JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
COMMENTARY

Angiotensin-converting enzyme 2 as a versatile player in the management of coronavirus disease 2019

INTRODUCTION

In view of the global coronavirus disease 2019 (COVID-19) pandemic, there are ongoing efforts aimed at predicting potential factors causing clinical exacerbation of COVID-19 and at seeking effective therapies for COVID-19.

Recent studies have shown that severe acute respiratory coronavirus 2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE2) as a receptor for cellular invasion and subsequent replication[1]. Furthermore, some reports suggest that the renin–angiotensin–aldosterone system (RAAS) inhibitors increase expression of ACE2[2]. These findings gave rise to the hypothesis that the use of RAAS inhibitors might increase the cellular invasion of SARS-CoV-2, and predispose patients to develop infection and increase the severity of COVID-19. In the first clinical case series, age, the presence of hypertension, diabetes and cardiovascular disease, which are relevant to the use of RAAS inhibitors, were identified as potential risk factors for severe conditions and mortality as a result of COVID-19[3]. However, as RAAS inhibitors are commonly used drugs worldwide for indications such as cardiovascular diseases, including hypertension, heart failure, myocardial infarction and diabetic complications of kidneys, their discontinuation as a result of COVID-19 should be carefully considered until sound evidence is available.

EPIDEMIOLOGICAL EVIDENCE OF RAAS INHIBITORS

Recently, in an epidemiological study, Abajo *et al.*[4] reported on the relationship between the use of RAAS inhibitors and the risk of COVID-19 requiring admission to hospital. In that study, a total of 1,139 consecutive patients, who were diagnosed with COVID-19 on the basis of polymerase chain reaction and required admission to hospital in Madrid, were studied. As a reference group, 11,390 patients, who individually matched the potential confounding factors, were sampled. Compared with other antihypertensive drugs, RAAS inhibitors were not associated with an increased risk of COVID-19 requiring admission to hospital, including fatal cases and those admitted to an intensive care unit (adjusted odds ratio 0.94, 95% confidence interval 0.77–1.15). Sex, age and potential confounding cardiovascular risks did not modify the adjusted odds ratio between the use of RAAS inhibitors and COVID-19. These results were consistent with those of two other epidemiological studies, and none of these studies found an increased risk of severe outcomes related to RAAS inhibitors. It is noteworthy that the authors considered exposure to ACE inhibitors before (7 days) or at admission to hospital, and during hospital stay in both studies. Thus, these findings suggest that RAAS inhibitors do not increase the risk of COVID-19 requiring admission to hospital, including fatal cases, as well as those admitted to intensive care units, and hence, RAAS inhibitors should not be discontinued to prevent a severe COVID-19 case.

DIABETES AS A RISK FACTOR OF COVID-19

Diabetes is the leading cause of morbidity, and its prevalence is predicted to increase exclusively in developed countries over the next few decades. Several reports showed that individuals with diabetes had a higher susceptibility to some infectious diseases than their healthy counterparts, presumably because of lower immunity. In the past decade, plasma glucose level and diabetes were proved to be independent predictors for mortality and morbidity in patients with SARS. Although diabetes has been reported as a risk factor for severe COVID-19, the underlying mechanism of this clinical observation is unknown. Experimental studies using diabetic mice have shown an increased activity of ACE exclusively in the lungs. Therefore, if this is the case in humans as well, the increased severity of COVID-19 in diabetes might be caused by an imbalance in the ACE : ACE2 ratio. In addition, this might explain the beneficial effect of RAAS inhibitors. In this context, another interesting finding by Abajo *et al.*[4] was a decreased risk of COVID-19 requiring admission to hospital among patients with diabetes who used RAAS inhibitors (adjusted odds ratio 0.53, 95% confidence interval 0.34–0.80). It is noteworthy that the use of RAAS inhibitors by outpatients with diabetes did not facilitate or aggravate infection, but rather improved the prognosis in this population. Further studies are required to identify the biological mechanism for this clinical observation.

SEX-BASED SUSCEPTIBILITY TO SARS-COV-2 BASED ON ACE2

Among various risk factors of severe COVID-19, elderly men with chronic illnesses might be more severely affected than their counterparts. A recent report showed that 70% of patients who died of COVID-19 in Italy were elderly men. Furthermore, the increased risk of elderly men with cardiovascular diseases and concomitant conditions could be

*Corresponding author. Tetsuya Amano
Tel.: +81-561-62-3311
Fax: +81-561-63-8482
E-mail address: amanot@aichi-med-u.ac.jp
Received 16 June 2020; revised 21 June 2020; accepted 24 June 2020

