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Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be harmful in patients with diabetes during COVID-19 pandemic

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) outbreak once again demonstrated the importance of the renin-angiotensin system (RAS) in patients with diabetes. Activation of the RAS increases in patients with diabetes. The virus attaches to the ACE2 enzyme at low cytosolic pH values and enters into the cell and causes infection. Especially in the presence of diabetes mellitus and accompanying comorbid conditions such as hypertension, obesity, old age, and smoking, cytosolic pH is low, thus the virus easily may enter the cell by attaching to ACE2. ACEIs and ARBs lead to a reduction in angiotensin II level by increasing the ACE2 level, thus they cause a low cytosolic pH. Increased cardiac ACE2 levels due to ACEIs and ARBs can trigger cardiac arrhythmias and myocarditis by causing the virus to easily enter the heart tissue. There is ACE2 activity in the rostral ventrolateral medulla in the brain stem. The release of angiotensin 1-7 in the brain stem leads to the activation of the sympathetic nervous system. This activation causes systemic vasoconstriction and the patient's blood pressure increases. The most important event is the increased sympathetic activity via the central stimulation, this activity increases pulmonary capillary leaking, causing the ARDS. As the cytosolic pH, which is already low in patients with diabetes will decrease further with the mechanisms mentioned above, the viral load will increase and the infection will be exacerbated. As a result, the use of ACEIs and ARBs in patients with diabetes can lead to increased morbidity and mortality of COVID-19.

Dear Sir,

The novel coronavirus disease 2019 (COVID-19) outbreak once again demonstrated the importance of the renin-angiotensin system (RAS) in patients with diabetes. Activation of the RAS increases in patients with diabetes [1]. Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II is a powerful vasoconstrictor that triggers oxidative stress, causing increased reactive oxygen species. Raised angiotensin II level causes insulin resistance, endothelial dysfunction, proteinuria, and elevated blood pressure. ACE2 uses angiotensin II as a substrate and produces angiotensin 1-7 [1–3]. ACE inhibitors (ACEIs) inhibit the formation of angiotensin II from angiotensin I. This event leads to the conversion of angiotensin I to angiotensin 1-9 [1–3]. Angiotensin 1-9 is converted to angiotensin 1-7 by ACE2 [1,2]. Angiotensin receptor antagonists (ARBs) prevent angiotensin II from binding to the receptor, thus ARBs inhibit the effect of angiotensin II. ARBs, like ACEI, also increase the ACE2 level [4]. Angiotensin II, which cannot bind to the receptor, is rapidly converted to angiotensin I-7 by increased ACE2 [5]. The formation of angiotensin 1-7 is the desired event for patients with diabetes. Angiotensin 1-7 lowers glucose, causes vasodilation and reduces oxidative stress [1–3]. The vast majority of patients with diabetes use ACEIs and ARBs due to their renoprotective effects, even without hypertension.

The COVID-19 outbreak continues to cause severe morbidity and mortality worldwide. The virus attaches to the ACE2 enzyme at low cytosolic pH values and enters into the cell and causes infection [5]. Most patients with diabetes have comorbid conditions. The virus causes serious infections especially in elderly, hypertensive, diabetic and obese patients and smokers [5]. Especially in the presence

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of diabetes mellitus and accompanying comorbid conditions such as hypertension, obesity, old age, and smoking, cytosolic pH is low, thus the virus easily may enter the cell by attaching to ACE2 [5,6]. The COVID-19 infection becomes more severe in these patients due to high viral load. Angiotensin II has a strong pH alkalizing effect. It alkalizes the pH even after strong acid loading [7]. ACEIs and ARBs lead to a reduction in angiotensin II level by increasing the ACE2 level, thus they cause a low cytosolic pH [5]. Unlike angiotensin II, angiotensin 1-7 does not affect on cytosolic pH [5]. Therefore, increased angiotensin 1-7 levels may not reduce the viral load [5]. RAS activity and angiotensin II levels decrease with aging [5]. Especially in elderly patients with diabetes, COVID-19 infection will be more severe since cytosolic pH will be lower.

Since angiotensin 1–7 has a vasodilator effect, it has been hypothesized that it may be protective against acute respiratory distress syndrome (ARDS) occurrence in COVID-19 infection [8]. It is doubtful that the increment of angiotensin 1-7 level has a preventive effect on ARDS development. The evidence for the protective role of angiotensin 1-7 is limited at present. In an experimental model, continuous infusion of angiotensin 1–7 has been shown to have a vasodilator effect only in female rats [9]. The reason why COVID-19 is less severe in women than men may be a protective effect of estrogen in premenopausal women [8]. On the other hand, ACE2 is present in many tissues such as the brain, heart, kidney, testicle, veins. ACEIs and ARBs have been shown to increase the ACE2 level in the brain, heart, and kidney [8]. There is no evidence in the lung tissue that these drugs increase the ACE2 level. Most patients with diabetes have coronary artery disease and carotid intima-media thickening even in the early stage due to hyperglycemia. Mortality is significantly higher in patients with cardiac involvement during COVID-19 infection compared to patients without cardiac involvement [8]. Increased cardiac ACE2 levels due to ACEIs and ARBs can trigger cardiac arrhythmias and myocarditis by causing the virus to easily enter the heart tissue. The use of hydroxychloroquine and azithromycin may also increase the risk of QT prolongation and arrhythmia. As the attachment rate of the virus to cardiac ACE2 increases, patients with diabetes with COVID-19 may be more likely to die from cardiac arrhythmia. There is ACE2 activity in the rostral ventrolateral medulla in the brain stem [8]. Interestingly, the release of angiotensin 1-7 in the brain stem leads to the activation of the sympathetic nervous system [10,11]. This activation causes systemic vasoconstriction and the patient's blood pressure increases [10,11]. Increased blood pressure activates Na^+/H^+ exchanger and lowers cytosolic pH [8]. The ARBs and ACEIs-induced lower angiotensin II level in the diabetic patient, and the increased NHE activation, further reduce the already low cytosolic ph, leading to an increase of virus infection. Besides, increased sympathetic activity by the central pathway further increases virus-induced damage to the myocardium [8,10,11]. The most important event is the increased sympathetic activity via the central stimulation, this activity increases pulmonary capillary leaking, causing the ARDS [8,10,11]. It has not been demonstrated that angiotensin 1-7 inhibits ARDS. In an experimental study, as we mentioned above, angiotensin 1-7 did not cause vasodilation in male rats [9]. Even if angiotensin 1–7 has a protective effect against ARDS, increased angiotensin 1-7 formation via ACE2 in the heart, kidneys, and vessels will not be protective against centrally induced ARDS and myocardial injuries. Patients with diabetes and associated comorbidities receive drugs like pioglitazone, glucagon-like peptide-1 agonists, statins, diuretics, and mineralocorticoid inhibitors. All these drugs cause an increase in ACE2 level [4]. However, the combined use of ACEIs and ARBs and these drugs during the COVID-19 outbreak could lead to a markedly raised ACE2 level. As the cytosolic pH, which is already low in patients with diabetes, will decrease further with the mechanisms mentioned above, the viral load will increase and the infection will be exacerbated. As a result, the use of ACEIs and ARBs in patients with diabetes can lead to increased morbidity and mortality of COVID-19.

Declaration of competing interest

This article is a letter to the editor. We confirm that the entire manuscript, or parts of it, have not been published previously or are not currently under consideration for publication elsewhere.

We declare that have no financial relationships involved in this study.

We declare that there is no conflict of interest.

All authors confirm to have contributed substantially to the submission of this study.

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