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LETTER TO THE EDITOR

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Comment on "Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19"

Dear Editor,

We read with great interest the article by Cheng et al[1] "Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19." The authors mentioned that angiotensin-converting enzyme 2 (ACE2) is protective against novel coronavirus disease 2019 (COVID-19). They reported that the ACE2 level was low in men and the elderly, therefore, the COVID-19 mortality was high in men and the elderly.[1] The beneficial or harmful effect of the ACE2 level on COVID-19 infection is still under discussion. Also, it is still unknown whether ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) that increase the ACE2 level will be discontinued in patients with COVID-19. We think that cytosolic pH, not ACE2 level, is associated with COVID-19 infection. We would like to explain how cytosolic pH increases the COVID-19 infection by affecting the ACE2. In addition, we would like to mention that amiloride, which increases the cytosolic pH, can be used in the COVID-19 treatment.

COVID-19 enters the cell using ACE2 as the host receptor and causes infection. ACE2 is on the X chromosome, so the ACE2 level is higher in women than in men.[1] However, COVID-19 infection frequency is approximately similar in both sexes. With aging, the ACE2 level decreases, thus the ACE2 level in young people is higher than in the elderly.[2] However, COVID-19-related mortality is significantly higher in men and the elderly. The frequent occurrence of COVID-19 infection in men and the elderly suggests that the infection is affected by other factors, not ACE2 levels. Human cytosolic pH is kept in a narrow range and under strict control. A decrease of cytosolic pH value makes it easier for the virus to attach to ACE2. Hydroxychloroquine (HQ), by increasing the cytosolic pH, prevents the virus from penetrating and entering the cell in regulatory regions of ACE2.[3] Although ACE2 level decreases with age, COVID-19 infection is more mortal. Decreasing of cytosolic pH due to aging[4] facilitates the connection of COVID-19 to ACE2 and increases the viral load.[3] Therefore, COVID-19 infection is more mortal in the elderly.

Estrogen increases the ACE2 level and serum angiotensin 1-7 level in women.[2] Long-term infusion of angiotensin 1-7 has been shown to cause vasodilation in female rats, not in male rats.[2] Young women have normal cytosolic pH values, therefore, angiotensin 1-7 may be protective against acute respiratory distress syndrome (ARDS) during COVID-19 infection in young women. COVID infection may be severe in women in the postmenopausal period since estrogen and cytosolic pH decrease by aging.[4] Renin-angiotensin system activity decreases with aging in both men and women.[5] Angiotensin II affects sodium (Na^+)/hydrogen (H^+) exchanger, increasing Na^+, lowering H^+, thereby increasing cytosolic pH.[6] Decreasing angiotensin II levels with aging[5] causes the cytosolic pH to reduce. Both ACEI and ARB increase the ACE2 level. ACEI inhibits the angiotensin II formation. ARBs block the binding of angiotensin II to the receptor and angiotensin II is rapidly converted to angiotensin 1-7 by ACE2. ACEI and ARBs cause to increase in the formation of angiotensin 1-7 from angiotensin II via increased ACE2.[7] However, angiotensin 1-7 has no effect on cytosolic pH.[6] It is doubtful that the ongoing increase of angiotensin 1-7 will protect against ARDS in men. ACEI and ARBs increase the viral load of COVID-19 by lowering the cytosolic pH and increasing the ACE2 level. Due to the increased viral load, the release of cytokine increases excessively, therefore the increase of angiotensin 1-7 cannot adequately protect against ARDS.

COVID-19 infection is frequently seen in hypertensive patients and its mortality is high in them. Na^+/H^+ exchanger excessive activation plays a key role in hypertension etiology and endothelial dysfunction.[8,9] Although Na^+/H^+ exchanger is activated, cytosolic pH is low in patients with hypertension. Cytosolic pH decreases as blood pressure increases.[8] Especially in elderly hypertensive patients, COVID-19 will be more mortal since cytosolic pH will be lower. COVID-19 causes more frequent infection and mortality in smokers and obese due to lowers cytosolic pH by hypercapnia.[10] In light of the information mentioned above, the most important reason for the increase of COVID-19 infection and its mortality is the decrease of cytosolic pH. If the cytosolic pH is low, the increased ACE2 level increases the viral load. HQ decreases the viral load by increasing the cytosolic pH.

Amiloride regulates the cytosolic pH by acting on Na^+/H^+ exchanger.[9] Amiloride is also effective in lung tissue. Amiloride is more potent than HQ. We speculate that amiloride can be used alone or with HQ in prophylaxis and treatment of COVID-19.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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