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EDITORIAL

Implications of renal ACE2 expression in the age of COVID-19

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This editorial refers to 'Hypertension and renin-angiotensin system blockers are not associated with expression of angiotensin-converting enzyme 2 (ACE2) in the kidney'†, by X. Jiang *et al.*, on page 4580.

The zinc metallopeptidase angiotensin-converting enzyme 2 (ACE2) has been of much research interest recently due to its role as a receptor for the severe acute respiratory syndrome coronavirus (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19). Hypertension, obesity, diabetes, older age, and male sex are the most common comorbidities among patients with COVID-19 infection.[1] This has led to the speculation that higher (than normal) ACE2 expression among patients with these conditions plays a role in their greater susceptibility to COVID-19 infection. Additionally, it was suggested that renin–angiotensin system (RAS) blockade with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) would lead to elevated ACE2 expression and, thus, greater binding of SARS-CoV-2 to ACE2, resulting in severe injury to the pulmonary epithelium and other tissues. This hypothesis was based on studies in the Lewis rat model, in which Ferrario *et al.*[2] showed that the administration of ACEIs increased cardiac ACE2 gene transcription. The same group showed that the use of ARBs increased cardiac ACE2 mRNA in a similar model.[3]

In the current issue of the *European Heart Journal*, Jiang *et al.*[4] examined a large number of renal tissues taken from patients with hypertension, diabetes, and obesity. They observed no significant association between renal expression of ACE2 at autopsy and the patients' history of hypertension, diabetes mellitus, or obesity. Furthermore, they observed no association of patients' treatment with antihypertensive agents, including ACEIs and ARBs, and renal expression of ACE2. They, however, did find a positive correlation between renal expression of ACE2 and estimated glomerular filtration rate (eGFR). The current study also shows a higher level of ACE2 expression in the kidney and subcutaneous adipose tissue in women compared with men, but a higher level of ACE2 in the aorta in men compared with women. There were no significant sex-related differences in ACE2 expression in the lungs, left ventricle, and atrial appendages. The implications of these findings on our understanding of COVID-19 are not clear, although higher ACE2 expression in the lungs has been postulated to be a cause of higher mortality related to COVID-19 in men (*Take home figure*).

The association between ACE2 and hypertension in humans is poorly understood. In a rat model, Crackower *et al.*[5] showed that hypertension was associated with a decrease in renal ACE2 mRNA levels. Gurley *et al.*[6] showed that the administration of angiotensin II (Ang II) to ACE2-deficient mice caused a larger increase in blood pressure compared with controls. Tikelli *et al.*[7] found that renal expression of ACE2 in spontaneously hypertensive rats (SHRs) was almost twice that seen in the normotensive Wistar Kyoto (WKY) rats at birth. A three-fold increase in renal ACE2 expression in WKY rats was observed at 6 weeks of age compared with that seen at birth; however, there was no significant change in renal ACE2 expression in SHRs between birth and 6 weeks of age, and the level of renal ACE2 expression in adult SHRs was half that seen in WKY animals. In contrast to the animal model, the current study shows that, in humans, hypertension is not associated with a difference in renal ACE2 expression. Jiang *et al.*[4] also showed that treatment with ACEIs and ARBs had no effect on renal ACE2 expression in humans or SHRs. These findings, in light of previous studies showing an increase in cardiac ACE2 expression in rats in response to ACEIs and ARBs,[2,3] suggest a possible tissue-dependent association between ACE2 expression, hypertension, and RAS blockade.

Additionally, the absence of a correlation between hypertension and ACE2 expression in the current study should be viewed with

