Comment on 'Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic?'

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We read with great interest the article by Esler and Esler [1] 'Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic?'. The authors emphasized a very important point. They reported that angiotensin II receptor blockers (ARB) use increased angiotensin-converting enzyme 2 (ACE2) expression, but angiotensin-converting enzyme inhibitors (ACEIs) use did not it [1]. We think ACEIs also increase ACE2 expression. In addition, other antidiabetic agents and statins may also be associated with novel coronavirus disease 2019 (COVID-19). We would like to mention the relationship between these agents with COVID-19.

COVID-19 infection is very common and mortal in hypertension and diabetes mellitus patients. ACE2 is a zinc carboxypeptidase, which plays an important role in the renin–angiotensin system. ACE2 inactivates the vasoconstrictive effect of angiotensin II and causes the formation of angiotensin 1–7, a vasodilating peptide. However, COVID-19 uses ACE2 as the host receptor. Fang *et al.* [2] reported that ACEI increased ACE2 expression. ACEI does not directly affect ACE2. However, it has been demonstrated that ACE2 can use both angiotensin I and angiotensin II as substrates [3]. Therefore, ACE2 expression may increase in patients using both ACEI and ARB. Patients with hypertension, diabetes mellitus, and heart failure often use ACEI or ARB. Using ACEI or ARB may increment the prevalence and disease severity of COVID-19 infection by increasing the ACE2 level. Salt loading has been reported to reduce the ACE2 level [3]. Diuretic and mineralocorticoid antagonist drugs increase the level of angiotensin II by decrease the sodium level, thus, they increase the level of ACE2 [1]. The use of sodium-glucose transport protein 2 inhibitors (SGLT2i) is gradually increased in patients with diabetes mellitus and heart failure. Like diuretic and mineralocorticoid antagonists, SGLT2i increases the formation of angiotensinogen by causing diuresis and natriuresis. The combination of ACEI or ARB with SGLT2i significantly increases the ACE2 level [4]. Therefore, the combination of ACEI or ARB with SGLT2i may significantly increase the risk of COVID-19 infection. Glucagon-like peptide-1 receptor (GLP-1) agonists have also been reported to increase the ACE2 level [5]. The GLP1 agonist directly enhances ACE2 expression by mRNA upregulation. The use of GLP-1 agonists has increased in most obese diabetic patients. Like these drugs, thiazolidinediones also increase the ACE2 level [1]. Most diabetes patients for the treatment uses a few combinations of these drugs, such as GLP-1 agonist, SGLT2i, ACEI, and ARB. In addition, the vast majority of hypertensive and diabetic patients use statins. Rosuvastatin increases the ACE2 level by mRNA upregulation [6]. Monotherapy or combined therapy of these drugs may cause COVID-19 to be seen frequently and to be mortal in hypertension and diabetes mellitus patients. For this reason, it may be beneficial for the patients to immediately discontinue the ACEI or ARB. The patients can take the beta blockers and calcium channel blockers. Some people with chronic diseases, such as diabetes mellitus and hypertension frequently use multivitamins. Most of the multivitamins contain all-trans-retinoic acid (ATRA). ATRA significantly increases ACE2 expression [7]. In particular, ATRA should not be used in combination with ACEI or ARB. During the COVID-19 outbreak, chronic patients may be discontinued in its supportive treatment.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID- 19 pandemic? *J Hypertens* 2020; 38:781–782.
2. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020; 8:e21.
3. Brosnihan KB, Neves LA, Chappell MC. Does the angiotensin-converting enzyme (ACE)/ACE2 balance contribute to the fate of angiotensin peptides in programmed hypertension? *Hypertension* 2005; 46:1097–1099.
4. de Albuquerque Rocha N, Neeland IJ, McCullough PA, Toto RD, McGuire DK. Effects of sodium glucose co-transporter 2 inhibitors on the kidney. *Diab Vasc Dis Res* 2018; 15:375–386.
5. Romani-Perez M, Outeirino-Iglesias V, Moya CM, Santisteban P, Gonzalez-Matias LC, Vigo E, *et al.* Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. *Endocrinology* 2015; 156:3559–3569.
6. Li YH, Wang QX, Zhou JW, Chu XM, Man YL, Liu P, *et al.* Effects of rosuvastatin on expression of angiotensin-converting enzyme 2 after vascular balloon injury in rats. *J Geriatr Cardiol* 2013; 10:151–158.
7. Tikellis C, Thomas MC. Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. *Int J Pept* 2012; 2012:256294.

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