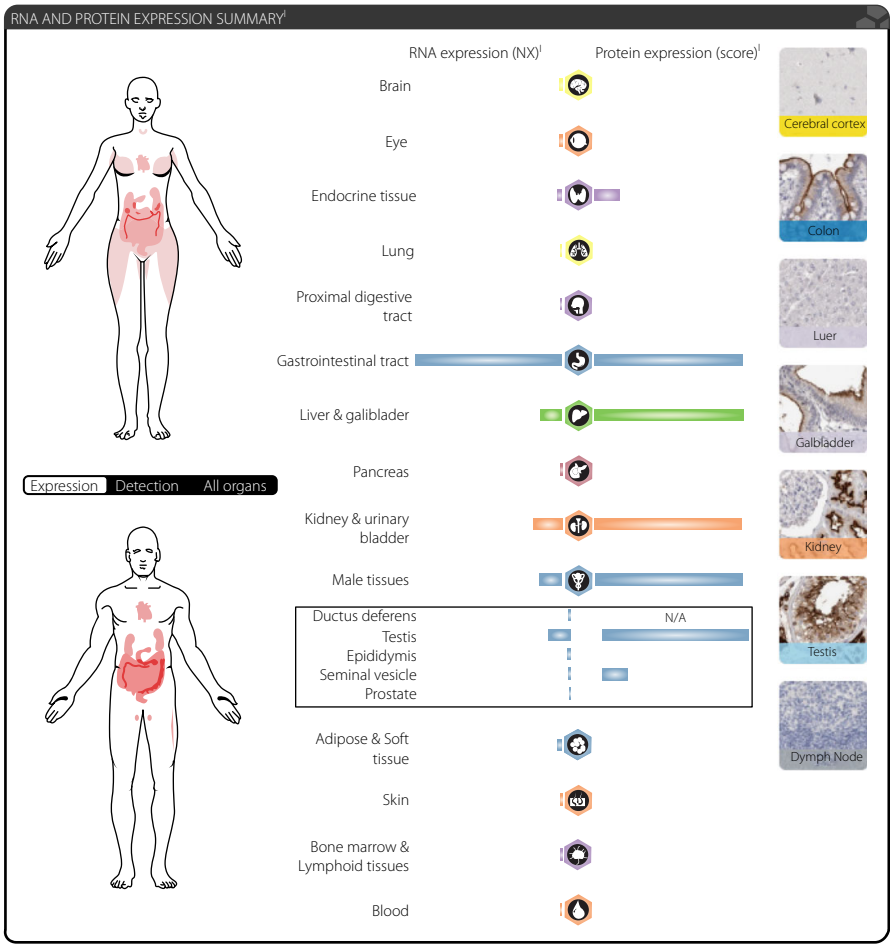

Figure 1 | Angiotensin-converting enzyme 2 gene and protein expression in human tissues. NX, normalized expression; RNA, ribonucleic acid. Adapted and reproduced with permission from Oxford University Press, *Eur Heart J*, 2020[5]. Copyright and all rights reserved. For permission to reuse, please contact the rights holder (some parts were changed by the author).

associated with increased concentrations of ACE2. Therefore, this might suggest that there are higher concentrations of ACE2 in men than in women.

Recently, Sama *et al.*[5] investigated the association between circulating plasma concentrations of ACE2 in men and women with heart failure and the effects of RAAS inhibitors. They measured ACE2 concentrations in 1,485 men and 537 women with heart failure as an index cohort. The results were validated in 1,123 men and 575 women as a validation cohort. They found that male sex (estimate 0.26, $P < 0.001$; and 0.19, $P < 0.001$, respectively) was the strongest predictor of elevated concentrations of ACE2 in both cohorts, and that the use of RAAS inhibitors was not associated with high plasma ACE2 concentrations. They concluded that plasma concentrations of ACE2 were higher in men than in women in two independent cohorts of patients with heart failure, and that RAAS inhibitors did not increase the risk for COVID-19 through increased plasma ACE2 concentrations. These findings could explain the increased susceptibility of men to SARS-CoV-2 and support the continued use of RAAS inhibitors in patients with heart failure, even during the COVID-19 pandemic.

ACE2 AS A VERSATILE PLAYER IN THE MANAGEMENT OF COVID-19

Given the recent study results that ACE2 is a human cell receptor with a binding affinity to SARS-CoV-2 and that ACE2 is expressed in a variety of organs (Figure 1)[5], it is rational to hypothesize that COVID-19-induced organ damage might be mediated by ACE2. However, a recent pathological study found some inflammatory mononuclear infiltrates in a tissue suggesting that COVID-19 might not directly impair the organs[6]. The equilibrium between plasma concentrations of ACE2 and membrane-bound ACE2 might influence COVID-19 pathogenesis and treatment options. These findings give rise to the question of whether ACE2 is just a trigger for SARS-CoV-2 infectivity or a therapeutic target in patients with various diseases as well as heart failure during the current SARS-CoV-2 pandemic. Further work is required to answer this question.

DISCLOSURE

The author declares no conflict of interest.

Tetsuya Amano*
Department of Cardiology, Aichi Medical University, Nagakute, Japan

REFERENCES

1. Li W, Moore MJ, Vasilieva N, *et al*. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; 426: 450–454.
2. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. *J Travel Med* 2020; 27: taaa041.
3. Yang X, Yu Y, Xu J, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8: 475–481.
4. Abajo FJ, Rodríguez-Martín S, Lerma V, *et al*. Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020: 395: 1705–1714.
5. Sama IE, Ravera A, Santema BT, *et al*. 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.
6. Xu Z, Shi L, Wang Y, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; 8: 420–422.

Doi: 10.1111/jdi.13346