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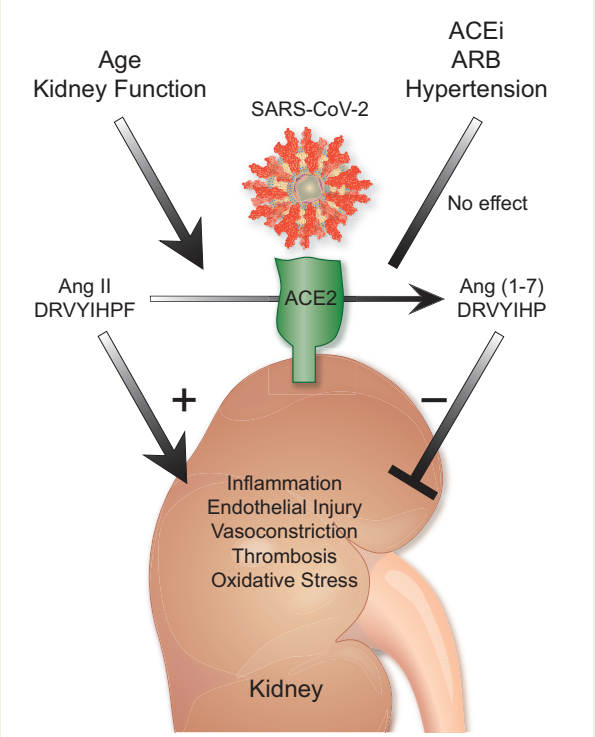
caution as the analysis was not done in age-matched kidney samples. Further, the current study did not evaluate the association between hypertension and ACE2 activity. In addition, the study did not take into account changes that can modify protein abundance and localization such as protein synthesis, degradation, modification, and cleavage to produce soluble ACE2. More studies examining the association between ACE2 tissue expression, ACE2 activity, and hypertension in different human tissues are needed to understand the pathophysiological role of ACE2 in hypertension.

The current study also shows that renal and lung ACE2 expression increases with age, consistent with the previous data in nasal epithelium.[8] The increase in ACE2 expression with age could reflect a compensatory response to age-related changes, such as an increase in blood pressure, chronic proinflammatory status, and decreased eGFR. As shown in animal models, ACE2 may counteract an increase in blood pressure, via its ability to metabolize Ang II into vasodilator peptide Ang-(1-7).[9] Ang-(1-7) has anti-inflammatory effects,[10] which can probably counteract the age-related proinflammatory state. The positively correlated association between eGFR and renal ACE2 expression might suggest a role for ACE2 in maintaining normal kidney function and counteracting the age-related decline in eGFR. This speculation is supported by the finding that many ACE2-co-expressed kidney genes play a role in maintaining the physiological functions of the kidney, such as reabsorption in the proximal tubule and regulation of urinary excretion of protein. Alternatively, the mechanism of this association is unclear but it could be related to tubular senescence when renal mass is lost.

The study of Jiang *et al.* shows sex-related differences in ACE2 expression that are dependent on the type of tissue. The authors conclude that this finding suggests that the ACE2 gene, which is located on the X chromosome, escapes inactivation in selected human tissue. The sex-related differences in ACE2 are not confined to tissue expression but are also seen in serum ACE2 levels, as noted recently by Sama *et al.*,[11] who observed higher serum ACE2 levels in men with heart failure compared with women. These findings, when viewed in conjunction with the study by Stelzig *et al.*[12] who observed down-regulation of ACE2 expression by 17β-estradiol in human bronchial epithelial cells, suggest important sex-related regulatory mechanisms. While the exact role of ACE2 in the development of hypertension and heart failure is not understood, this sex- and tissue-related difference might, in part, explain the higher prevalence of hypertension and heart failure among men compared with women.

While this study shows a negative association between renal ACE2 expression and the most common comorbidities in COVID-19 infection (hypertension, obesity, and diabetes mellitus) as well as ACEI/ARB use, several questions still need to be answered. The association between these conditions and ACE2 activity and serum level is not clear. The role of higher ACE2 expression, activity, and serum level as a possible cause of higher susceptibly and worse prognosis in COVID-19 infection is not well established. In fact, Monteil *et al.*[13] recently showed that soluble recombinant ACE2 can significantly inhibit SARS-CoV-2 infection and decrease viral load. Further, Imai *et al.*[14] showed that recombinant ACE2 can protect mice from severe lung injury. These findings suggest a possible protective value for ACE2 in COVID-19 and other infections causing lung injury. This warrants further investigation with clinical trials examining the effect of recombinant ACE2 and synthetic ACE2 inhibitors in such infections.



Take home figure The ACE2 enzyme is key to the effects of SARS-CoV-2 in the kidney and other tissues. It is the mechanism of cell entry for the virus, but also modulates actions of the renin–angiotensin system by converting angiotensin II (Ang II) to Ang-(1-7). Lower amounts of ACE2 increase the injurious effects of Ang II on the kidney and other tissues while increased ACE2 leads to more conversion to Ang-(1–7) and less injury. The study by Jiang *et al.* shows that age and kidney function are positively associated with ACE2 expression, but hypertension and antihypertensives which block the renin–angiotensin system have no effect. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 . The one-letter amino acid sequences of Ang II and Ang-(1-7) are shown.

