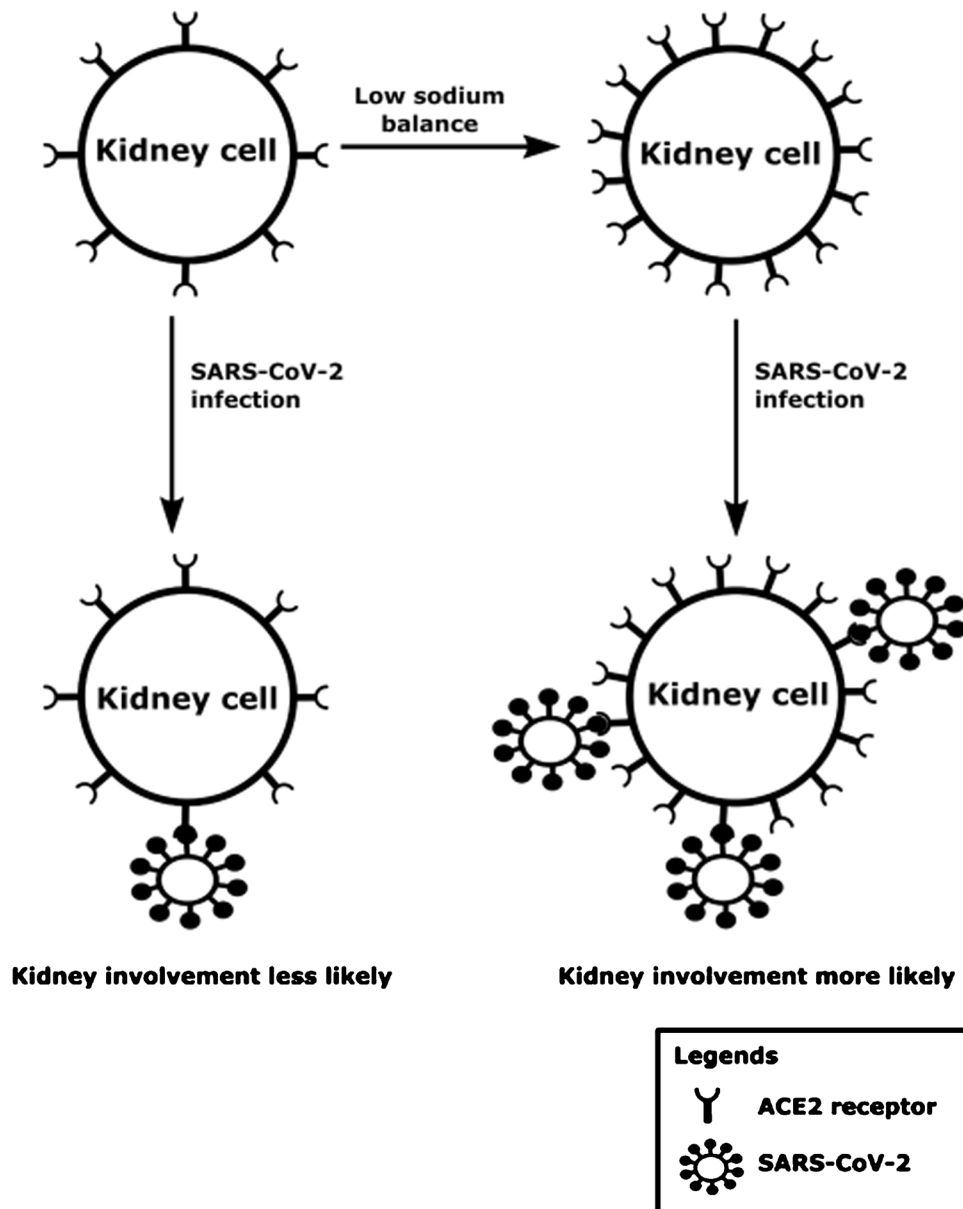


Fig. 1. A schematic overview of the hypothesized interaction between sodium balance, the ACE2 receptor expression, SARS-CoV-2 and the kidney.

**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>.

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