The clinical relevance of the association of renal ACE2 protein abundance with kidney injury depends on whether injury is caused by viral infection of kidney parenchyma or endothelium or by other infection-associated factors such as an imbalance of the levels of counter-regulatory angiotensin peptides. While several studies suggested that the kidney may be directly infected by SARS-CoV-2, the largest autopsy series did not show evidence of renal infection.[15] If direct infection of the kidney is a rare event, the significance of renal ACE2 abundance may be more related to the balance between Ang II and Ang-(1-7).

The variations in tissue collection and the retrospective nature of the study are major limitations. The latter is particularly worrisome wherein the autopsy data and the patient's medical history and medications were correlated. Despite these limitations, the authors were able to collect a large number of tissue samples and provide important data on renal ACE2 expression.

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Conflict of interest: none declared.

References

1. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;**323**:2052–2059.
2. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 2005;**111**:2605–2610.
3. Ishiyama Y, Gallagher PE, Averill DP, Tallant A, Brosnihan BK, M. Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension* 2004;**43**:970–976.
4. Jiang X, Eales JM, Scannali D, Nazgiewicz A, Prestes P, Maier M, Denniff M, Xu X, Saluja S, Cano-Gamez E, Wystrychowski W, Szulinska M, Antczak A, Byars S, Skrypnik D, Glyda M, Król R, Zywiec J, Zukowska-Szczechowska E, Burrell LM, Woolf AS, Greenstein A, Bogdanski P, Keavney B, Morris AP, Heagerty A, Williams B, Harrap SB, Trynka G, Samani NJ, Guzik TJ, Charchar FJ, Tomaszewsk M. Hypertension and renin-angiotensin system blockers are not associated with expression of angiotensin-converting enzyme 2 (ACE2) in the kidney. Eur Heart J 2020;**41**:4580–4588.
5. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, Oliveira-dos-Santos AJ, da Costa J, Zhang L, Pei Y, Scholey J, Ferrario CM, Manoukian AS, Chappell MC, Backx PH, Yagil Y, Penninger JM. Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature* 2002;**417**:822–828.
6. Gurley SB, Allred A, Le TH, Griffiths R, Mao L, Philip N, Haystead TA, Donoghue M, Breitbart RE, Acton SL, Rockman HA, Coffman TM. Altered blood pressure responses and normal cardiac phenotype in ACE2-null mice. *J Clin Invest* 2006;**116**:2218–2225.
7. Tikellis C, Cooper ME, Bialkowski K, Johnston CI, Burns WC, Lew RA, Smith AI, Thomas MC. Developmental expression of ACE2 in the SHR kidney: a role in hypertension? *Kidney Int* 2006;**70**:34–41.
8. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA* 2020;**323**:2427–2429.
9. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J* 2004;**383**:45–51.
10. Simões e Silva AC, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *Br J Pharmacol* 2013;**169**:477–492.
11. Sama IE, Ravera A, Santema BT, van Goor H, Ter Maaten JM, Cleland JGF, Rienstra M, Friedrich AW, Samani NJ, Ng LL, Dickstein K, Lang CC, Filippatos G, Anker SD, Ponikowski P, Metra M, van Veldhuisen DJ, Voors AA. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors. *Eur Heart J* 2020;**41**:1810–1817.
12. Stelzig KE, Canepa-Escaro F, Schiliro M, Berdnikovs S, Prakash YS, Chiarella SE. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2020;**318**:L1280–L1281.
13. Monteil V, Kwon H, Prado P, agelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Hurtado Del Pozo C, Prosper F, Romero JP, Wirnsberger G, Zhang H, Slutsky AS, Conder R, Montserrat N, Mirazimi A, Penninger JM. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 2020;**181**:905–913.
14. Imai Y, Kuba K, Rao S, Imai Y, Kuba K, Rao S. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;**436**:112–116.
15. Santoriello D, Khairallah P, Bomback AS, Xu K, Kudose S, Batal I, Barasch J, Radhakrishnan J, D'Agati V, Markowitz G. Postmortem kidney pathology findings in patients with COVID-19. *J Am Soc Nephrol* 2020;**31**:2158–2167.

Corrigendum

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In Table 2, the unit for baseline CRP and peak CRP should have been mg/L and not mg/Dl. This has been corrected in the online version of the article.